

determination of preproopiomelanocortin demonstrated that the cleavage of this precursor protein produces not only  $\beta$ -endorphin but also several other neuropeptides including methionine-enkephalin, adrenocorticotropic hormone (ACTH), and  $\alpha$ -melanocyte stimulating hormone. Amino acid sequence of preproenkephalin indicates that four methionine enkephalins and one leucine-enkephalin are cleaved from this precursor. Furthermore, the primary structure of preprodynorphin, the precursor of dynorphin, gives rise to dynorphin, leumorphin, and neoendorphin—ligands for the  $\kappa$ -opioid receptor.

Orphanin FQ or nociceptin, a novel endogenous opioid peptide with a significant sequence homology to dynorphin, was isolated in 1995<sup>3,4</sup> and so named because it

lowered pain threshold under certain conditions in contrast to other endogenous opioid peptides. Pharmacologic and physiologic studies have demonstrated that orphanin FQ/nociceptin has behavioral and pain modulatory properties distinct from those of the three classic opioid peptides.<sup>31</sup> However, studies of the effect of orphanin FQ/nociceptin on pain sensitivity have produced conflicting results, which may suggest that the effects of orphanin FQ/nociceptin on pain sensitivity depend on the underlying behavioral state of the animal. Prepronociceptin, the precursor of orphanin FQ/nociceptin, was cloned, and its amino acid sequence suggested the existence of prepronociceptin-derived neuropeptides other than orphanin FQ/nociception.<sup>32</sup>

The search for endogenous ligand binding with the  $\mu$  receptor with high affinity and high selectivity led to the discovery of a class of novel endogenous opioids termed endomorphin-1 and endomorphin-2.<sup>33</sup> These peptides are tetrapeptides with the sequence Tyr-Pro-Trp-Phe and Tyr-Pro-Phe-Phe, respectively. An endomorphin gene has yet to be cloned, and much remains to be learned about the anatomic distribution, mode of interaction with the opioid receptors, function in vivo, and potential existence of other related peptides that are highly selective for each of the opioid receptors. It was recently demonstrated that both endomorphin-1 and endomorphin-2 given centrally and peripherally produced potent antiallodynic activities in a mouse model of neuropathic pain,<sup>34</sup> and downregulation of endomorphin-2 correlates with mechanical allodynia in a rat bone cancer pain model.<sup>35</sup>

## INTRACELLULAR SIGNAL TRANSDUCTION MECHANISM OF OPIOID RECEPTORS

The opioid receptors belong to the G-protein-coupled receptor family. It has been demonstrated that activation of the opioid receptors leads to activation of the pertussis toxin-sensitive G proteins ( $G_i$  or  $G_o$  or both). Expression of the cloned opioid receptors in cultured cells by transfection of the cloned cDNAs has facilitated analysis of the intracellular signal transduction mechanisms activated by the opioid receptors (Fig. 24.6).<sup>2</sup> Adenylate cyclase is inhibited by opioid receptor activation, with a resulting reduction of the cellular cyclic adenosine monophosphate (AMP) content. Electrophysiologically, the voltage-gated  $\text{Ca}^{2+}$

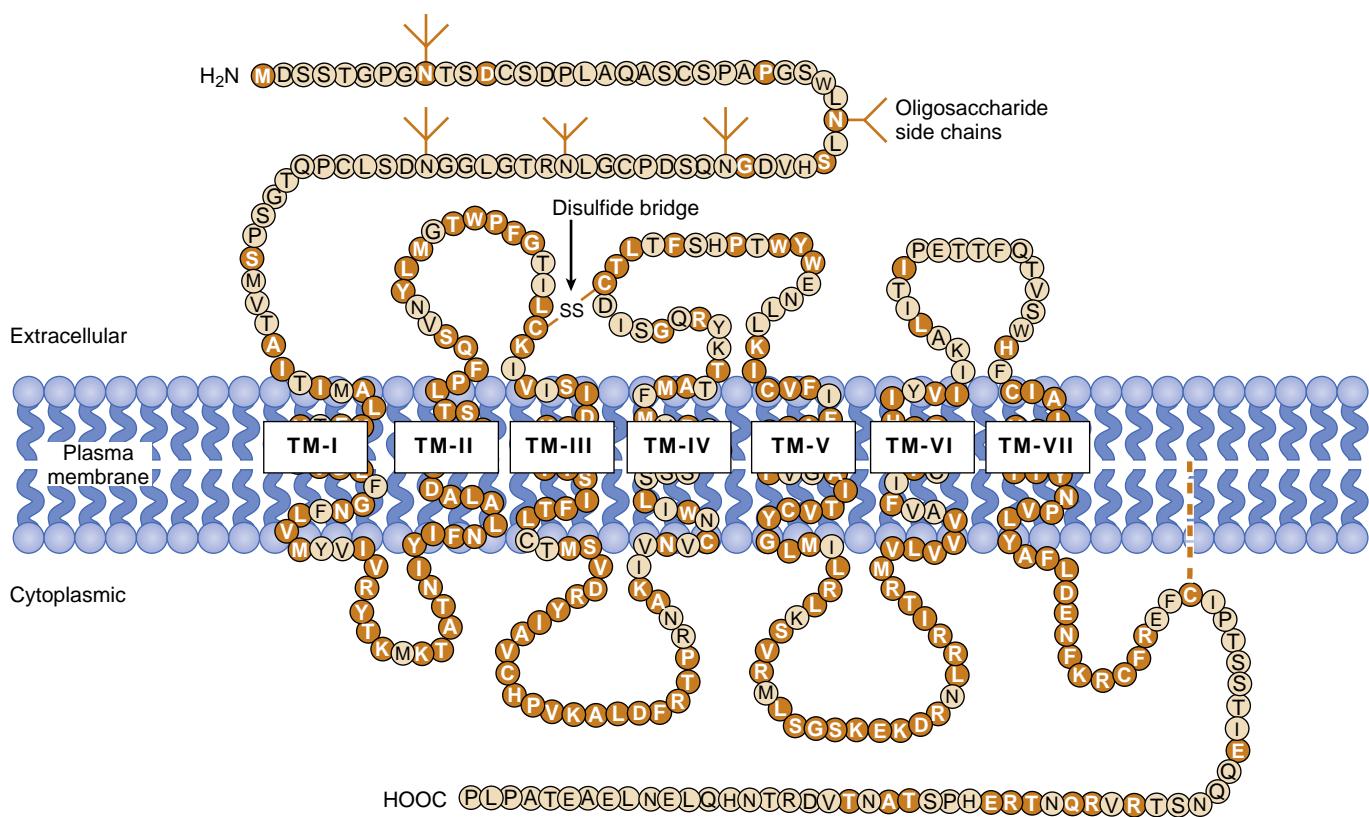
**TABLE 24.2** Pharmacologic Actions of Opioids and Opioid Receptors in Animal Models

ACTIONS OF			
	Receptor	Agonists	Antagonists
<b>ANALGESIA</b>			
Supraspinal	$\mu, \delta, \kappa$	Analgesic	No effect
Spinal	$\mu, \delta, \kappa$	Analgesic	No effect
Respiratory function	$\mu$	Decrease	No effect
Gastrointestinal tract	$\mu, \kappa$	Decrease transit	No effect
Psychotomimesis	$\kappa$	Increase	No effect
Feeding	$\mu, \delta, \kappa$	Increase feeding	Decrease feeding
Sedation	$\mu, \kappa$	Increase	No effect
Diuresis	$\kappa$	Increase	
<b>HORMONE SECRETION</b>			
Prolactin	$\mu$	Increase release	Decrease release
Growth hormone	$\mu$ and/ or $\delta$	Increase release	Decrease release
<b>NEUROTRANSMITTER RELEASE</b>			
Acetylcholine	$\mu$	Inhibit	
Dopamine	$\delta$	Inhibit	

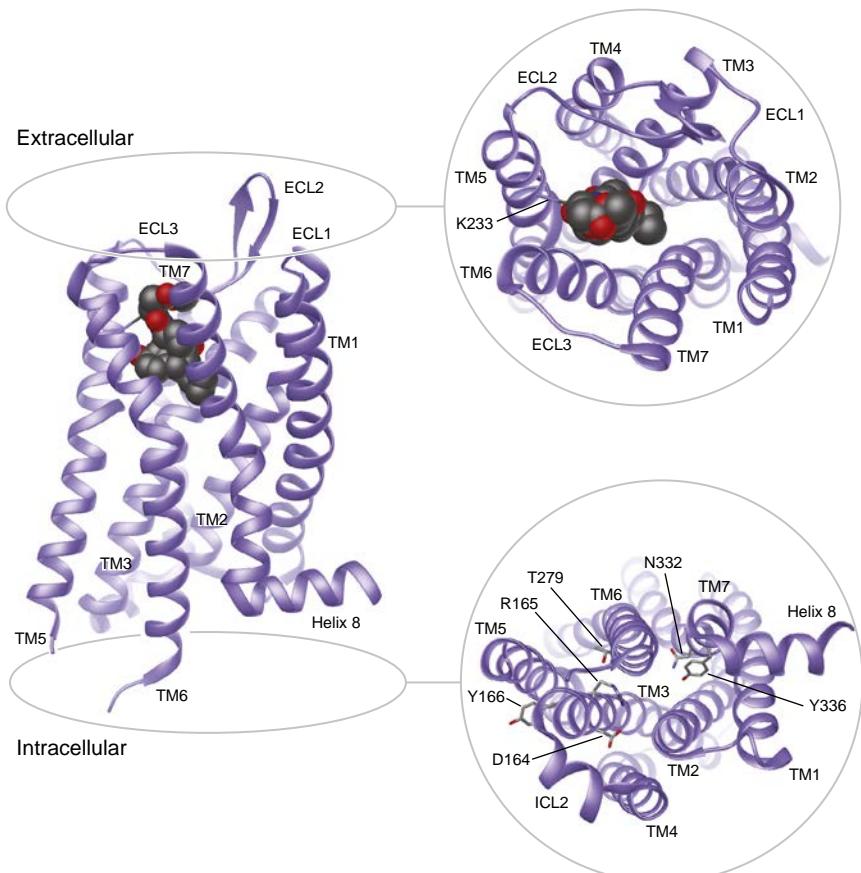
**TABLE 24.3** Characteristics of Opioid Receptors

$\mu$	$\delta$	$\kappa$	Nociceptin
Tissue bioassay	Guinea pig ileum	Mouse vas deferens	Rabbit vas deferens
Endogenous ligand	$\beta$ -Endorphin, Endomorphin	Leu-enkephalin, Met-enkephalin	Dynorphin
Agonist	Morphine, Fentanyl, DAMGO	DPDPE, Deltorphin	Buprenorphine, Pentazocine, U50488H
Antagonist	Naloxone, Naltrexone	Naloxone, Naltrindole	Naloxone, NorBNI
Coupled G protein	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Adenylate cyclase	Inhibition	Inhibition	Inhibition
Voltage-gated $\text{Ca}^{2+}$ channels	Inhibition	Inhibition	Inhibition
Inward rectifier $\text{K}^+$ channels	Activation	Activation	Activation

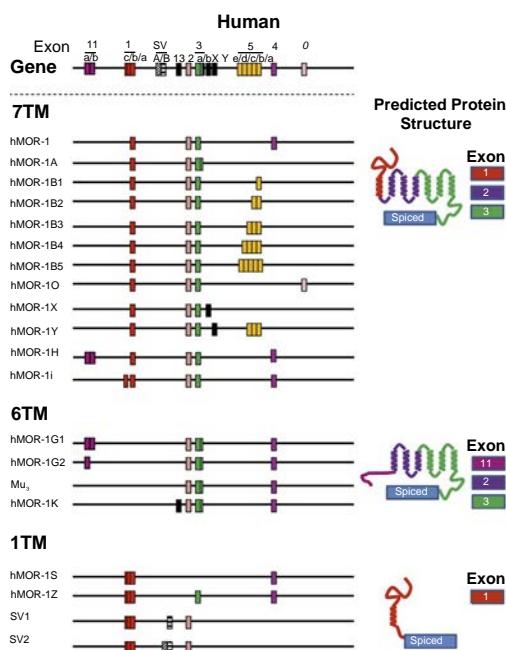
DAMGO, [d-Ala<sup>2</sup>, MePhe<sup>4</sup>, Gly-ol<sup>8</sup>]enkephalin; DPDPE, [D-penicillamine<sup>2</sup>, D-penicillamine<sup>5</sup>]enkephalin; NorBNI, norbinaltorphimine.



**Fig. 24.2 Proposed structure of the  $\mu$ -opioid receptor.** Black circles indicate amino acid residues identical in the  $\mu$ - and  $\delta$ -opioid receptors. TM-I to VII show putative transmembrane segments composed of hydrophobic amino acid residues.



**Fig. 24.3 Overall view of the  $\mu$ -opioid receptor structure.** Views from within the membrane plane (left), extracellular side (top), and intracellular side (bottom) show the typical 7-transmembrane G-protein-coupled receptor architecture of the  $\mu$ -opioid receptor.  $\beta$ -FNA, a semisynthetic opioid antagonist derived from morphine, is shown in black spheres. (From Manglik A, Kruse AC, Kobilka TS, et al. Crystal structure of the  $\mu$ -opioid receptor bound to a morphinan antagonist. *Nature*. 2012;485:321–326.)



**Fig. 24.4  $\mu$ -opioid receptor splicing in humans.** Variants are grouped as full length, 7-transmembrane (7TM), 6-transmembrane (6TM), and 1-transmembrane (1TM) with the predicted structure shown to the right and the exons color-coded to match the splicing schematic. (From Pasternak GW, Pan YX. Mu opioids and their receptors: evolution of a concept. *Pharmacol Rev*. 2013;65:1257–1317.)

channel is inhibited and the inwardly rectifying potassium ( $K^+$ ) channels are activated by the opioid receptors. As a result, neuronal excitability is reduced by activation of the opioid receptors. However, the role of adenylate cyclase in opioid receptor activation is complex. For example, long-term tolerance to opioids has been thought to be associated with superactivation of adenylate cyclase activity, which is a counterregulatory response to the decrease in cyclic AMP levels seen after acute opioid administration.<sup>36</sup> That this effect is prevented by pretreatment of cells with pertussis toxin demonstrates involvement of G proteins ( $G_i$  or  $G_o$  or both).

Beyond adenylate cyclase, other regulatory components participate in the coupling of opioid receptor binding and a cellular response. It was shown that extracellular signal-related kinase, a class of mitogen-activated protein kinases, is activated by the opioid receptors.<sup>37</sup> Opioid-induced activation of extracellular signal-related kinase can lead to increase in arachidonate release<sup>37</sup> and expression of immediate early genes, *c-fos* and *junB*.<sup>38</sup>

Chronic exposure of the opioid receptors to agonists induces cellular adaptation mechanisms, which may be involved in opioid tolerance, dependence, and withdrawal symptoms. Several investigators have shown that short-term desensitization probably involves phosphorylation of the opioid receptors through protein kinase C.<sup>39</sup> A number of other kinases also have been implicated, including protein kinase A and  $\beta$ -adrenergic receptor kinase (BARK), a member of the G-protein-coupled receptor kinase (GRK).<sup>40</sup> BARKs selectively phosphorylate agonist-bound receptors and thereby promote interactions with  $\beta$ -arrestins, which interfere with G-protein coupling and promote receptor internalization.  $\beta$ -Arrestin 2 functions as a scaffolding

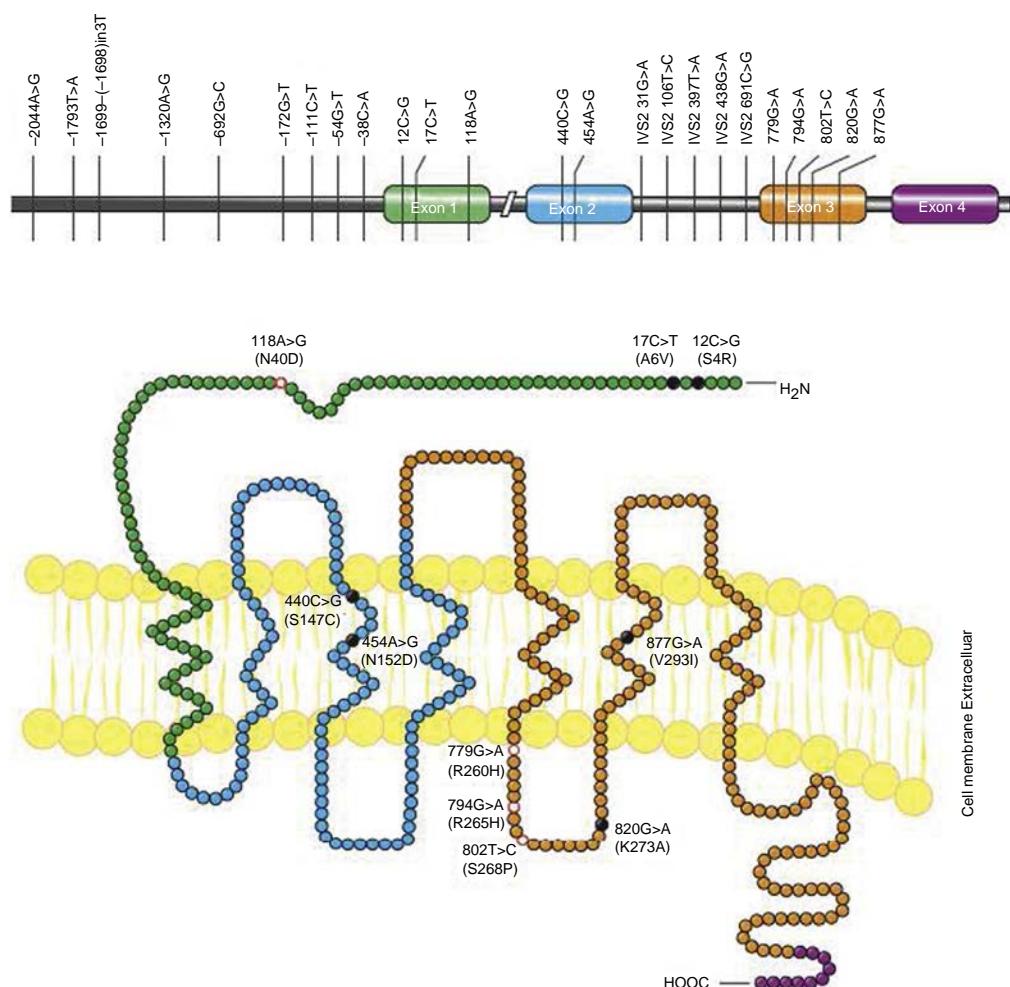
protein that interacts with signal transducers, and the recruitment of  $\beta$ -arrestin 2 induced by opioid receptor activation is involved in the regulation of activity of c-Src, Akt, and mitogen-activated protein kinases (Fig. 24.7).<sup>41</sup> The c-Src inhibitor, dasatinib, attenuated and reversed morphine-induced tolerance in mice, suggesting that c-Src recruited by  $\beta$ -arrestin 2 is involved in the morphine-induced tolerance.<sup>42</sup> Acute morphine-induced analgesia was enhanced in mice lacking  $\beta$ -arrestin 2, suggesting that this protein contributes to regulation of responsiveness to opioids *in vivo*.<sup>43</sup> Therefore,  $\beta$ -arrestin modification by associated kinases serves a critical role in the coupling between agonist binding to opioid receptors and their ability to develop and sustain an analgesic response.

Like other G-protein-coupled receptors, the opioid receptors can undergo rapid agonist-mediated internalization by a classic endocytic pathway.<sup>44,45</sup> These processes may be induced differentially as a function of the class of the ligand. For example, certain agonists, such as etorphine and enkephalins, cause rapid internalization of the  $\mu$  receptor, whereas morphine, which decreases adenylate cyclase activity equally well, does not cause  $\mu$  receptor internalization in all cell types such as HEK293 cells.<sup>46</sup> Although these findings may suggest that different ligands induce different conformational changes in the receptor that lead to divergent intracellular events, they also have revealed that rapid morphine-dependent  $\mu$  receptor endocytosis is still possible in subpopulations of central nervous system (CNS) neurons such as striatal neurons.<sup>47</sup> Taken together, they may help provide an explanation for differences in the efficacy and abuse potential of various opioids.<sup>48</sup>

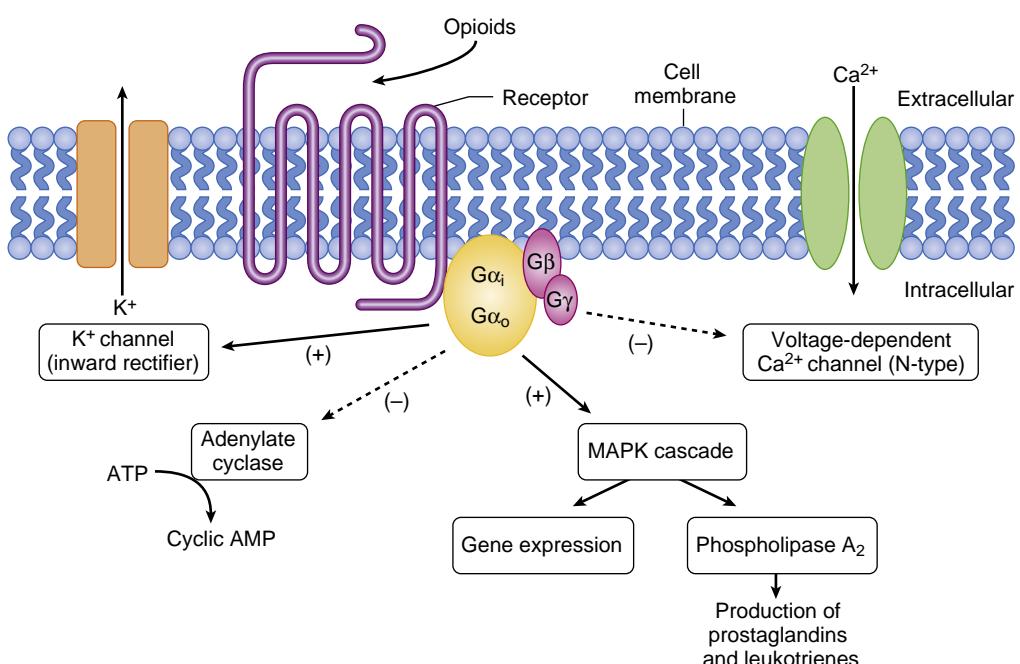
## BIASED AGONISM

Chemically distinct ligands binding to the same G-protein-coupled receptor can stabilize the receptor in multiple active conformations. In this way, differential activation of G-protein-coupled cell signaling pathways may produce divergent physiologic outcomes, a phenomenon known as biased agonism. Biased agonism can be exploited to design drugs that selectively activate desired signaling pathways, while minimizing other signaling pathways via the same receptor subtype and associated side effects.

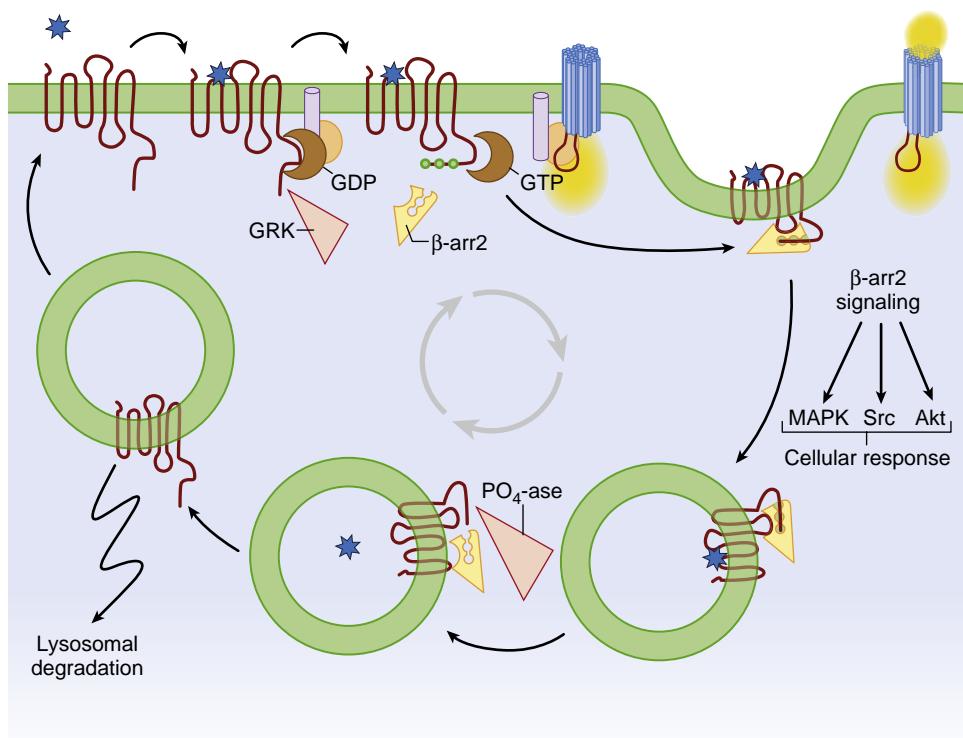
Morphine binds to the  $\mu$ -opioid receptor protein to form an active complex with signaling proteins, including  $G_{i/o}$  and  $\beta$ -arrestin. The  $G_{i/o}$  signaling pathway is thought to mediate analgesic action of morphine, whereas  $\beta$ -arrestin signaling results in unwanted side effects including euphoria, which can lead to addiction, respiratory depression, and gastrointestinal effects. Consistently, it was shown that the analgesic properties of morphine were enhanced but morphine-induced respiratory depression and constipation were attenuated in  $\beta$ -arrestin 2 knockout mice.<sup>49</sup> Emerging research in this evolving field includes a report by Manglik and associates, who computationally screened 3 million molecules, resulting in the compound PZM21, which showed high  $G_{i/o}$ -biased signaling and suppressed pain in mice without constipation, respiratory depression, hyperlocomotion, and addiction-related behaviors.<sup>50</sup> The clinical importance of these findings awaits further confirmation given other reports showing little difference in adverse effect profiles between morphine and PZM21 in



**Fig. 24.5 Reported mutations in the  $\mu$ -opioid receptor related to the exonic organization of the gene.** Twenty-four mutations that produce an amino acid exchange and are frequently reported (>1%) or are proposed to have functional consequences are indicated in the gene. Amino acids are symbolized as circles, colored according to the exons by which they are coded. Black circles represent a naturally occurring mutation at the respective position, and red circles when functional consequences are shown at molecular level. Mutations are indicated by the nucleotide exchange and the resulting amino acid exchange. (From Lötsch J, Geisslinger G. Are  $\mu$ -opioid receptor polymorphisms important for clinical opioid therapy? *Trends Mol Med*. 2005;11:82–89.)



**Fig. 24.6 Intracellular signal transduction mechanisms linked with the opioid receptors.** Opioid agonists bind with the opioid receptors, leading to activation of the G protein and the voltage-dependent calcium ( $Ca^{2+}$ ) channels is suppressed. On the other hand, inward rectifier potassium ( $K^+$ ) channels and mitogen-activated protein kinase (MAPK) cascade are activated. AMP, Adenosine monophosphate; ATP, adenosine triphosphate.



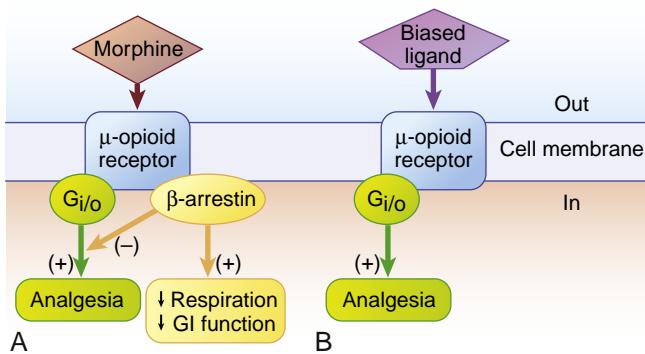
**Fig. 24.7  $\beta$ -Arrestin 2 and G protein in  $\mu$ -opioid receptor recycling, signaling, and degradation.** The blue star represents an opioid agonist and the trimeric membrane-associated complex in brown, green, and blue represents G protein  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits, respectively. The  $\alpha$  subunit is shown associated with guanosine diphosphate (GDP; resting state) or guanosine triphosphate (GTP; activated state). The  $\beta\gamma$  dimer interacts directly with the voltage-activated  $\text{Ca}^{2+}$  channel to inhibit calcium ( $\text{Ca}^{2+}$ ) influx (indicated in yellow).  $\beta\text{-arr}2$ ,  $\beta$ -arrestin 2; GRK, G-protein-coupled receptor kinase; MAPK, mitogen-activated protein kinase;  $\text{PO}_4\text{-ase}$ , phosphatase. (From Hales TG. Arresting the development of morphine tolerance and dependence. *Br J Anaesth*. 2011;107:653–655.)

mice.<sup>51</sup> However, TRV130, a “G protein-biased”  $\mu$ -opioid ligand with G-protein–coupling efficacy similar to that of morphine, but markedly reduced receptor phosphorylation, recruitment of  $\beta$ -arrestin 2, and internalization, was tested in a randomized, double-blind, placebo-controlled crossover study in healthy volunteers.<sup>52</sup> TRV130 produced greater analgesia than morphine, but less respiratory depression and less severe nausea (Fig. 24.8). As additional biased-agonist candidates of the  $\mu$ -opioid receptor emerge, so does the hope for a new generation of clinically effective analgesics with a reduced profile of harm.

## MECHANISM OF OPIOID ANALGESIA

### Brain

Pain control by opioids needs to be considered in the context of brain circuits modulating analgesia and the functions of the various types of receptors in these circuits.<sup>53</sup> It is well established that the analgesic effects of opioids arise from their ability to inhibit directly the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain, through the rostral ventromedial medulla (RVM), to the spinal cord dorsal horn. Petrovic and colleagues used an experimental pain model and positron emission tomography (PET) to study mechanisms of action of the short-acting  $\mu$ -opioid agonist remifentanil and found drug-induced activation of the rostral anterior cingulate cortex, insula, orbitofrontal cortex, and brainstem areas.<sup>54</sup>



**Fig. 24.8 Biased agonism.** (A) Morphine binding to the  $\mu$ -opioid receptor not only activates the G protein ( $\text{G}_{i/o}$ ) analgesic effect, but also recruits  $\beta$ -arrestin, which inhibits G protein coupling and promotes hypoventilation and gastrointestinal dysfunction. (B) TRV130, a G protein-biased agonist, engages G-protein coupling similarly to morphine but with less  $\beta$ -arrestin recruitment, resulting in analgesic effect similar to morphine and less effects on respiratory and gastrointestinal function.

The activated brainstem regions overlapped with brain areas that have been implicated in pain modulation, such as the periaqueductal gray (PAG). Interestingly, placebo analgesia acts similarly on the activity of these brain areas, presumably via endogenous opioid release.<sup>55</sup>

Immunohistochemical studies and in situ hybridization analysis have demonstrated that opioid receptors are expressed in various areas in the CNS.<sup>56</sup> These areas include

the amygdala, the mesencephalic reticular formation, the PAG, and the RVM. However, the role of the opioid receptors in all of these areas has not been completely clarified.

Microinjection of morphine into the PAG or direct electrical stimulation of this area produces analgesia that can be blocked by naloxone. Opioid actions at the PAG influence RVM, which in turn modulates nociceptive transmission in the dorsal horn of the spinal cord through the action of the descending inhibition pathway. Thus, opioids produce analgesia by direct actions on the spinal cord, as well as by neurally mediated action in the region separated from the site of opioid administration. Interestingly, a study by Dogru and Seyrek reported that spinal serotonin 5-HT<sub>7</sub> receptors play an important role on the antinociceptive effects of systemic morphine.<sup>57</sup>

It is well known that the actions of opioids in bulbospinal pathways are critical to their analgesic efficacy. It is clear that opioid actions in the forebrain contribute to analgesia, because decerebration prevents analgesia when rats are tested for pain sensitivity using the formalin test,<sup>58</sup> and microinjection of opioids into several forebrain regions are analgesic in this test.<sup>59</sup> Analgesia induced by systemic administration of morphine in both the tail-flick and formalin tests was disrupted either by lesioning or reversibly inactivating the central nucleus of the amygdala, thereby demonstrating that opioid actions in the forebrain contribute to analgesia after tissue damage, as well as after acute phasic nociception.<sup>60</sup>

The distribution of opioid receptors in descending pain control circuits indicates substantial overlap between  $\mu$  and  $\kappa$  receptors. Interactions between the  $\kappa$  receptor and the  $\mu$  receptor may be important for modulating nociceptive transmission from higher nociceptive centers, as well as in the spinal cord dorsal horn. The  $\mu$  receptor produces analgesia within descending pain control circuits, at least in part, by the removal of  $\gamma$ -aminobutyric acidergic inhibition of RVM-projecting neurons in the PAG and spinally projecting neurons in the RVM.<sup>53</sup> The actions of  $\mu$ -receptor agonists are invariably analgesic, whereas those of  $\kappa$ -receptor agonists can be either analgesic or antianalgesic. The pain-modulating effects of the  $\kappa$ -receptor agonists in the brainstem appear to oppose those of  $\mu$ -receptor agonists.<sup>61</sup>

## Spinal Cord

Analgesic actions of systemic morphine are in part mediated by a net inhibitory effect from the PAG and RVM on nociceptive processing in the spinal dorsal horn. It was demonstrated that morphine increased 5-HT release in the spinal dorsal horn by activation of serotonergic neurons in the RVM, and intrathecal pretreatment with ondansetron attenuated the analgesic effect of morphine in normal rats, suggesting the involvement of the 5-HT<sub>3</sub> serotonergic receptor in morphine analgesia.<sup>62</sup>

Local spinal mechanisms, in addition to descending inhibition, underlie the analgesic action of opioids. In the spinal cord, opioids act at synapses either presynaptically or postsynaptically. Opioid receptors are abundantly expressed in the substantia gelatinosa, where glutamate and substance P release from the primary sensory neuron is inhibited by opioids. Histamine receptors are known to participate in spinal cord nociceptive transmission, and previous studies have suggested that histaminergic receptors are also

involved in the analgesic effects of morphine. An H<sub>1</sub> antagonist and H<sub>3</sub> agonist were found to potentiate the analgesic and antiedematogenic effects of morphine, suggesting that histaminergic and opioid spinal systems may be explored for means of improving analgesia, as well as peripheral antiinflammatory effects.<sup>63</sup>

Opioid-receptor ligand binding has been identified in both presynaptic and postsynaptic sites in the dorsal horn of the spinal cord. It is well known that opioids decrease the pain-evoked release of tachykinins from primary afferent nociceptors. However, the degree that opioids can suppress tachykinin signaling in response to noxious stimulation remains controversial.<sup>64</sup> These results suggest that although opioid administration may reduce tachykinin release from primary afferent nociceptors, the reduction may not be a major modulator on the actions of tachykinins on postsynaptic pain-transmitting neurons.

## Peripheral Mechanism

Opioids may also produce analgesia through the peripheral mechanism.<sup>65</sup> Immune cells infiltrating the inflammation site may release endogenous opioid-like substances, which act on the opioid receptors located on the primary sensory neuron.<sup>65</sup> Interestingly, in cannabinoid receptor type 1 and type 2 knockout mice, the antinociceptive effect of morphine injected into the paw in the inflammatory phase of the formalin test was decreased by 87% and 76%, respectively.<sup>66</sup> This finding may suggest the possibility that the release of endogenous cannabinoids in structures along the pain pathway is involved in opioid analgesia by the peripheral mechanism.

## Acupuncture

Acupuncture and electroacupuncture have been shown to block pain by activating a variety of bioactive chemicals through peripheral, spinal, and supraspinal mechanisms. Mechanistically, endogenous opioids and opioid receptors have been shown to be involved in acupuncture- and electroacupuncture-induced analgesia in various pain models.<sup>67</sup> Studies in carrageenan-induced inflammatory rat pain models show that an intraplantar injection of naloxone or selective antagonists against  $\mu$ -,  $\delta$ -, or  $\kappa$ -opioid receptors 1 hour before electroacupuncture treatment at acupoint *Zusanli* (ST36) dose-dependently blocked electroacupuncture-produced inhibition of mechanical hyperalgesia assessed through paw-pressure threshold.<sup>68</sup> In a capsaicin-induced inflammatory hind paw pain model, stimulation by 2 Hz of four-train pulses with 100 Hz of intratrain frequency at *Houxi* (SI3) and *San-yangluo* (TE8) on the forelimb significantly raised the mechanical pain threshold of the injected paw. This analgesic effect was blocked by intrathecal  $\mu$ - or  $\delta$ -opioid receptor antagonists but not by a  $\kappa$ -opioid receptor antagonist.<sup>69</sup> Precise mechanisms for acupuncture and electroacupuncture, including the involvement of physiologic systems other than the opioid receptors, remain to be elucidated.

## MECHANISM OF MOOD ALTERATIONS AND REWARDING PROPERTIES

The mechanisms by which opioids produce euphoria, tranquility, and other alterations of mood (including rewarding

properties) remain an area of active investigation, especially given the expanding scope of opioid diversion and misuse. Behavioral and pharmacologic evidence points to the role of dopaminergic pathways, particularly involving the nucleus accumbens (NAcc), in drug-induced reward. Functional magnetic resonance imaging studies demonstrated that a small intravenous dose (4 mg) of morphine induces positive signal changes in reward structures, including the NAcc, sublenticular extended amygdala, orbitofrontal cortex, and hippocampus, and decreases signal in cortical areas similar to the action of sedative-hypnotics such as propofol and midazolam.<sup>70</sup> These observations are consistent with results of pharmacologic studies.

The shell of the NAcc is the site that may be involved directly in the emotional and motivational aspects of drug-induced reward. All three opioid receptor types are present on the NAcc and are thought to mediate, at least in part, the motivational effects of opioid drugs.<sup>56</sup> Selective  $\mu$ - and  $\delta$ -receptor agonists are rewarding when defined by place preference and intracranial self-administration paradigms. Conversely, selective  $\kappa$ -receptor agonists produce aversive effects. Positive motivational effects of opioids are partially mediated by dopamine release at the level of the NAcc.

The locus ceruleus contains both noradrenergic neurons and high concentrations of opioid receptors and is postulated to play a critical role in feelings of alarm, panic, fear, and anxiety. Neural activity in the locus ceruleus is inhibited by both exogenous opioids and endogenous opioid peptides.

## ANALYSIS OF KNOCKOUT MICE

The physiologic roles of the opioid receptors and endogenous opioid peptides have been investigated mainly by pharmacologic and physiologic methods. However, it has been difficult to analyze functional roles of these proteins. With analysis of knockout mice, in which a specific gene is inactivated by molecular biologic methods, additional insight into the physiologic role of the respective opioid receptors and/or endogenous opioid peptide precursors can be determined.<sup>71</sup>

In the  $\mu$ -receptor knockout mice, analgesia, the reward effect, and the withdrawal effect of morphine were lost.<sup>72</sup> Morphine-induced respiratory depression was not observed in the  $\mu$ -receptor knockout mice.<sup>73</sup> Therefore, the  $\mu$ -receptor is a mandatory component of the opioid system for morphine action. In the  $\mu$ -receptor knockout mice, ketamine-induced respiratory depression and antinociception are diminished,<sup>74</sup> a finding suggesting that ketamine interacts with the  $\mu$  receptor to lead to these phenomena. Furthermore, minimum alveolar concentration (MAC) of sevoflurane was significantly higher in the  $\mu$ -receptor knockout mice than wild-type mice, an observation suggesting the involvement of the  $\mu$  receptor in the anesthetic potency of sevoflurane.<sup>75</sup> The  $\delta$ -receptor knockout mice displayed a markedly reduced analgesic effect of opioids selective for  $\delta$ -receptors at the spinal cord level.<sup>75</sup> However, at the supraspinal level, analgesia could be induced by  $\delta$ -receptor agonists in  $\delta$ -receptor knockout mice, a finding suggesting the existence of a second  $\delta$ -like analgesic system. Disruption of the  $\kappa$  receptor abolished the analgesic, hypolocomotor, and aversive actions of the  $\kappa$ -receptor agonists and induced

hyperreactivity in the abdominal constriction test; this finding indicates that the  $\kappa$  receptor is involved in the perception of visceral chemical pain.<sup>76</sup> Using gene knockout mice, a pharmacologic study demonstrated that the antinociceptive effect of  $N_2O$  may not be mediated by  $\mu$ -receptor<sup>77</sup>; rather  $N_2O$  exerts its antinociceptive action and reduces MAC of volatile anesthetics in mice through complex mechanisms including activation of the  $\kappa$  receptor and the descending inhibitory pathway in the spinal cord, whereas its hypnotic potency is not dependent on  $\kappa$ -receptor activation.<sup>78</sup>

In the mice lacking  $\beta$ -endorphin, morphine induced normal analgesia, but naloxone-reversible stress-induced analgesia could not be observed.<sup>79</sup> The preproenkephalin knockout mice were more anxious than wild-type mice, and males displayed increased offensive aggressiveness.<sup>80</sup> The mutant mice showed marked difference from controls in supraspinal, but not in spinal, responses to painful stimuli.

Thus, the functional roles of individual components of the opioid system continue to be elucidated by analysis of knockout mice. The  $\mu$ -opioid receptor continues to be recognized as a predominant signaling receptor for both the affective and antinociceptive action of opioid agonism.

## ACTIONS OF OPIOIDS ON TARGETS OTHER THAN OPIOID RECEPTORS

Molecular pharmacologic analyses have shown that opioids can interact with molecules other than the opioid receptors. In cardiac myocytes, morphine can inhibit voltage-dependent sodium ( $Na^+$ ) current in a naloxone-insensitive manner, a finding suggesting the existence of a signal transduction mechanism that is not dependent on the opioid receptors.<sup>81</sup> Buprenorphine, a partial  $\mu$ -opioid receptor agonist, also has a local anesthetic property and blocks voltage-gated  $Na^+$  channels through the local anesthetic binding site.<sup>82</sup> Meperidine is an agonist of both  $\mu$  and  $\kappa$  receptors. In addition, meperidine can block voltage-dependent  $Na^+$  channels in amphibian peripheral nerves,<sup>83</sup> as well as in the *Xenopus* oocyte expression system.<sup>84</sup> Furthermore, meperidine exerts agonist activity at the  $\alpha_{2B}$ -adrenoreceptor subtype.<sup>85</sup> Yamakura and associates have shown that high concentrations of opioids, including meperidine, morphine, fentanyl, codeine, and naloxone, directly inhibit the N-methyl-D-aspartate (NMDA) receptor expressed in *Xenopus* oocytes.<sup>86</sup> Methadone is clinically used as a racemic mixture of the *l* and *d* isomers. The opioid-like activity of the racemate seems to be almost entirely the result of *l*-methadone, whereas *d*-methadone acts as an NMDA antagonist.<sup>87</sup> The commercially available remifentanil solution (Ultiva), which contains glycine, directly activates the NMDA receptor expressed in *Xenopus* oocytes.<sup>88</sup> Furthermore, an electrophysiologic study in rat spinal cord showed that remifentanil hydrochloride does not directly activate NMDA receptors, the NMDA current recorded after application of Ultiva is related to the presence of glycine, and the glycine-induced NMDA current is potentiated by application of remifentanil hydrochloride through a pathway involving the  $\mu$ -opioid receptor.<sup>89</sup> The serotonin type 3A (5-HT<sub>3A</sub>) receptor, which is directly and indirectly linked to gastrointestinal motility, visceral pain, nausea, and vomiting, is competitively inhibited by morphine and hydromorphone, as well as naloxone; however, fentanyl-like opioids did not

significantly affect activity of the 5-HT<sub>3A</sub> receptor.<sup>90,91</sup> The mechanism for tramadol analgesia is complex and appears to be composed of two actions that include reuptake inhibition of the noradrenergic serotonergic system and activation of the  $\mu$ -opioid receptor. Tramadol's analgesic effect is only partially reversed by the  $\mu$ -opioid receptor antagonist, naloxone. Furthermore, tramadol also acts as an agonist of transient receptor potential vanilloid-1 (TRPV1) heterologously expressed in cultured cells.<sup>92</sup> Tramadol may activate TRPV1 in sensory neurons, followed by local release of vasoactive neuropeptides and marked desensitization of the afferent fibers. Inhibition of the nicotinic acetylcholine receptor by tramadol has also been reported.<sup>93</sup> It remains to be clarified which of these "off-target" actions of opioids have physiologic or clinical implications.

### PHYSIOLOGIC ROLE OF NOCICEPTIN/ ORPHANIN FQ

Nociceptin or orphanin FQ is a 17-amino-acid peptide, the sequence of which resembles those of opioid peptides. Nociceptin or orphanin FQ precursor mRNA and peptide are present throughout the descending pain control circuits. In the spinal cord, nociceptin or orphanin FQ-receptor mRNA expression is stronger in the ventral horn than in the dorsal horn, but higher levels of ligand binding occur in the dorsal horn. Targeted disruption of the nociceptin or orphanin FQ receptor in mice had little effect on basal pain sensitivity in several measures, whereas targeted disruption of the N nociceptin or orphanin FQ precursor consistently elevated basal responses in the tail-flick test, findings suggesting an important role for nociceptin or orphanin FQ in regulating basal pain sensitivity.<sup>94,95</sup> Intrathecal injections of nociceptin or orphanin FQ have been shown to be analgesic<sup>96</sup>; however, supraspinal administration has produced hyperalgesia, antiopioid effects, or a biphasic hyperalgesic-analgesic response.<sup>97</sup> Nociceptin or orphanin FQ inhibits both pain-facilitating and analgesia-facilitating neurons in the RVM.<sup>98</sup> The effects of nociceptin or orphanin FQ on pain responses appear to depend on the preexisting state of pain in the animal. Involvement of nociceptin or orphanin FQ in physiologic functions such as regulation of feeding, body weight homeostasis, and stress response, and in psychiatric disorders such as depression, anxiety, and drug or alcohol dependence has also been reported.<sup>99</sup>

Systemic administration of nonpeptide nociceptin or orphanin FQ receptor agonists revealed that such compounds were effective analgesics in animal pain models. It was reported that a nociceptin or orphanin FQ receptor agonist, Ro64-6198, has antinociceptive and antiallodynic potency and efficacy without side effects of opioids such as itching, respiratory depression, and addiction in monkeys.<sup>100</sup> As nociceptin or orphanin FQ and opioid receptor agonists modulate pain by different targets, combining both mechanisms may constitute a novel approach for the development of innovative analgesics. Cebranopadol, a newly synthesized compound possessing nociceptin or orphanin FQ and opioid receptor agonist activity, exhibits highly potent and efficacious antinociceptive and antihyperalgesic effects in several rat models of acute and chronic pain (tail-flick, rheumatoid arthritis, bone cancer, spinal nerve ligation, diabetic neuropathy).<sup>101</sup> In a phase 1 clinical trial, it

was shown that cebranopadol produced respiratory depression with a ceiling effect, in contrast to apnea produced by full  $\mu$ -opioid receptor agonists.<sup>102</sup>

Expression of opioid receptors on peripheral blood mononuclear cells is controversial. Williams and associates reported that human peripheral blood mononuclear cells express the nociceptin receptor, but not  $\mu$ -,  $\delta$ -, or  $\kappa$ -opioid receptors.<sup>103</sup> Nociceptin, produced by the peripheral blood mononuclear cells, is involved in the control of immune functions.

## Neurophysiologic Effects of Opioids

### CHARACTERISTICS OF THE ANALGESIC ACTION OF OPIOIDS

In human beings, morphine-like drugs produce analgesia, drowsiness, changes in mood, and mental clouding. A significant feature of opioid analgesia is that it is not typically associated with loss of consciousness. When morphine in the same dose is given to a normal, pain-free individual, the experience may be unpleasant. The relief of pain by morphine-like opioids is relatively selective, in that other sensory modalities are not affected. Patients frequently report that the pain is still present, but that they feel more comfortable. It is also important to distinguish between pain caused by stimulation of nociceptive receptors and transmitted over intact neural pathways (nociceptive pain) and pain that is caused by damage to neural structures, often involving neural supersensitivity (neuropathic pain). Although nociceptive pain usually is responsive to opioid analgesics, neuropathic pain may respond poorly to opioid analgesics and require higher doses of drug.<sup>104</sup>

The analgesic effects, as well as side effects, of opioids vary greatly among individuals. A pharmacogenomic twin study has shown that the interindividual variations in opioid effects are likely the result of genetic and environmental factors.<sup>105,106</sup> Animal and human studies indicate the existence of sex-related differences in opioid-mediated behavior.<sup>107</sup> Sarton and associates examined the influence of morphine on experimentally induced pain in healthy volunteers, and demonstrated the gender differences in morphine analgesia, with greater morphine potency but slower speed of onset and offset in women.<sup>108</sup> In contrast, in a study examining interindividual variability in alfentanil analgesic sensitivity in experimental pain models in humans, no gender differences were detected.<sup>109</sup> In a study examining the effects of genetic factors on pain sensitivity, it was shown that males had higher pain thresholds in both thermal skin pain and muscle pressure pain than females.<sup>110</sup> The mechanism of the gender difference in pain sensitivity and opioid effects remains to be clarified.

The pharmacokinetic and pharmacodynamic characteristics of opioids often vary throughout the day, as demonstrated for oral morphine in chronic pain.<sup>111</sup> The duration of intrathecal sufentanil analgesia exhibited a temporal pattern, with 30% variation throughout the day in women in the first stage of labor.<sup>112</sup> Scavone and colleagues reported that the time of day of administration does not seem to influence duration of labor analgesia with spinal-epidural

administration of fentanyl or with systemic hydromorphone administration.<sup>113</sup> The potential impact of chrono-biology on clinical practice is not clear, and research on the influence of circadian rhythms on the actions of opioids is warranted.

Some controversy remains regarding analgesia produced by peripheral actions of opioids. One review concluded from meta-analysis that intraarticularly administered morphine has a definite but mild analgesic effect.<sup>114</sup> It may be dose dependent, and a systemic effect cannot be completely excluded. The addition of opioids in brachial plexus block improves the success rate and postoperative analgesia.<sup>115</sup> In contrast, the addition of sufentanil may not prolong the duration of brachial plexus block.<sup>116</sup>

Despite variations in effect ascribed to the type of pain stimuli, genetics, gender, time of administration, or site of action (central versus peripheral), opioids remain one of the most potent classes of analgesic drugs.

## EFFECTS OF OPIOIDS ON CONSCIOUSNESS

Cortical acetylcholine originates in the basal forebrain and is essential for maintaining normal cognition and arousal. Injection of morphine to the substantia innominata or intravenous morphine administration significantly decreased acetylcholine release within the prefrontal cortex in the rat, and this effect may be the neurochemical basis of opioid-induced change in consciousness.<sup>117</sup> Although unconsciousness in humans can be produced with high doses of opioids alone, opioid-based anesthesia can be unpredictable and inconsistent.<sup>118</sup> Therefore, opioids are not suitable as sole intravenous induction agents.<sup>119</sup> The anesthetic potential of opioids was tested by measurement of MAC.<sup>120</sup> Fentanyl can reduce the MAC of isoflurane at skin incision in patients by at least 80%.<sup>121</sup> The relationship between the plasma fentanyl concentration and reduction in MAC is not linear, and fentanyl has a sub-MAC ceiling effect on reduction of the MAC of isoflurane. The MAC of sevoflurane was also dose dependently reduced by fentanyl, with 3 ng/mL resulting in a 61% reduction in MAC.<sup>122</sup> A ceiling effect was observed for MAC; 6 ng/mL fentanyl provided only an additional 13% reduction in the MAC of sevoflurane. Even potency ratios have been established for the “reduction of volatile anesthetic MAC” for most opioids such as sufentanil, fentanyl, remifentanil, and alfentanil. However, the MAC-reducing capabilities of the opioids are not complete; that is, these are not complete anesthetics. The opioids must be combined with other anesthetics to produce a “complete anesthetic.”<sup>121,123-125</sup> Esmolol, a short-acting  $\beta_1$ -receptor antagonist, significantly decreased the MAC of isoflurane in the presence of alfentanil, although it did not significantly affect this parameter in the absence of alfentanil.<sup>126</sup> The mechanism of the interaction is unknown. Epidural fentanyl infusion reduces the awakening concentration of isoflurane more than does intravenous fentanyl infusion despite the lower plasma concentration, possibly by modulating the afferent nociceptive inputs in the spinal cord.<sup>127</sup>

The MAC that prevents movement in response to laryngoscopy and tracheal intubation in 50% of patients (MAC-TI) is higher than the MAC that prevents movement in response to surgical incision (MAC). The MAC-TI of sevoflurane was 3.55% and was reduced markedly to 2.07%,

1.45%, and 1.37% by the addition of fentanyl 1, 2, and 4  $\mu$ g/kg, respectively, with no significant difference in the reduction between 2 and 4  $\mu$ g/kg, thus showing a ceiling effect.<sup>128</sup> The MAC that prevents sympathetic responses to surgical incision in 50% of patients (MAC-BAR) decreased with increasing concentrations of fentanyl in plasma, and the initial steep reduction followed by a ceiling effect.<sup>122</sup>

The bispectral index (BIS) is often used to determine the level of consciousness under anesthesia. In the presence of fentanyl, alfentanil, remifentanil, or sufentanil, loss of consciousness occurred at a lower effect-site concentration of propofol and at a higher BIS value as compared with propofol alone.<sup>129</sup> Furthermore, Wang and associates reported that infusion of remifentanil (0.1-0.4  $\mu$ g/min) did not significantly change the median effective concentration (EC<sub>50</sub>) of propofol necessary to lower the BIS value to 50 or less.<sup>130</sup> These results suggest that the hypnotic effect of propofol is enhanced by analgesic concentrations of opioids without changes in the BIS value. Conversely, infusion of remifentanil (effect-site target concentrations of 0.25, 2.5, and 10 ng/mL), combined with propofol infusion adjusted to a BIS of approximately 60, dose dependently decreased the BIS, thus suggesting a sedative or hypnotic effect of remifentanil.<sup>131</sup> Response surface analysis showed considerable synergy between opioids and hypnotics for sedation and suppression of responses to various noxious stimuli.<sup>132</sup> In contrast to the effect of opioids administered during anesthesia on the BIS, the impact of chronic opioid use on BIS is unknown. It was recently reported that the end-tidal concentration of sevoflurane necessary to maintain the BIS under 50 was 0.84% for chronic opioid users who received a stable dose of oral morphine of at least 60 mg/day according to the morphine equivalent daily dose for at least 4 weeks, which was lower than for opioid-naïve patients (1.18%).<sup>133</sup>

Opioids administered as a mainstay of postsurgical pain management can inhibit sleep on the first night after surgery. However, the effects of opioids on sleep and circadian rhythm are not clearly understood. A human study demonstrated that an overnight constant infusion of remifentanil inhibited rapid eye movement sleep without suppressing the nocturnal melatonin surge, findings that may suggest a minimal effect of opioids on the circadian pacemaker.<sup>134</sup>

Taken together, perioperative opioids have consistently been shown to dose dependently reduce the MAC and are well known to synergize with hypnotics to produce sedation; however, their ability to effect the BIS may vary depending on the context of opioid administration.

## HALLUCINATION

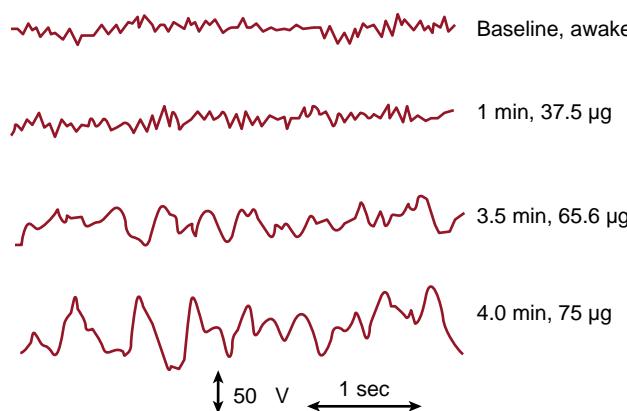
Opioid-induced hallucination is an uncommon yet significant adverse effect of opioid treatment, frequently attributed to underlying psychiatric disease or personality disorder rather than a direct neurobiologic effect of opioids.<sup>135</sup> Hallucinations attributed to opioids have been typically described as auditory, visual, or rarely, tactile hallucinations. Although many reports have cited morphine as the causative agent, there is no evidence that across a population, one particular class of opioid is associated with a lower incidence of hallucinations. Moreover, there are reports of fentanyl, methadone, tramadol, hydromorphone,

buprenorphine, pentazocine, and/or oxycodone–associated hallucinations and/or changes in mental status. Nevertheless, accumulation of morphine metabolites, particularly morphine-3-glucoronide, has been linked to the development of neurologic phenomena.<sup>136</sup> Many hypotheses have been advanced to explain the etiology of opioid-induced hallucinations. One common feature of these hypotheses involves opioid-induced dopamine dysregulation. Overactivation of the dopaminergic pathways is thought to result in auditory and visual hallucinations.<sup>137</sup> The simplest treatment for opioid-induced hallucination is discontinuing opioid therapy if practical. There are reports describing the successful use of naloxone and  $\kappa$ -selective opioid antagonists in the treatment of hallucinations associated with schizophrenia, although such  $\kappa$ -selective agents are known to be associated with hallucinations in subjects or patients without a diagnosis of mental illness.<sup>138</sup>

## ELECTROENCEPHALOGRAPHY

Increasing concentrations of inhaled anesthetics produce a continuum of electroencephalogram (EEG) changes and eventually result in burst suppression and a flat EEG. In contrast, a ceiling effect is reached with opioids. Once this ceiling has been obtained, increasing opioid dosage does not further affect the EEG.<sup>139</sup>

Although the potency and rate of equilibrium between plasma and brain are different among opioids, the effects of fentanyl, alfentanil, sufentanil, and remifentanil are consistent (Fig. 24.9).<sup>140</sup> Small doses of fentanyl (2-5  $\mu$ g/kg) produce minimal EEG changes, whereas higher doses (30-70  $\mu$ g/kg) result in high-voltage slow ( $\delta$ ) waves suggesting a state consistent with anesthesia. Although transient isolated (usually frontotemporal) sharp wave activity can be observed after large doses of fentanyl and other opioids, it is not generalized. In a study examining the effect of morphine (3-10 mg) on EEG in patients (14.8  $\pm$  2.8 years) who stayed overnight for pain relief after otologic surgery, it was



**Fig. 24.9 Representative 4-s electroencephalogram (EEG) tracings during infusion of sufentanil** (total dose shown in the right column). The awake baseline EEG consists of mixed  $\beta$  and  $\alpha$  activity. At 1 minute, the EEG showed loss of  $\beta$  activity and the presence of primarily  $\alpha$  waves (8-13 Hz). At 3.5 minutes, the EEG consisted of mixed  $\theta$  (4-7 Hz) and  $\delta$  (<4 Hz) waves, and at 4.0 min, it consisted of  $\delta$  waves of high amplitude. (From Scott JC, Cooke JE, Stanski DR. Electroencephalographic quantitation of opioid effect: comparative pharmacodynamics of fentanyl and sufentanil. *Anesthesiology*. 1991;74:34-42.)

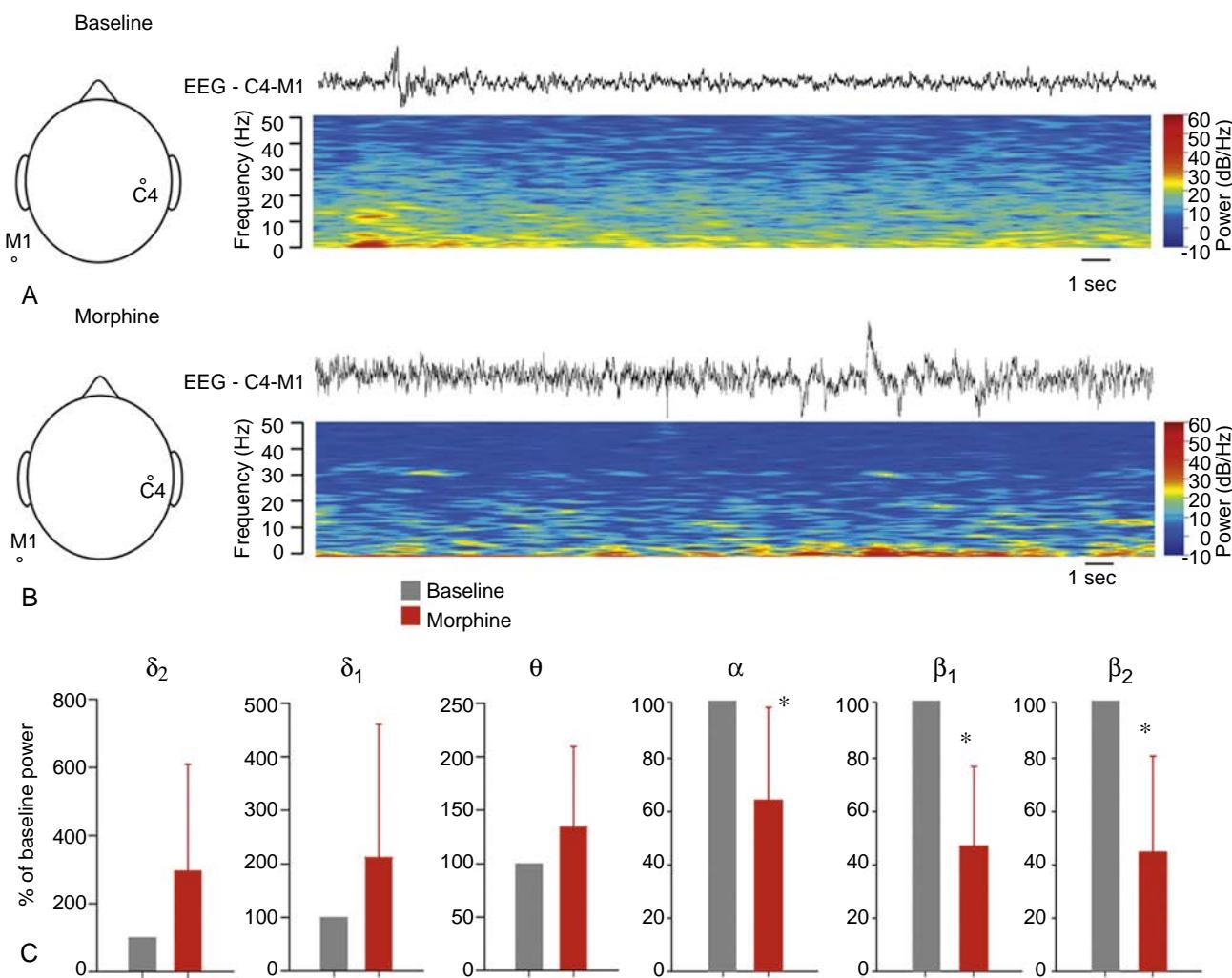
demonstrated that morphine reduced high-frequency  $\beta_1$  (13.5-20 Hz) and  $\beta_2$  (20-30 Hz) EEG powers and decreased coherence between frontal and occipital  $\beta_2$  EEG activities compared to wakefulness and non-rapid eye movement sleep, indicating that morphine induced a deep sedative state (Fig. 24.10).<sup>141</sup> Khodayari-Rostamabad and associates studied the effect of remifentanil administration on resting EEG functional connectivity and its relationship to cognitive function and analgesia in healthy volunteers.<sup>142</sup> Remifentanil administration was associated with significant changes in functional cortical connectivity, which seem to disrupt the complex cortical network subserving normal brain function and can have the potential to be a biomarker for the sedative effects of opioids.

As an effect-site measure, EEG can be employed to assess onset of drug action and drug potency ratios. The spectral edge and serum concentration are closely parallel for remifentanil,<sup>143</sup> whereas a significant time lag is found for recovery of the spectral edge for fentanyl and sufentanil (Fig. 24.11).<sup>144</sup> In healthy volunteers, approximate entropy derived from a parietal montage showed significant correlation with remifentanil concentration, and it was shown to be appropriate for the assessment of the remifentanil effect on the EEG.<sup>145</sup> Potency ratios based on EEG studies are similar to those obtained from studies determining the plasma drug levels of each opioid necessary to reduce the MAC of isoflurane by 50%. Overall, opioids produce dose-dependent changes in the EEG that can mimic those of volatile anesthetics, however opioids show a ceiling effect at higher doses.

## EVOKED RESPONSES

Because opioids do not appreciably alter sensory-evoked potentials elicited at the posterior tibial or median nerve, sensory-evoked potentials can be used for spinal cord function monitoring during anesthesia using opioids.<sup>146</sup> Although remifentanil produced dose-dependent reduction in auditory-evoked potentials,<sup>147</sup> it was also reported that remifentanil infusion (target plasma concentrations of 1, 2, and 3 ng/mL) did not affect evoked potential amplitudes and latencies.<sup>148</sup> In healthy human volunteers receiving 3  $\mu$ g/kg fentanyl, amplitude and latency of motor-evoked responses to transcranial stimulation were not significantly affected.<sup>149</sup> This is consistent with the report by Kawaguchi and colleagues that intraoperative myogenic motor-evoked potential monitoring is feasible during isoflurane or sevoflurane anesthesia with fentanyl.<sup>150</sup>

Middle latency auditory-evoked potentials (MLAEPs) and their derivatives are increasingly used as a surrogate measure of the level of anesthesia. Changes in MLAEPs following the administration of opioids occur and may result from either a direct depressant effect of opioids on MLAEPs itself or an indirect effect reflecting the action of opioids in attenuating CNS arousal associated with noxious stimuli. Wright and associates examined the effect of remifentanil (1 or 3  $\mu$ g/kg/min) on MLAEPs in tracheally intubated and nonintubated patients and showed that remifentanil has an effect on MLAEPs in attenuating the arousal associated with tracheal intubation but had no effect in the absence of a stimulus.<sup>151</sup> Similarly, Schraag and associates found no significant contribution of remifentanil alone on MLAEPs,



**Fig. 24.10 Impacts of morphine on electroencephalography (EEG) spectral content.** EEG activity of a representative 30-s epoch and power spectrograms of C4-M1 (C4 = central electrode; M1 = mastoid electrode) derivation at baseline and after morphine administration. In a representative patient (A) and in the analyzed group data (B and C), high-frequency power ( $\alpha$ ,  $\beta_1$ , and  $\beta_2$ ) was decreased by morphine. Mean data for 10 patients showed that morphine decreased  $\alpha$  ( $P = .039$ ,  $n = 10$ ),  $\beta_1$  ( $P = .003$ ,  $n = 10$ ), and  $\beta_2$  ( $P = .020$ ,  $n = 10$ ) powers but did not change  $\delta_2$  ( $P = .375$ ,  $n = 10$ ),  $\delta_1$  ( $P = .922$ ,  $n = 10$ ), and  $\theta$  ( $P = .331$ ,  $n = 10$ ) powers. Data are shown as mean  $\pm$  95% CI. \*mean values significantly different from baseline with a  $P < .05$ . (From Montandon G, Cushing SL, Campbell F, et al. Distinct cortical signatures associated with sedation and respiratory rate depression by morphine in a pediatric population. *Anesthesiology*. 2016;125:889–903.)

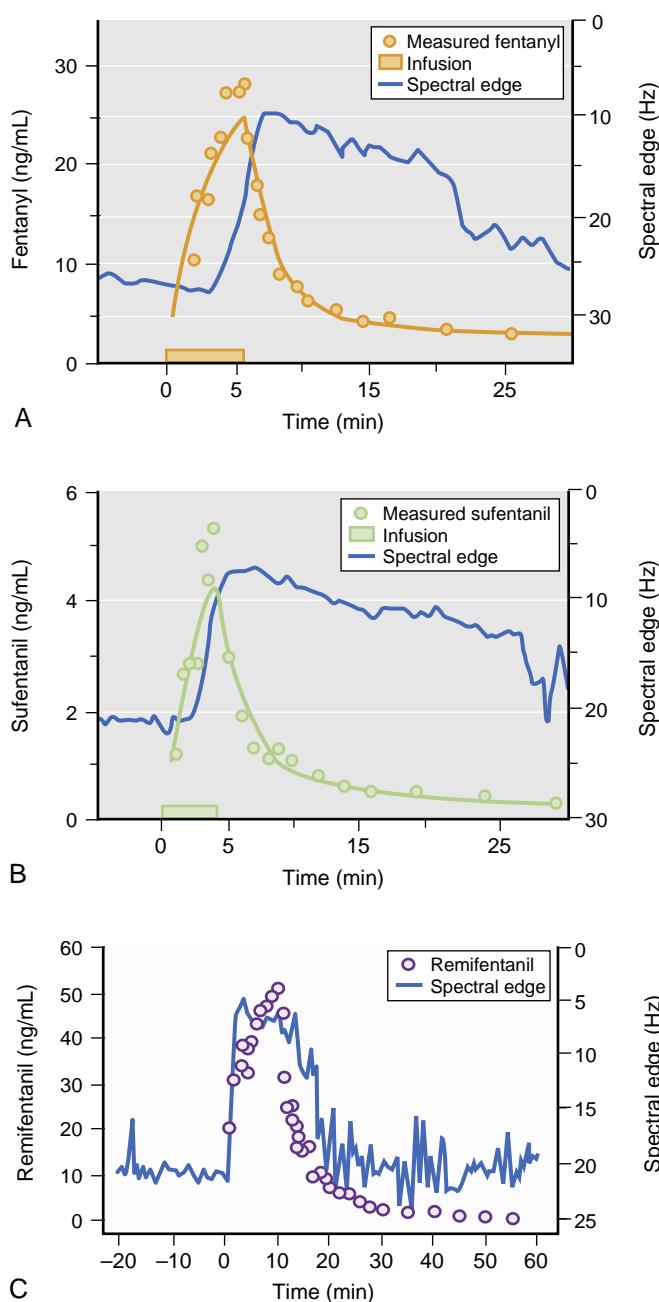
whereas increasing the concentration of remifentanil led to a significant decrease of the calculated propofol effect-site concentrations necessary for unconsciousness.<sup>152</sup>

### CEREBRAL BLOOD FLOW AND CEREBRAL METABOLIC RATE

Opioids generally produce modest decreases in cerebral metabolic rate and intracranial pressure (ICP), although the changes are influenced by the concomitant administration of other agents and anesthetic drugs, as well as by the patients' conditions. When vasodilation is produced by coadministered anesthetics, opioids are more likely to cause cerebral vasoconstriction. Opioids also decrease cerebral blood flow (CBF) when they are combined with nitrous oxide ( $N_2O$ ). When opioids are administered alone or when the coadministered anesthetics cause cerebral vasoconstriction, opioids usually have no influence or result in a small increase in CBF.

Endogenous opioid activity is present in the cerebral arteries, although exogenously administered opioids were found to exert little effect on pial artery diameter in several animal models.<sup>153</sup> In the piglet, fentanyl, alfentanil, and sufentanil decreased arteriolar diameter in a dose-dependent naloxone-reversible manner.<sup>154</sup> In human volunteers, PET demonstrated that CBF changes induced by fentanyl are regionally heterogeneous.<sup>155</sup>

In healthy volunteers, sufentanil (0.5  $\mu$ g/kg intravenously [IV]) produces no significant effect on CBF.<sup>156</sup> Alfentanil (25–50  $\mu$ g/kg IV), administered to patients receiving isoflurane (0.4%–0.6%)- $N_2O$  anesthesia, produces minimal reductions in middle cerebral artery flow velocity.<sup>157</sup> A PET study in human volunteers showed that remifentanil induced dose-dependent changes in relative regional CBF in areas involved in pain processing, such as the lateral prefrontal cortex, inferior parietal cortex, and supplementary motor area.<sup>158</sup> In patients scheduled to undergo a supratentorial tumor surgical procedure and receiving  $N_2O$ ,



**Fig. 24.11 Time course of spectral edge and serum opioid concentration.** Fentanyl (A) and sufentanil (B) were infused at 150  $\mu\text{g}/\text{min}$  and 18.75  $\mu\text{g}/\text{min}$ , respectively. Remifentanil (C) was administered at 3  $\mu\text{g}/\text{kg}/\text{min}$  for 10 minutes. The spectral edge changes lag behind the serum concentration changes in the case of fentanyl and sufentanil, whereas the spectral edge and serum concentration closely parallel in the cases of remifentanil. (From Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology*. 1985;62:234–241; and Egan TD, Minto CF, Hermann DJ, et al. Remifentanil versus alfentanil: comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. *Anesthesiology*. 1996;84:821–833.)

remifentanil (1  $\mu\text{g}/\text{kg}/\text{min}$ ), similar to fentanyl (2  $\mu\text{g}/\text{kg}/\text{min}$ ), reduced CBF and did not significantly affect cerebrovascular carbon dioxide ( $\text{CO}_2$ ) reactivity.<sup>159</sup>

Opioid-induced neuroexcitation and focal seizure activity can cause regional increases in brain metabolism. Regional increases in glucose use induced by high doses of alfentanil

in the rat were associated not only with epileptiform activity but also with neuropathic lesions.<sup>160</sup> In humans, PET evaluation demonstrated that a 1 to 3  $\mu\text{g}/\text{kg}/\text{min}$  infusion of remifentanil induces significant increase in the cerebral metabolic rate for glucose.<sup>161</sup> In summary, opioids, in general, do not significantly effect measures of CBF.

## INTRACRANIAL PRESSURE

Opioids are generally thought to affect ICP minimally under conditions of controlled ventilation. When given with background anesthesia (isoflurane- $\text{N}_2\text{O}$ ), opioids do not cause significant increases in ICP undergoing craniotomy for supratentorial space-occupying lesions.<sup>162,163</sup> Opioid sedation does not alter ICP in patients with head injuries.<sup>164</sup> Light sedation with remifentanil (4.2  $\pm$  1.8  $\mu\text{g}/\text{kg}/\text{h}$ ) does not result in higher ICP than that observed with propofol (4.3  $\pm$  2.5  $\text{mg}/\text{kg}/\text{h}$ ) in patients undergoing stereotactic brain tumor biopsy, and cerebral perfusion pressure might be better preserved with remifentanil.<sup>165</sup>

Opioids may produce increases in ICP in patients undergoing craniotomy for excision of supratentorial space-occupying lesions, especially if intracranial compliance is compromised. In a study of patients with severe head injury who have preserved and impaired autoregulation, morphine (0.2  $\text{mg}/\text{kg}$ ) and fentanyl (2  $\mu\text{g}/\text{kg}$ ) moderately increased ICP, a finding suggesting that mechanisms other than vasodilation could be implicated in the opioid-induced ICP elevation.<sup>166</sup> Investigators also demonstrated no change in ICP in hydrocephalic children after administration of alfentanil (70  $\mu\text{g}/\text{kg}$ ).<sup>167</sup> Whether these discrepancies of the opioid effects on ICP reflect pressure assessment methods or the effects of other drugs is not clear. If opioids do increase ICP, whether cerebrovascular dilatation is directly induced by opioids or indirectly resulted from opioid-induced decrease in blood pressure is not known.

## NEUROPROTECTION

Although certain early studies suggested potentially adverse effects of  $\mu$ -opioid agonists on ischemic brain, other studies documented that certain opioid agents, such as the  $\kappa$ -agonists, can be neuroprotective in animal models of focal ischemia.<sup>168</sup> Investigators also showed that activation of  $\delta$ -opioid receptors increases survival time of mice during lethal hypoxia.<sup>169</sup> An in vitro study using rat cerebellar brain slices demonstrated that pretreatment with morphine at clinically relevant concentrations induced acute neuroprotection mediated by activation of the  $\delta_1$ -opioid receptors, activation of adenosine triphosphate (ATP)-sensitive  $\text{K}^+$  channels, and free radical production in mitochondria.<sup>170</sup> In the rat focal ischemia model, fentanyl neither increased nor decreased brain injury compared with awake unanesthetized rats.<sup>171</sup> It was demonstrated that at a supraclinical concentration remifentanil had no pronecrotic effect but exerted ex vivo antiapoptotic action on the immature mouse brain, involving the opioid and NMDA receptors, and the mitochondrial-dependent apoptotic pathway.<sup>172</sup> A recent study reported that  $\kappa$ -opioid receptors were upregulated and played a critical role in brain ischemia and reperfusion in mice, and that  $\kappa$ -opioid receptor activation could potentially protect the brain and improve neurologic

outcome via blood-brain barrier protection, apoptosis reduction, and inflammation inhibition.<sup>173</sup> Although there is contradicting evidence for a potential neuroprotection in animal models, there is no clear evidence for neuroprotective effects in humans.

## MUSCLE RIGIDITY

Opioids can increase muscle tone and may cause muscle rigidity. The incidence of rigidity noted with opioid anesthetic techniques varies greatly because of differences in dose and speed of opioid administration, the concomitant use of N<sub>2</sub>O, the presence or absence of muscle relaxants, and the patient's age. Opioid-induced rigidity is characterized by increased muscle tone that sometimes progresses to severe stiffness and associated clinical challenges (Table 24.4). Clinically significant opioid-induced rigidity usually begins just as, or after, a patient loses consciousness. Mild manifestations of rigidity, such as hoarseness, can occur in conscious patients. Vocal cord closure is primarily responsible for the difficult ventilation with bag and mask that follows the administration of opioids. Although opioids are generally thought to affect ICP minimally, it was demonstrated that alfentanil-induced rigidity can cause increase in ICP in rats.<sup>174</sup> Delayed or postoperative rigidity may be related to second peaks that can occur in plasma opioid concentrations, similar to the recurrence of respiratory depression.

The precise mechanism by which opioids cause muscle rigidity is not clearly understood. Muscle rigidity is not the result of a direct action on muscle fibers because it can be decreased or prevented by pretreatment with muscle relaxants. Mechanisms of opioid-induced muscle rigidity involving the CNS have been postulated. The nucleus raphe pontis within the reticular formation and the caudate nucleus within the basal ganglia have been implicated mechanistically.<sup>175</sup> Pharmacologic investigation using selective agonists and antagonists suggests that systemic opioid-induced muscle rigidity is primarily caused by the activation of central  $\mu$ -receptors, whereas supraspinal  $\delta_1$  and  $\kappa_1$  receptors may attenuate this effect.<sup>176</sup> Some aspects of opioid-induced catatonia and rigidity (increased incidence with age, muscle movements resembling extrapyramidal side effects) are similar to Parkinson disease and suggest similarities in neurochemical mechanisms. Patients with Parkinson disease, particularly if they are inadequately treated,

may experience reactions such as dystonia following opioid administration.<sup>177</sup>

Pretreatment with or concomitant use of nondepolarizing muscle relaxants can decrease the incidence and severity of rigidity. Opioid-induced muscle rigidity can also be reversed with the  $\mu$ -receptor antagonist naloxone. Induction doses of sodium thiopental and subanesthetic doses of diazepam and midazolam can prevent, attenuate, or successfully treat rigidity.

## NEUROEXCITATORY PHENOMENA

Fentanyl causes seizure activity seen on the EEG in animals, but EEG evidence of seizure activity after fentanyl, alfentanil, or sufentanil is generally lacking in humans. Remifentanil induced generalized tonic-clonic seizure-like activity in an otherwise healthy adult.<sup>178</sup> Morphine produces tonic-clonic activity after epidural and intrathecal administration.<sup>179</sup> Focal neuroexcitation on the EEG (e.g., sharp and spike wave activity) occasionally occurs in humans after large doses of fentanyl, sufentanil, and alfentanil.

The mechanisms underlying opioid-induced neuroexcitatory phenomena are not completely clear. Excitatory opioid actions may be related to coupling to mitogen-activated protein kinase cascades.<sup>180</sup> Local increases in CBF and metabolism are also of theoretic concern because prolonged seizure activity, even if focal, could lead to neuronal injury and/or cellular death. Fentanyl, alfentanil, and sufentanil in large doses also induced hypermetabolism and histopathologic alterations of the limbic system in rats.<sup>181</sup> Experimental study using excised mouse hippocampus showed that the proconvulsive effect of morphine is mediated by selective stimulation of the  $\mu$ - and  $\kappa$ -opioid receptors but not the activation of the  $\delta$ -opioid receptor.<sup>182</sup> In rats, midazolam, naloxone, and phenytoin prevented EEG seizure activity and histologically evident brain damage induced by large doses of fentanyl.<sup>183</sup>

Measurement of CBF by magnetic resonance imaging in human volunteers indicated that the cingulate cortex is the most susceptible to activation by remifentanil (0.05–0.2  $\mu$ g/kg/min), and susceptibility is affected by the apolipoprotein E genotype.<sup>184</sup> These findings support the notion that neuroactivation of limbic areas by the perioperative use of opioids may have a role in the genesis of postoperative cognitive dysfunction.

## PUPIL SIZE

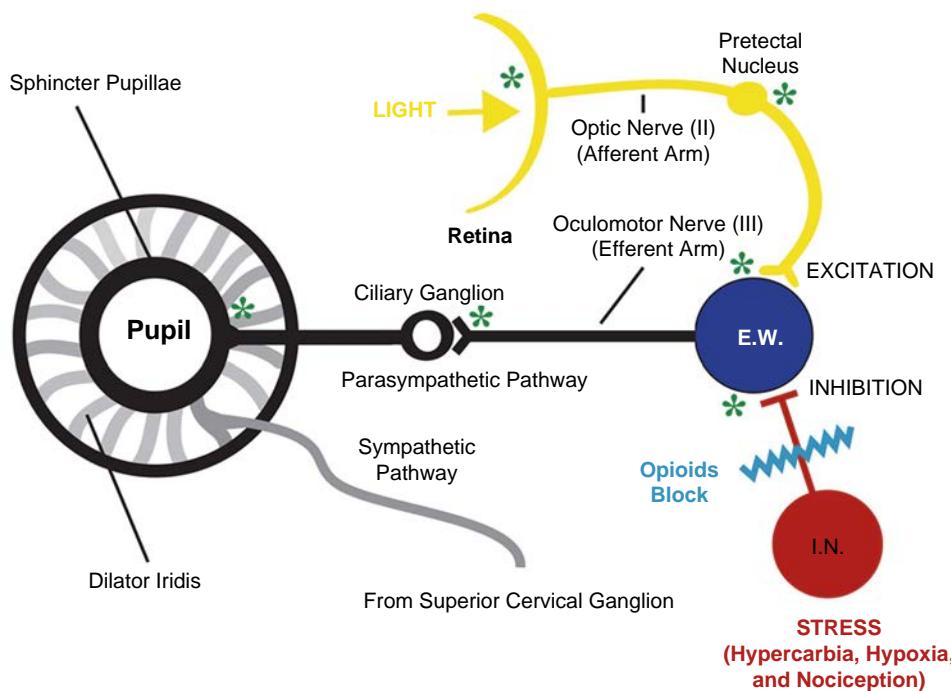
Morphine and most  $\mu$ - and  $\kappa$ -agonists cause constriction of the pupil by an excitatory action on the parasympathetic nerve innervating the pupil. Light induces excitation of the Edinger-Westphal nucleus leading to pupillary constriction, which is inhibited by hypercarbia, hypoxia, and nociception. Opioids release the effect of inhibitory neurons on the Edinger-Westphal nucleus, resulting in pupillary constriction (Fig. 24.12).<sup>185</sup> After intravenous administration of morphine (0.125 mg/kg) in one report, a 26% decrease in pupil diameter occurred at 1 hour, and a period of more than 6 hours was necessary for complete recovery of pupil diameter.<sup>186</sup> The pupillary dilatation reflex has been successfully used to assess the analgesic component of a balanced anesthetic regimen. The pupillometer may be a valuable tool to

**TABLE 24.4** Potential Problems Associated With Opioid-Induced Rigidity

System	Problem
Hemodynamic	↑ CVP, ↑ PAP, ↑ PVR
Respiratory	↓ Compliance, ↓ FRC, ↓ ventilation Hypercarbia, Hypoxemia
Miscellaneous	↑ Oxygen consumption, ↓ Intracranial pressure, ↑ Fentanyl plasma levels

CVP, Central venous pressure; FRC, functional residual capacity; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

Modified from Bailey PL, Egan TD, Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia*. 8th ed. Philadelphia: Saunders; 2015. An imprint of Elsevier Inc., p. 876.



**Fig. 24.12 Pathways and nerve centers that control pupil size and the pupillary light reflex in humans.** Colored structures are the central nerve centers and pathways that modify the pupillary light reflex. Edinger-Westphal (E.W.) nucleus neurons are pacemaker cells that are modified by excitatory and inhibitory inputs. Opioids block the inhibition of the EW nucleus. Green asterisks (\*) show locations where hypercarbia, hypoxia, and opioids might potentially interfere with the light reflex. \* = locations where hypercarbia, hypoxia, and opioids might potentially interfere with the light reflex. IN, Inhibitory neuron. (From Rollins MD, Feiner JR, Lee JM, et al. Pupillary effects of high-dose opioid quantified with infrared pupillometry. *Anesthesiology*. 2014;84:1037–1044.)

guide morphine administration in the immediate postoperative period.<sup>187</sup> A prospective randomized study evaluated the impact of intraoperative pupillometry monitoring on perioperative opioid consumption in major gynecologic surgery. It was demonstrated that the use of pupillometry to guide intraoperative analgesia reduced intraoperative remifentanil consumption and postoperative morphine requirements.<sup>188</sup> Pupillary unrest is the fluctuation in pupil diameter, and pupillary unrest under ambient light (PUAL) is present even in well-rested individuals. Although the underlying mechanisms are unknown, PUAL is depressed by opioids. Administration of fentanyl to healthy volunteers diminishes PUAL, and the decrease is proportionally larger than the change in pupil diameter.<sup>189</sup> The pretreatment magnitude of PUAL is correlated with the analgesic response to opioid therapy, and patients who exhibit higher levels of PUAL change after opioid administration have a more beneficial analgesic effect from opioids.<sup>190</sup>

Pupillary constriction represents a well-known phenomenon following opioid administration and the use of pupillometry may help guide intraoperative opioid dosing to optimize analgesia.

## THERMOREGULATION AND SHIVERING

Opioid-based anesthesia probably reduces thermoregulatory thresholds to a degree similar to that of the potent inhaled anesthetics.<sup>191</sup> However, meperidine is unique among opioids in its ability to effectively terminate or attenuate shivering. The antishivering effect of meperidine is primarily related to a reduction in the shivering threshold,<sup>192</sup>

and seems to be mediated by meperidine's activity on the  $\kappa$  receptor.<sup>193</sup> However, the relatively specific  $\kappa$ -receptor agonist, nalbuphine, did not show significant antishivering activity.<sup>194</sup> Meperidine exerts agonist activity at the  $\alpha_{2B}$ -adrenoreceptor subtype, a finding suggesting the involvement of this action in the antishivering action of meperidine.<sup>85</sup> Alfentanil, morphine, and fentanyl are not as effective as meperidine in the treatment of postoperative shivering. However, alfentanil and nefopam, a centrally acting analgesic, additively reduce the shivering threshold in humans.<sup>195</sup> Tramadol (0.5 mg/kg) suppressed postepidural anesthetic shivering in parturients as effectively as meperidine (0.5 mg/kg).<sup>196</sup> A quantitative systematic review of randomized controlled trials found that meperidine 12.5 to 35 mg and tramadol 35 to 220 mg were more effective than control for parenteral pharmacologic interventions for the prevention of postoperative shivering.<sup>197</sup>

Remifentanil is associated with an increased incidence of postanesthetic shivering, which is not related with intraoperative hypothermia. The higher incidence of postanesthetic shivering with higher doses of remifentanil probably reflects acute opioid tolerance and stimulation of the NMDA receptors.<sup>198</sup> A small dose of ketamine, 0.5 mg/kg at induction of anesthesia followed by infusion at 0.3 mg/kg/hour, can prevent remifentanil-induced postanesthetic shivering.

## PRURITUS

Opioid-induced pruritis is one of several perpetual challenges associated with opioid-based analgesia. With the possible exception of morphine, histamine release, once

thought to underlie this phenomenon, is not causative because non-histamine-releasing opioids also produce pruritus. Both central and peripheral nervous system mechanisms have been explored. Facial itching may not necessarily be a manifestation of direct opioid action at the level of the trigeminal nucleus, but rather, it may be a reflection of opioid-triggered neural transmission at a distant site. It is not known why the face is prone to pruritus even after spinal opioids. Interestingly, pruritus due to cholestasis is ameliorated by opioid antagonists.<sup>199</sup> Intrathecal morphine-induced itching in monkeys was suggested to be mediated by the  $\mu$  receptor.<sup>200</sup> Activation of a  $\mu$ -opioid receptor isoform MOR1D<sup>11</sup> by morphine induced activation of the gastrin-releasing peptide receptor that heterodimerized with MOR1D, thus resulting in activation of phospholipase  $\beta$ 3 and intracellular  $\text{Ca}^{2+}$  increase in neurons leading to itch sensation in mice.<sup>201</sup>

Naloxone reverses opioid-induced itching, but opioid antagonists are not ideal therapeutic agents against pruritus because opioid analgesia is often reversed by these agents. A subcutaneous administration (12 mg) of methylnaltrexone bromide, a peripherally acting  $\mu$ -opioid antagonist, did not reduce the overall severity or incidence of pruritus in women having elective cesarean section under spinal anesthesia with intrathecal morphine 100  $\mu\text{g}$ , suggesting that peripheral mechanisms do not significantly contribute to spinal opioid-induced pruritus.<sup>202</sup> Ondansetron, a serotonin 5-HT<sub>3</sub> receptor antagonist has been proposed to treat spinal or epidural morphine-induced pruritus,<sup>203</sup> and a meta-analysis has demonstrated that prophylactic use of 5-HT<sub>3</sub> antagonists significantly reduced the severity and the need for treatment of pruritus.<sup>204</sup> Another meta-analysis showed that prophylactic intravenous administration of 8 mg ondansetron does not decrease the incidence of fentanyl- or sufentanil-induced pruritus but may decrease the need for pruritus rescue medication.<sup>205</sup> The application of mixed or partial opioid agonists, such as nalbuphine and butorphanol, are growing in popularity as antipruritics because they may partially antagonize  $\mu$  receptor function with intact  $\kappa$  actions to maintain analgesia.<sup>206</sup> In fact, activation of the  $\kappa$ -opioid receptor inhibits pruritus evoked by subcutaneous and intrathecal morphine in animal models.<sup>207</sup>

Other agents that have been investigated include pentazocine (15 mg), an agonist of the  $\kappa$ -opioid receptor and partial agonist of the  $\mu$ -opioid receptor. Pentazocine has been found to be superior to 4 mg of ondansetron for the treatment of pruritus induced by intrathecal morphine in parturients undergoing cesarean delivery.<sup>208</sup> It was recently reported that the antipruritic effect of  $\kappa$ -receptor agonists may not require interaction between the  $\kappa$  receptor and  $\beta$ -arrestins.<sup>209</sup> Tenoxicam, a nonsteroidal antiinflammatory drug (NSAID), was reported to be effective for pruritus induced by epidural fentanyl.<sup>210</sup> Other approaches include intravenous administration of droperidol (1.25 mg), propofol (20 mg), or alizapride (100 mg), which reduced the incidence of pruritus induced by the use of morphine 0.2 mg intrathecally in patients undergoing cesarean section under spinal anesthesia.<sup>211</sup> Preoperative gabapentin prevents pruritus induced by intrathecal morphine in patients undergoing lower limb surgery with spinal anesthesia.<sup>212</sup>

As opioid-induced pruritis continues to be a clinical challenge, current strategies have shifted away from the

consequences of histamine release (morphine) and are focused on exploiting partial blockade/activation of the  $\mu$ -opioid receptor, activation of the  $\kappa$ -receptor, and non-opioid receptor pathways.

## OPIOID-INDUCED HYPERALGESIA

There is growing evidence that opioid-induced hyperalgesia (OIH) can represent a major adverse effect of opioid administration, especially when driven by potent formulations and escalating dosages. Experimentally, opioids have elicited hyperalgesia in animal models after repeated opioid administration or continuous delivery.<sup>213</sup> A systematic review to evaluate the clinical implication of OIH demonstrated that high intraoperative doses of remifentanil are associated with small but significant increases in acute pain after surgery as assessed by: pain intensity at rest 24 hours after surgery, 24-hour morphine use, pain intensity on movement, and hyperalgesia measured after an operation.<sup>214</sup> In a randomized, double-blind, crossover study with 24 healthy male volunteers, it was demonstrated that when compared with low-dose (1  $\mu\text{g}/\text{kg}$ ) fentanyl, high-dose fentanyl (10  $\mu\text{g}/\text{kg}$ ) increased the area of hyperalgesia from 4.5 to 6.5 hours after fentanyl administration. This result suggests that fentanyl can also produce OIH in humans.<sup>215</sup>

OIH was shown to be due to spinal sensitization to glutamate and substance P.<sup>216</sup> Activation of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) contributes to remifentanil-induced hyperalgesia by regulating NMDA receptor plasticity in the spinal dorsal horn,<sup>217</sup> and further demonstrated that GSK-3 $\beta$  inhibition prevented remifentanil-induced postoperative hyperalgesia via regulating  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) expression and function in the spinal dorsal horn.<sup>218</sup> Importantly, abrupt withdrawal of opioid administration may also contribute to induction of OIH, although its mechanism is not clear. In contrast to the high incidence of hyperalgesia induced after abrupt withdrawal of remifentanil (administered at 2.5  $\text{ng}/\text{mL}$  for 30 minutes), no hyperalgesia was observed after gradual withdrawal by 0.6  $\text{ng}/\text{mL}$  every 5 minutes.<sup>219</sup>

There have been reports that OIH and subsequent acute opioid tolerance can be prevented by ketamine, suggesting the involvement of the NMDA receptor.<sup>220,221</sup> Methadone is unique in possessing both  $\mu$ -opioid receptor activating and NMDA antagonist properties. Opioid-induced hyperalgesia resulted from the presence in the racemate of the *l*-methadone ( $\mu$ -opioid agonist) and was antagonized by the presence of the *d*-methadone (NMDA antagonist).<sup>222</sup> Low-dose buprenorphine (25  $\mu\text{g}/\text{h}$  for 24 h), an opioid with NMDA antagonist activity, in patients receiving remifentanil infusion during major lung surgery prevented postoperative secondary hyperalgesia.<sup>223</sup> Butorphanol (0.2  $\mu\text{g}/\text{kg}$ ) was also effective for prevention of postoperative hyperalgesia after laparoscopic cholecystectomy performed with remifentanil (0.3  $\mu\text{g}/\text{kg}/\text{min}$ ).<sup>224</sup>  $\text{N}_2\text{O}$ , an inhalation anesthetic, is an effective NMDA antagonist. Intraoperative 70%  $\text{N}_2\text{O}$  administration significantly reduced postoperative opioid-induced hyperalgesia in patients receiving propofol (approximately 120  $\mu\text{g}/\text{kg}/\text{min}$ ) and remifentanil (0.3  $\mu\text{g}/\text{kg}/\text{min}$ ).<sup>225</sup> A randomized, double-blind, prospective study showed that a relatively high dose of remifentanil (0.2  $\mu\text{g}/\text{kg}/\text{min}$ ) enhances periincisional hyperalgesia in patients

undergoing thyroidectomy, and intraoperative magnesium sulfate (30 mg/kg at induction followed by 10 mg/kg/h) can prevent remifentanil-induced hyperalgesia.<sup>226</sup>

Other strategies have focused on the upregulation of spinal cyclooxygenase-2 (COX-2) and increased prostaglandin E2 release in the spinal cord after morphine withdrawal in rats.<sup>227</sup> In humans, hyperalgesia after a 30-minute intravenous infusion of remifentanil (0.1 µg/kg/min) can be prevented by administration of parecoxib, a COX-2 inhibitor, before remifentanil infusion,<sup>228</sup> suggesting the involvement of COX-2 in OIH. Alternatively, it was reported that an ultra-low dose of naloxone blocked remifentanil-induced hyperalgesia but did not change opioid tolerance in rats under inhaled anesthesia, and that the MAC increase associated with hyperalgesia was also blocked by naloxone.<sup>229</sup> In patients undergoing elective thyroid surgery, intraoperative use of naloxone (0.05 µg/kg/h) reduced postoperative hyperalgesia after remifentanil infusion of 4 ng/mL.<sup>230</sup>

Genetic variants of the  $\beta_2$ -adrenergic receptor gene may explain some part of the differences between various strains of mice to develop OIH, and the selective  $\beta_2$ -adrenergic receptor antagonist butoxamine was shown to dose dependently reverse OIH.<sup>231</sup> In mice, systemic or intrathecal injection of the 5-HT<sub>3</sub> receptor antagonist, ondansetron, was shown to prevent or reverse opioid-induced tolerance or hyperalgesia.<sup>232</sup>

Interestingly, the occurrence of OIH might be affected by general anesthetics coadministered with opioids. When women undergoing breast cancer surgery were anesthetized with sevoflurane or propofol to keep BIS value at 40 to 50, postoperative hyperalgesia induced by intraoperative remifentanil infusion (effect-site target 4 ng/mL) was significant with sevoflurane anesthesia, but not apparent with propofol anesthesia.<sup>233</sup>

A follow-up study on the postoperative course of cardiac surgery demonstrated that intraoperative remifentanil was predictive for chronic thoracic pain 1 year after surgery in a dose-dependent manner.<sup>234</sup> It can be anticipated that hyperalgesia during the perioperative period is linked to peripheral and central pain sensitization and thereby correlates with the development of postoperative chronic pain.<sup>235</sup> This suggests that hyperalgesia due to remifentanil in the early postoperative period may explain the higher incidence of chronic pain.

Overall, human data generally support the existence of OIH in a few specific settings. Clinically relevant mechanisms of OIH include involvement of the NMDA receptor with ketamine as an appealing remedy. Although all potent opioids such as fentanyl are apparently capable of inducing OIH, ultrapotent opioid agonists such as remifentanil may pose even greater risks. The conditions under which OIH is expressed should be clarified and the extent of its clinical significance remains to be elucidated.<sup>236</sup>

## Respiratory Effects of Opioids

The respiratory depressant actions of opioids represent their most serious adverse effect. Although some early studies indicated the involvement of both  $\mu$ - and  $\delta$ -opioid receptors, activation of the  $\mu$ -opioid receptor in the caudal medullary raphe region, which is important for regulating pain and

respiration, inhibits the ventilatory response to hypercapnia in anesthetized rats.<sup>237</sup> Furthermore, administration of morphine or M6G did not produce significant respiratory depression in the  $\mu$ -opioid receptor knockout mice.<sup>238</sup> Polymorphism of the  $\mu$ -opioid receptor at nucleotide position 118, which is known to affect M6G-induced analgesia, does not significantly change the susceptibility of respiratory depressive effect of M6G.<sup>19</sup> This result suggests that analgesia and respiratory depression may be mediated by different signal transduction mechanisms activated by the  $\mu$ -opioid receptor.

## EFFECTS ON AIRWAYS

The antitussive actions of opioids are well known and central in origin. Opioids blunt or eliminate somatic and autonomic responses to tracheal intubation. They allow patients to tolerate endotracheal tube placement without coughing or “bucking.” Conversely, two successive doses of 1.5 µg/kg fentanyl did not effectively prevent laryngospasm in children aged 2 to 6 years old who were anesthetized with sevoflurane.<sup>239</sup> Opioids can also help avoid increases in bronchomotor tone in asthma. In addition, fentanyl also has antimuscarinic, antihistaminergic, and antiserotonergic actions and may be more effective than morphine in patients with asthma or other bronchospastic diseases.

Nevertheless, several studies have reported a depressant effect of morphine on respiratory mucus transport, which is one of the most important defenses against respiratory tract infections. However, morphine had no effect on the beating frequency of nasal cilia in vitro.<sup>240</sup> Opioids can affect pharyngeal function, airway protection, and coordination of breathing and swallowing. A sedative dose of morphine (0.1 mg/kg) was associated with increased incidence of pharyngeal dysfunction and disordinated breathing and swallowing, a combination impairing airway protection and potentially increasing the risk for pulmonary aspirations.<sup>241</sup>

More potent opioids such as remifentanil (effect-site concentration of 2 ng/mL) can suppress coughing induced by extubation after propofol or sevoflurane anesthesia.<sup>242</sup> In contrast, fentanyl, sufentanil, and alfentanil curiously elicit a brief cough in up to 50% of patients when the drug is injected by intravenous bolus. Fentanyl, administered through a peripheral intravenous cannula, provoked cough when it was injected rapidly, but the incidence of cough decreased significantly as the injection time was increased,<sup>243</sup> as well as by the administration of 1.5 mg/kg lidocaine 1 minute before fentanyl administration.<sup>244</sup> A meta-analysis showed that the lowest effective dose of lidocaine on the risk of opioid-induced cough was 0.5 mg/kg.<sup>245</sup> It was also reported that preemptive use of fentanyl 25 µg, administered 1 minute before bolus injection of fentanyl (125 or 150 µg), can effectively suppress fentanyl-induced cough.<sup>246</sup> Propofol,  $\alpha_2$  agonists (clonidine, dexmedetomidine), inhalation of  $\beta_2$  agonists (terbutaline, salbutamol), and NMDA-receptor antagonists (ketamine, dextromethorphan) were also effective for suppression of fentanyl-induced cough.<sup>247</sup> A prospective randomized controlled study demonstrated that a huffing maneuver, consisting of a forced expiration against open glottis, just before intravenous fentanyl administration significantly reduced

the incidence and severity of fentanyl-induced coughing in the majority of the patients.<sup>248</sup> Li and associates reported that nonsmoking women undergoing gynecological surgery who develop fentanyl-induced cough during induction of anesthesia have a higher incidence of postoperative nausea and vomiting (PONV).<sup>249</sup>

In summary, opioids engender potent antitussive properties that can help blunt airway responsiveness to endotracheal intubation. However, depending on the class of opioid and rate of administration, they may evoke a brief cough that can be subverted through the use of preadministered agents such as lidocaine. Ultimately, caution should be exercised in the administration of opioids as they can also interfere with protective aspects of airway physiology.

## RESPIRATORY DEPRESSION

The lack of adequate pain relief can cause shallow respiration leading to postoperative respiratory dysfunction including atelectasis, and therefore opioids can serve as a foundational component of postoperative analgesia to prevent or correct respiratory impairment. However, opioids can also dose dependently depress respiration, representing the most feared adverse effect. The incidence of opioid-induced respiratory depression varies from 0.1% to 37%, depending on the route of opioid administration, the type of opioid, the definition and method of monitoring opioid-induced respiratory depression, and the prospective versus retrospective nature of the study, and is a significant cause of death and brain damage in the perioperative period.<sup>250</sup>

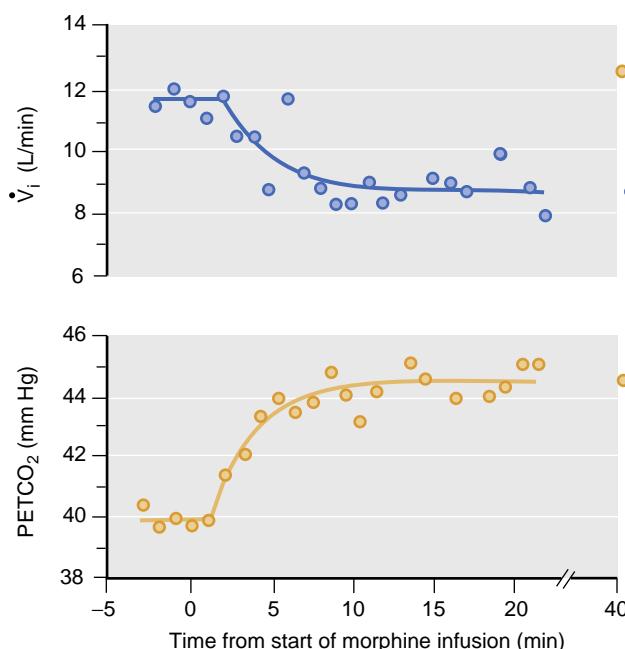
Opioids activating the  $\mu$  receptor cause dose-dependent depression of respiration, primarily through a direct action on brainstem respiratory centers.<sup>251</sup> The stimulatory effect of  $\text{CO}_2$  on ventilation is significantly reduced by opioids. Hypercapnic responses can be separated into central and peripheral components. In one report, morphine-induced changes in the central component were equal in men and women, whereas changes in the peripheral component were larger in women.<sup>252</sup> In addition, the apneic threshold and pressure of end-tidal carbon dioxide ( $\text{PETCO}_2$ ) are increased by opioids (Fig. 24.13). Opioids also decrease hypoxic ventilatory drive.

Respiratory rate is usually drastically decreased in opioid overdose, although hypoxic CNS insult can counter this effect. The prolonged expiratory time in the respiratory cycle induced by opioids frequently results in greater reductions in respiratory rate than in tidal volume. Monitoring of breath intervals can sensitively detect fentanyl-induced respiratory depression and can be used as a measure of dynamic opioid effect.<sup>253</sup> High doses of opioids usually eliminate spontaneous respirations without necessarily producing unconsciousness. Patients receiving high doses of opioids may still be responsive to verbal command and often breathe when they are directed to do so.

Peak onset of respiratory depression after an analgesic dose of morphine is slower than after comparable doses of fentanyl, and respiratory depression induced by small doses of morphine usually lasts longer than after equipotent doses of fentanyl. Plasma fentanyl concentrations of 1.5 to 3.0 ng/mL are associated with significant decreases in  $\text{CO}_2$  responsiveness. With higher doses of fentanyl (50-100  $\mu\text{g}/\text{kg}$ ), respiratory depression can persist for many hours. When

moderately large doses (20-50  $\mu\text{g}/\text{kg}$  or greater) of fentanyl are used, the potential need for postoperative mechanical ventilation should be anticipated. The effects of remifentanil are attenuated rapidly and completely within 5 to 15 minutes following termination of its administration. In healthy humans, the  $\text{EC}_{50}$  for depression of minute ventilation with remifentanil and alfentanil was 1.17 ng/mL and 49.4 ng/mL, respectively.<sup>254</sup> In healthy volunteers, fentanyl 1  $\mu\text{g}/\text{kg}$  and remifentanil 0.5  $\mu\text{g}/\text{kg}$  had similar maximum decreases in minute ventilation (~50%), but the onset of and recovery from ventilatory depression were faster with remifentanil.<sup>255</sup> Naloxone has been accepted as a standard therapy for opioid-induced respiratory depression. However, reports have noted naloxone-resistant respiratory depression after intrathecal morphine administration.<sup>256</sup>

A major component of the excitatory synaptic drive necessary for respiratory rhythrogenesis and activation of respiratory motoneurons is *via* the amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) type of glutamate receptors.<sup>257</sup> This finding has led to investigations of ampkine (positive modulators of AMPA receptors) therapy to alleviate opioid-induced respiratory depression.<sup>258</sup> 5-HT released from the raphe nuclei potently alters the excitability of respiratory motoneurons, the preBötzinger complex (preBötC), and other brainstem respiratory nuclei. The activation of 5-HT<sub>1A</sub> receptors with befireadol alleviates fentanyl-induced respiratory depression in rats.<sup>259</sup> PreBötC, the main region of respiratory rhythm-pattern generation, is the main target of opioid-induced respiratory depression.



**Fig. 24.13** Influence of morphine administration (bolus dose of 100  $\mu\text{g}/\text{kg}$  given at the start of the infusion [0 minute], followed by a continuous infusion of 30  $\mu\text{g}/\text{kg}/\text{h}$ ) on resting inspired minute ventilation ( $V_i$ ) and resting pressure of end-tidal carbon dioxide ( $\text{PETCO}_2$ ) in a single subject. A one-component exponential was fitted to the data. The estimated time constant for the  $V_i$  data is 3.0 minutes and for  $\text{PETCO}_2$  data is 2.6 minutes. The time delays are between 1 and 2 minutes. (From Sarton E, Teppema L, Dahan A. Sex differences in morphine-induced ventilatory depression reside within the peripheral chemoreflex loop. *Anesthesiology*. 1999;90:1329-1338.)

However, it has been demonstrated that preBötC partially mediates opioid effects on respiratory phase timing, but does not mediate the opioid-induced depression of respiratory rate.<sup>260</sup> By the use of knockout mice and pharmacologic approaches, G-protein-gated inwardly rectifying  $\kappa$  channels were shown to contribute to respiratory depression by  $\mu$ -opioid receptors and opioids.<sup>261</sup> In healthy humans, GAL021, a calcium-activated potassium (BKCa) channel blocker possessing a stimulatory effect on ventilation at the carotid bodies, was preliminarily shown to reverse alfentanil-induced respiratory depression.<sup>262</sup>

### FACTORS AFFECTING OPIOID-INDUCED RESPIRATORY DEPRESSION

Many factors affect the magnitude and duration of opioid-induced respiratory depression (Box 24.2).

Older patients are more sensitive to the anesthetic and respiratory depressant effects of opioids and experience higher plasma concentrations of opioids administered on a weight basis. In addition, morphine can produce greater respiratory depression on a weight basis in neonates than adults, because morphine easily penetrates the brain of neonates and infants with incomplete blood-brain barriers.

The respiratory depressant effects of opioids are increased or prolonged (or both) when these drugs are administered with other CNS depressants, including potent inhaled anesthetics, alcohol, barbiturates, benzodiazepines, most intravenous sedatives, and hypnotics. However, droperidol, scopolamine, and clonidine do not enhance the respiratory depressant effects of fentanyl or other opioids. Curiously, Setnik and associates observed a decrease in end-tidal  $\text{CO}_2$  when 0.7 g/kg ethanol was administered in addition to 80 mg oral morphine, suggesting a stimulatory effect of ethanol on opioid-induced respiratory depression.<sup>263</sup> However, it was reported that ethanol (1 g/L of breath ethanol concentration) caused a significant increase in the apneic events and increased end-tidal  $\text{CO}_2$  induced by 20 mg oxycodone per os in opioid-naïve healthy volunteers.<sup>264</sup>

Although opioid action is usually dissipated by redistribution and hepatic metabolism, rather than by urinary excretion, the adequacy of renal function may influence the duration of opioid activity. In renal insufficiency, the

#### BOX 24.2 Factors Increasing the Magnitude and/or Duration of Opioid-Induced Respiratory Depression

- High dose
- Sleep
- Old age
- Central nervous system depressant
  - Inhaled anesthetics, alcohol, barbiturates, benzodiazepines
- Renal insufficiency
- Hyperventilation, hypocapnia
- Respiratory acidosis
- Decreased clearance
  - Reduction of hepatic blood flow
- Secondary peaks in plasma opioid levels
  - Reuptake of opioids from muscle, lung, fat, and intestine
- Pain

respiratory depressant properties of morphine and hydrocodone, as well as of the morphine metabolite M6G, become evident as these accumulate.

Hypocapnic hyperventilation enhances and prolongs postoperative respiratory depression after fentanyl (10 and 25  $\mu\text{g}/\text{kg}$ ). Intraoperative hypercarbia produces the opposite effects. Possible explanations for these findings include increased brain opioid penetration (increased un-ionized fentanyl with hypocapnia) and removal (decreased CBF with hypocapnia). In patients who hyperventilate because of anxiety or pain, even small doses of intravenous opioids can result in transient apnea because of acute shifts in apneic thresholds. Respiratory depression by remifentanil (50  $\mu\text{g}$  infused over 60 seconds) was more pronounced in hyperoxia (inhaling 50%  $\text{O}_2$ ) than normoxia as determined by minute ventilation, end-tidal  $\text{PCO}_2$ , and respiratory rate.<sup>265</sup> During hyperoxia, respiratory depression may be masked when measuring  $\text{SpO}_2$  as pulse oximetry remains in normal values during the first minutes of respiratory depression.

All opioid agonists with a longer plasma half-life than naloxone have a hypothetical potential to show renarcotization with time, especially when a bolus dose of naloxone is used to treat opioid-induced respiratory depression.

Overall, opioids exert their primary respiratory depressant effects through  $\mu$ -receptor activation in the brainstem respiratory center, although other pathways have been defined. Dose-dependent opioid respiratory depression increases the apneic threshold, and reduces the respiratory stimulatory drive of  $\text{CO}_2$  and hypoxia. Research efforts to block or reverse opioid-induced respiratory depression are ongoing and include a focus on AMPA, 5-HT<sub>1A</sub>, and calcium-activated potassium channels. The  $\mu$ -receptor antagonist, naloxone, continues to be the most commonly used clinical intervention to reverse opioid-induced respiratory depression, however its effectiveness may be limited if the administered opioid has a greater binding affinity and/or half-life than naloxone.

### Cardiovascular Effects of Opioids

Numerous reports have demonstrated that large doses of opioid, administered as the sole or primary anesthetic, result in hemodynamic stability throughout the operative period. This remarkable physiologic state is a result of a number of complementary mechanisms.

### NEUROLOGIC MECHANISMS

Key areas of the brainstem that integrate cardiovascular responses and maintain cardiovascular homeostasis are the nucleus solitarius, the dorsal vagal nucleus, the nucleus ambiguus, and the parabrachial nucleus. The nucleus solitarius and parabrachial nucleus play an important role in the hemodynamic control of vasopressin secretion. Enkephalin-containing neurons and opioid receptors are distributed in these regions. The direct administration of  $\mu$ -agonists into the CNS of rats most commonly, but not always, produces hypotension and bradycardia.<sup>266</sup> The ventrolateral PAG region, a key central site mediating opioid analgesia, also affects hemodynamic control.<sup>267</sup> In addition, opioids can modulate the stress response through

receptor-mediated actions on the hypothalamic-pituitary-adrenal axis. Most opioids reduce sympathetic and enhance vagal and parasympathetic tone. Patients who are volume depleted, or individuals depending on high sympathetic tone or exogenous catecholamines to maintain cardiovascular function, are predisposed to hypotension after opioid administration.

The predominant and usual effect of opioids on heart rate is bradycardia resulting from stimulation of the central vagal nucleus. Blockade of sympathetic actions may also play a role in opioid-induced bradycardia. Meperidine, in contrast to other opioids, rarely results in bradycardia, but it can cause tachycardia. Tachycardia after meperidine may be related to its structural similarity to atropine, to normeperidine, its principal metabolite, or to early manifestations of its toxic CNS effects.

## CARDIAC MECHANISMS

The direct cardiac actions of opioids, in particular the effects on myocardial contractile mechanisms, are significantly less pronounced than are those of many other intravenous and inhaled anesthetics. However, opioid receptors exist in cardiac myocytes of several species.

### Contractility

Morphine decreases  $\text{Ca}^{2+}$  transients but not cardiac contraction and enhances myofilament  $\text{Ca}^{2+}$  sensitivity through the action on the  $\delta_1$ -opioid receptor expressed in the heart.<sup>268</sup> In rabbit ventricular myocytes, morphine prolonged action potential duration by increasing L-type  $\text{Ca}^{2+}$  current, an effect mediated by  $\delta$ - and  $\kappa$ -opioid receptors, and hyperpolarized cardiac resting membrane potential by increasing the inwardly rectifying  $\text{K}^+$  current, which is not mediated by opioid receptors.<sup>269</sup> Conversely, investigators demonstrated that morphine decreased the isometric force of contraction in atrial muscles from nonfailing and failing human hearts through a naloxone-insensitive mechanism.<sup>270</sup> Fentanyl produces little or no change in myocardial contractility.<sup>271</sup> Usually, most hemodynamic variables remain unchanged after large doses of fentanyl. Alfentanil, at concentrations achieved in clinical practice, increases contraction in ventricular cells by a mechanism involving an increase in the sensitivity of the contractile apparatus to  $\text{Ca}^{2+}$ .<sup>272</sup> The negative inotropic effect of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) on ventricular myocytes caused by disruption of sarcoplasmic reticulum  $\text{Ca}^{2+}$  handling and  $\text{Ca}^{2+}$  transient was reported to be ameliorated by alfentanil, but this response may not be mediated by opioid receptors.<sup>273</sup> A study using trans-thoracic echocardiography demonstrated that continuous target-controlled infusion of remifentanil (target effect-site concentration 2 ng/mL, infusion rate 0.08–0.09  $\mu\text{g}/\text{kg}/\text{min}$ ) did not affect systolic and diastolic left ventricular function in young healthy subjects during spontaneous breathing.<sup>274</sup>

### Cardiac Rhythm Conduction

Opioid-induced bradycardia is primarily mediated by the CNS. However, there have been reports on direct effects of opioids on cardiac pacemaker cells. Fentanyl may depress cardiac conduction by a mechanism mediated by direct

membrane actions, as opposed to opioid receptor interactions.<sup>275</sup> During induction of anesthesia in patients undergoing coronary artery bypass graft surgery, the QT interval increased significantly after the injection of fentanyl.<sup>276</sup> However, pretreatment with fentanyl 2  $\mu\text{g}/\text{kg}$  or remifentanil 1  $\mu\text{g}/\text{kg}$  significantly attenuated QTc prolongation associated with laryngoscopy and tracheal intubation during propofol or sevoflurane induction.<sup>277,278</sup> Both sufentanil and alfentanil have been demonstrated to be devoid of electrophysiologic effects on the normal or accessory pathways in patients with Wolff-Parkinson-White syndrome.<sup>279,280</sup> Clinically, cardiac conduction disturbances attributable to opioids are rare, but they may be more likely to occur in the presence of  $\text{Ca}^{2+}$  channel or  $\beta$ -adrenergic blockers.

The overall effect of opioid anesthesia is antiarrhythmic. Naloxone, morphine, and levorphanol protected against arrhythmia induced by coronary artery occlusion in rats.<sup>281</sup> A direct effect on ionic currents in cardiac muscle was suggested as the mechanism of antiarrhythmic activity of opioids. It was also reported that opioid antagonists are more antiarrhythmogenic than agonists in rats.<sup>282</sup> Some of the electrophysiologic actions of opioids resemble those of class III antiarrhythmogenic drugs.

### Myocardial Ischemia

Determining the effects and consequences of opioid action on myocardial ischemia is complex because results can depend on such factors as the species studied and experimental design. In an experimental model of myocardial ischemia in rabbits, fentanyl had antiarrhythmic and antiischemic action with central and peripheral opioid receptor involvement.<sup>283</sup> Opioids can mimic ischemic preconditioning. Opioid receptor stimulation results in a reduction in infarct size similar to that produced by ischemic preconditioning.<sup>284</sup> Although the preconditioning effect of opioids is mediated mainly by the cardiac  $\kappa$ - and  $\delta$ -opioid receptors,<sup>285</sup> part of the protective effect of remifentanil may be produced by  $\mu$ -agonist activity outside the heart.<sup>286</sup> Preconditioning with small doses of intrathecal morphine can provide comparable cardioprotection to myocardial ischemic preconditioning and preconditioning with intravenous morphine, and the effect seems to involve  $\mu$ -,  $\delta$ -, and  $\kappa$ -opioid receptors.<sup>287</sup> Late preconditioning, in which cardioprotective effects can be observed 24 hours after drug administration, was also produced by morphine-induced activation of the opioid receptor in rat hearts.<sup>288</sup>

It was found that remote preconditioning by brief ischemia of other distant organs, such as intestine, kidney, and limb, similarly provides cardioprotection that is as effective as classic ischemic preconditioning. The myocardial  $\kappa$ -opioid receptors were demonstrated to mediate cardioprotection by remote preconditioning.<sup>289</sup> Brief cycles of ischemia and reperfusion during the early phase of reperfusion protect the heart from infarction. This phenomenon, termed postconditioning, was shown to be induced by activation of the  $\delta$ -opioid receptor in the heart.<sup>290</sup> Volatile anesthetics may also be capable of producing protection against ischemic injury when these drugs are administered solely on reperfusion. This anesthetic-induced postconditioning can be enhanced by morphine through the activation of phosphatidyl-3-kinase and opioid receptors.<sup>291</sup> It has been shown that brief exposure to exercise (1–3 days

of moderate-intensity exercise) preconditions the heart against tissue injury and death resulting from myocardial ischemia–reperfusion. It was demonstrated that endogenous opioids produced in the heart mediate exercise-induced cardioprotection against ischemia–reperfusion injury through its action on the  $\delta$ -opioid receptor in rats.<sup>292</sup> Stimulation of  $\delta_1$ -opioid receptor also generates oxygen radicals through mitochondrial ATP-sensitive K<sup>+</sup> channels, with resulting attenuation of oxidant stress and cell death in cardiomyocytes.<sup>293</sup> Involvement of adenosine A1 receptor and protein kinase C in the cardioprotective effect of opioids was also suggested.<sup>294,295</sup> Whether the experimental results showing protective effects of opioid against myocardial ischemia will translate into reductions in morbidity and mortality in patients with coronary artery disease has yet to be established by clinical trials.<sup>296</sup> Clinically, high doses of opioids can maintain myocardial perfusion and the O<sub>2</sub> supply–demand ratio as well or better than can inhalation-based techniques.

### Coronary Circulation

Opioids appear to have no significant effect on coronary vasomotion or myocardial metabolism, do not produce steal phenomena, nor diminish the ability of large coronary arterioles to respond to vasoactive agents.<sup>297</sup> Coronary conductance is regulated by arterial baroreflex control, and vasodilator response is induced by a rise in aortic pressure. This baroreflex control is enhanced by low plasma concentration of fentanyl (1–2 ng/mL), but appears to be depressed at increased concentrations of fentanyl.<sup>298</sup>

### Circulatory Reflexes

In an experiment examining baroreceptor reflex responses induced by perfusion of the carotid sinus at predetermined levels, baroreceptor reflexes were well preserved by moderate doses of fentanyl while high doses of fentanyl depressed baroreceptor reflexes.<sup>299</sup> The oculocardiac reflex, which is caused by traction of extraocular muscles during strabismus surgery, was significantly augmented by fentanyl, sufentanil, and remifentanil.<sup>300</sup> Among pediatric patients undergoing strabismus surgery, anesthetized with propofol (12 mg/kg/h) and alfentanil (0.04 mg/kg/h), virtually all patients developed oculocardiac reflex and atrioventricular rhythm disorders were frequent.<sup>301</sup>

### HISTAMINE RELEASE

It is well known that morphine causes histamine release and sympathoadrenal activation. Increases in plasma histamine after morphine cause dilation of terminal arterioles and direct positive cardiac chronotropic and inotropic actions. In patients pretreated with both H<sub>1</sub>- and H<sub>2</sub>-antagonists, the cardiovascular responses are significantly attenuated despite comparable increases in plasma histamine concentrations. Codeine and meperidine are examples of other opioids that can induce mast cell activation with the release of histamine, probably by a mechanism other than the  $\mu$ -opioid receptors.<sup>302</sup> Unlike morphine or meperidine, the opioids fentanyl, alfentanil, sufentanil, and remifentanil do not produce increases in plasma histamine, subsequently hypotension is less frequent with their administration.

### VASCULAR MECHANISMS

The pharmacologically defined opioid receptor subtype  $\mu_3$  is expressed in human endothelial cells and coupled to vasodilation via nitric oxide (NO) production. Although  $\mu_3$  is opiate alkaloid sensitive it is insensitive to opioid peptides including peptides previously shown to have affinities for the  $\mu$ -opioid receptors. Morphine-induced vasodilation may be partially caused by activation of the  $\mu_3$  receptor.<sup>303</sup> Other pharmacologic studies evaluating alfentanil, fentanyl, and sufentanil in the dog also demonstrate direct peripheral vessel smooth muscle relaxation although exact mechanism(s) remains under study.<sup>304,305</sup> For example, measurement of forearm blood flow after infusion of sufentanil into the brachial artery indicated that sufentanil has a direct vasodilatory effect on human vascular tissue that is likely independent of a neurogenic or systemic mechanism.<sup>306</sup> A supraclinical dose of alfentanil attenuates the phenylephrine-induced contraction via an inhibitory effect on calcium influx by blocking the L-type calcium channels in the rat aortic vascular smooth muscle.<sup>307</sup> Remifentanil can cause transient instability in hemodynamic variables. However, this change may not be solely the result of autonomic or central nervous system inhibition or of centrally mediated vagal stimulation. A pharmacologic study using rat thoracic aortic rings indicated that remifentanil vasodilates by an endothelium-dependent mechanism, involving prostacyclin and NO released from the endothelium, and an endothelium-independent vasodilation probably mediated by the suppression of voltage-sensitive Ca<sup>2+</sup> channels.<sup>308</sup> In patients with a total artificial heart in which cardiac output is preload-independent, remifentanil induces a dose-dependent and significant systemic vasodilation without significant effects on capacitance vessels.<sup>309</sup>

Opioids may affect the pulmonary vasculature as well as systemic circulation. It was shown that phenylephrine-induced contraction of canine pulmonary artery is primarily mediated by  $\alpha_{1B}$ -adrenergic receptor activation, and is attenuated by fentanyl by binding to and directly inhibiting the  $\alpha_{1B}$ -adrenergic receptor.<sup>310</sup> Pharmacologic studies in cats demonstrated that sufentanil and remifentanil have potent vasodepressor activity in the pulmonary vascular bed and these responses may be mediated by histamine and opioid receptor-sensitive pathway.<sup>311,312</sup>

### OPIOIDS IN SHOCK

Opioids are often administered for patients requiring surgical intervention for the control of hemorrhage. An animal study demonstrated that pretreatment with morphine before inducing shock state decreases leukocyte adhesion and vascular permeability in the microcirculation of the mesenteric venule, suggesting the survival benefit for use of morphine during acute resuscitation.<sup>313</sup>

It has been shown that endogenous opioids contribute to the pathophysiology of hypovolemic shock through central and peripheral sympathetic inhibition and contributes to hypotension during severe hemorrhage. Liu et al. reported that the selective  $\delta$ -opioid receptor antagonist (ICI 174,864) may be beneficial for the early management of traumatic hemorrhagic shock in rats, suggesting a pathophysiological role of the  $\delta$ -opioid receptor in hemorrhagic shock.<sup>314</sup>

## Endocrinologic Effects of Opioids

Opioids can induce a variety of endocrinological responses (Table 24.5).<sup>315</sup> In humans, opioids generally increase growth hormone, thyroid stimulating hormone, and prolactin, and decrease luteinizing hormone, testosterone, estradiol, and oxytocin. The effects of opioids on arginine vasopressin and ACTH are conflicting. The primary endocrine disorder that results from opioid misuse is hypogonadism, particularly in males.

Hormonal and metabolic responses to surgery are often extreme and are thought to contribute to operative mortality. Opioids are capable of reducing the stress response by modulating nociception at several levels of the neuraxis, as well as by influencing centrally mediated neuroendocrine responses. The main components of the neuroendocrine stress response are the corticotropin-releasing hormone brain centers (e.g., paraventricular hypothalamic nucleus) and the locus ceruleus-norepinephrine/autonomic nervous system. Increased levels of stress hormones are considered undesirable because they promote hemodynamic instability and intraoperative and postoperative metabolic catabolism. Opioids are potent inhibitors of the pituitary-adrenal axis.<sup>316</sup> Endogenous opioid peptides may serve as stress hormones themselves and not just as modulators of other hormones' secretion. This is suggested by the finding that  $\beta$ -endorphin and ACTH are derived from the same precursor preproopiomelanocortin and cosecreted during stress.

Morphine modifies hormonal responses to surgical trauma in a dose-related fashion through blockade of ACTH release, suppression of surgically induced increases in plasma cortisol, and attenuation of the pituitary-adrenal response to surgical stress. Morphine can increase some stress-responding hormones due to increases in plasma

histamine release, adrenal medullary release mechanisms, and catecholamine release from sympathetic nerve endings.

Fentanyl and its congeners are more effective than morphine in modifying hormonal responses to surgery. The efficacy of fentanyl in controlling the hormonal manifestations of the stress response can be dose-dependent. Fentanyl doses greater than or equal to 50  $\mu$ g/kg can help to reduce the hyperglycemic response to cardiac surgery in pediatric patients to less than 200 mg/dL throughout operation.<sup>317</sup> In contrast, it has been demonstrated that neither fentanyl nor sufentanil alone can completely block sympathetic and hormonal stress responses and that perhaps no dose-response relationship exists for opioid-associated stress response control.<sup>318</sup> A randomized controlled trial showed that remifentanil (0.85  $\mu$ g/kg/min), when compared with fentanyl (total doses of 15 and 28  $\mu$ g/kg), blunts the hypertensive responses and cortisol excretion associated with cardiac surgery but is associated with more hypotension.<sup>319</sup>

### STRESS REDUCTION AND OUTCOME

Anesthetic techniques or agents that minimize the stress response may reduce morbidity and mortality in a variety of circumstances. Anand and Hickey<sup>320</sup> evaluated the impact of sufentanil versus morphine-halothane anesthesia on hormonal and metabolic responses and morbidity and mortality in neonates undergoing cardiac surgery. Most strikingly, a difference in postoperative mortality was observed (0 of 30 given sufentanil versus 4 of 15 given halothane plus morphine). Mangano et al.<sup>321</sup> also reported that, after myocardial revascularization, patients receiving intense postoperative analgesia with sufentanil (1  $\mu$ g/kg/h) experience a decrease in the incidence and severity of electrocardiographically documented ischemia compared with patients receiving intermittent IV morphine (2.2  $\pm$  2.1 mg/h) for postoperative analgesia. It was also shown that large-dose opioids (remifentanil 0.85  $\mu$ g/kg/min or fentanyl 28  $\mu$ g/kg) were associated with a decreased rate of myocardial infarction after cardiac surgery.<sup>319</sup>

Many different hormonal changes induced by surgery have been described. However, the concomitant neural, cellular, immune, and biochemical changes have been less well defined, and little is understood or proven with regard to how modifying hormonal responses alters outcome.<sup>322</sup> Additional studies are necessary for complete elucidation of the relationship between control of the surgery-induced hormonal responses and outcome.

In summary, the mechanisms underlying the ability of opioids to provide perioperative cardiovascular stability include: a reduced sympathetic tone and enhanced parasympathetic activity often producing bradycardia; minimal changes in cardiac contractility; function generally as an antiarrhythmic; potentially function as cardioprotective agents to reduce the effect of ischemia by mimicking an endogenous opioid-peptide/preconditioning pathway; have no significant effect on the coronary circulation; produce modest vascular smooth muscle relaxation with the exception of a morphine-induced histaminergic mechanism; reduce the surgical stress response through the nervous system and adrenal-pituitary axis—depending on the opioid class.

**TABLE 24.5** Summary of the Effects of Acute and Chronic Opioids on the Endocrine Systems of Animals and Humans

Hormone	ACUTE		CHRONIC	
	Animals	Humans	Animals	Humans
GH	↑	↑	=	?
PRL	↑	↑	↑	↑/=
TSH	↓	↑	?	↑/=
ACTH	↑	↓	↓/↑	↓/=
LH	↓	↓	↓	↓
FSH	=	=	=	=
Estradiol	↓	↓	=	↓=
Testosterone	↓	↓	↓	↓
AVP	↑/↓	↑/↓	↑/↓	↑/↓
OT	↓	↓	↓/=	↓/=

↑, Stimulation; ↓, inhibition; ↓↑, conflicting; =, no change; ?, not studied.

ACTH, Adrenocorticotrophic hormone; AVP, arginine vasopressin; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; OT, oxytocin; PRL, prolactin; TSH, thyroid stimulating hormone. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2852206/>

From Vuong C, Van Uum SH, O'Dell LE, et al. The effects of opioids and opioid analogs on animal and human endocrine systems. *Endocr Rev*. 2010;31:98–132.

## OPIOID TOLERANCE

The precise mechanism(s) that drive opioid dependence and tolerance are not known, however they appear to encompass a range of factors including: genetic, molecular, cellular, physiologic, and functional. In the locus ceruleus, the major noradrenergic nucleus in the brain, long-term opioid exposure results in inhibition of adenylyl cyclase, reduced activity of protein kinase A, and upregulation of the cyclic AMP pathway.<sup>323</sup> Changes in  $\mu$ -receptor density that occur prior to or during the development of tolerance do not appear to be essential for development of opioid tolerance.<sup>324</sup> Possible mechanisms involve protein kinase signal transduction cascades that link extracellular signals to cellular changes by regulating target gene expression. Central glucocorticoid receptors (GRs) have been implicated in the cellular mechanism of neuronal plasticity that has many cellular steps in common with the mechanism of opioid tolerance. It was shown that the development of tolerance to the antinociceptive effect of morphine was substantially attenuated when the GR antagonist was coadministered with morphine but the GR agonist dexamethasone facilitated the development of morphine tolerance, suggesting an important role of spinal GRs in the cellular mechanisms of morphine tolerance in rats.<sup>325</sup> Cholecystokinin and NMDA-NO system were also shown to be involved in development of acute tolerance to opioids,<sup>326</sup> which is also affected by spinal serotonin activity.<sup>327</sup> Neuroinflammation driven by chemokines may represent one of the major mechanisms underlying pathologic pain. A chemokine, CXCL1, was upregulated in both opioid-tolerant patients and rodents, and the onset and extent of opioid tolerance was affected by antagonizing intrathecal CXCL1/CXCR2 signaling.<sup>328</sup> A chemokine, CXCL12, was significantly upregulated in the cerebrospinal fluid of opioid-tolerant patients, and CXCL12 neutralizing antibody and antagonist for CXCR4, a receptor which interacts with CXCL12, attenuated morphine tolerance in rats.<sup>329</sup>

Morphine tolerance occurs more rapidly in younger rats than older rats and is unlikely to be the result of differences in drug metabolism or clearance, suggesting that aging may impact molecular processes involved in development of tolerance.<sup>330</sup> It has been suggested that activation of glial cells, including astrocytes and microglia, at the level of the spinal cord plays an important role in the development of opioid tolerance.<sup>331,332</sup> However, the mechanism for opioid-induced activation of glial cells is not completely understood.

Although the notion that opioid tolerance and dependence occur only after chronic administration has been widespread, it has now become recognized that tolerance can also develop rapidly after acute opioid exposure in animals and humans.<sup>333,334</sup> Intraoperative remifentanil infusion (0.3  $\mu$ g/kg/min) in patients undergoing major abdominal surgery under desflurane anesthesia increased postoperative pain and morphine requirement compared with low-dose remifentanil (0.1  $\mu$ g/kg/min), suggesting the development of acute remifentanil tolerance.<sup>335</sup> In contrast, there is a report that target-controlled infusion of alfentanil and remifentanil for postoperative analgesia does not lead to opioid tolerance.<sup>336</sup> In human volunteers, continuous infusion of remifentanil (0.08  $\mu$ g/kg/min) for

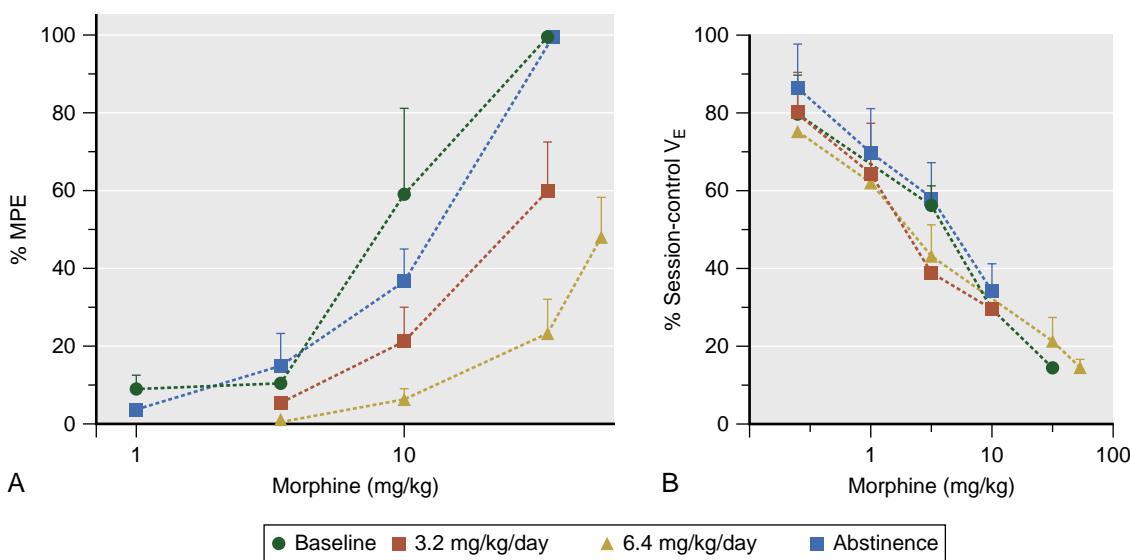
3 hours did not decrease the pain threshold.<sup>337</sup> On the other hand, intraoperative use of 0.3  $\mu$ g/kg/min remifentanil for approximately 3 hours did not induce acute tolerance, but the administration of 0.6 and 0.9  $\mu$ g/kg/min remifentanil to young children resulted in acute tolerance for 24 hours after surgery revealed by increased use of postoperative fentanyl in an apparently dose-related manner.<sup>338</sup> Differences in these outcomes may reflect divergent methodologies and limited sample size and are an area of ongoing investigation.

Differential opioid tolerance, an important phenomenon in clinical opioid pharmacology, proposes that different targets of opioid drugs do not develop tolerance at the same rate and to the same degree.<sup>339</sup> In a study using rhesus monkeys, acute morphine administration predictably induced dose-dependent analgesia, and chronic morphine administration induced dose-dependent tolerance to the analgesic effect, while no tolerance development to the respiratory depressive effect could be demonstrated in the chronically opioid-treated animals (Fig. 24.14).<sup>340</sup> In humans, patients receiving chronic opioids for pain control, especially at high doses, most likely have developed opioid tolerance. However, there is little data to help predict the magnitude or clinical impact of an individual's loss of opioid-induced analgesia or potentially their resistance/vulnerability to the respiratory depressive effects of opioids. As discussed later, individuals chronically consuming opioids are dose dependently at increased risk for overdose and death.

## MANAGEMENT OF OPIOID-DEPENDENT PATIENTS

A variety of problems should be taken into consideration for anesthetic management of opioid-dependent patients or patients suffering from opioid use disorder (OUD).<sup>341</sup> Complications in opioid-addicted patients include cardiopulmonary problems, renal problems, and anemia. Long-term morphine administration causes adrenal hypertrophy and impairs corticosteroid secretion. Viral and nonviral hepatitis, acquired immunodeficiency syndrome, osteomyelitis, muscle weakness, and neurologic complications may be found in patients suffering from OUD or poly substance use disorder. As it is common to underestimate and under-treat pain in opioid-dependent patients, it is important to identify the goals in their acute pain management (Box 24.3).<sup>342</sup> Anesthetic management for the opioid-dependent or patient with OUD should include adequate premedication with opioids, administration of supplemental intraoperative and postoperative opioids, and providing nonopioid analgesics and neural blockade. There is no ideal anesthetic agent or technique to employ in the patient with OUD or in the patient with an acute opioid overdose—with the possible exception of judicious use of an opioid antagonist as indicated. As mentioned previously, combined techniques utilizing regional anesthetic approaches, as well as concurrent use of low-dose ketamine and  $\alpha$ 2-agonists have been successful. Support of the circulatory system with fluids and monitoring of arterial blood gases and pulmonary function are essential.

Owing to the high risk of relapse, overdose, and death in individuals with OUD, medication-assisted treatment (MAT) in which opioids with different pharmacokinetic



**Fig. 24.14 The effects of chronic opioid administration on analgesia and respiratory response in rhesus monkeys.** The animals were studied under baseline conditions, after receiving 3.2 or 6.4 mg/kg/day for 4 weeks, and after abstinence. After each treatment course, they were challenged with various doses of morphine, and analgesic and respiratory responses were assessed. Analgesic effects were assessed by tail withdrawal latency and shown as percentage of maximum possible effect (MPE); respiratory depression was shown as decrease in minute ventilation ( $V_E$ ). The results show development of reversible tolerance to the analgesic effects of opioids (A), but no tolerance development to the respiratory depression (B). (From Paronis CA, Woods JH. Ventilation in morphine-maintained rhesus monkeys. *ii: tolerance to the antinociceptive but not the ventilatory effects of morphine*. *J Pharmacol Exp Ther*. 1997;282:355–362.)

### BOX 24.3 Goals of Acute Pain Management in Opioid-Dependent Patients

1. Identification of the population of at-risk patients receiving long-term opioid therapy for various chronic pain situations (musculoskeletal disease, neuropathic conditions, sickle cell disease, HIV-related disease, palliative care), persons recovering in opioid maintenance programs
2. Prevention of withdrawal symptoms and complications
3. Symptomatic treatment of psychological affective disorders such as anxiety
4. Effective analgesic treatment in the acute phase
5. Rehabilitation to an acceptable and suitable maintenance opioid therapy

HIV, Human immunodeficiency virus.

and pharmacodynamic properties such as methadone or buprenorphine are commonly prescribed. Because of the injection-deterring potential of naloxone hydrochloride and a better safety profile compared with methadone, daily administration of combined buprenorphine and naloxone is becoming a first-line choice for MAT in a number of countries.<sup>343</sup> Other treatment approaches have emerged including rapid opioid detoxification with high-dose naloxone or naltrexone. For this treatment, general anesthesia is induced before the start of opioid antagonization and maintained for several hours to prevent perception of withdrawal symptoms by the patient.<sup>344,345</sup> Blockade of  $\mu$ -opioid receptors by naloxone (total dose of 12.4 mg) in opioid-addicted patients induces sympathetic neural activation, including increase in plasma catecholamine concentration and cardiovascular stimulation, which can be managed in part by  $\alpha_2$ -agonists.<sup>346</sup> Long-term opioid abstinence is not guaranteed, even with an ongoing program that includes MAT,

given the neurobiology, societal factors involved in addiction, and potential for repeat exposure—often medically in the perioperative period.<sup>347</sup>

### Renal and Urodynamic Effects of Opioids

Opioids can have significant effects on renal function.  $\mu$ -receptor activation causes antidiuresis and decreases electrolyte excretion.  $\kappa$ -receptor stimulation predominantly produces diuresis with little change in electrolyte excretion. Indirect actions may involve inhibiting or altering the secretion of ADH and atrial natriuretic peptide. The absence of increases in plasma ADH, renin, and aldosterone indicate that fentanyl, sufentanil, alfentanil, and probably remifentanil most likely preserve or minimally alter renal function in humans. If renal function does change during opioid anesthesia and surgery, it is probably due to secondary changes in systemic and renal hemodynamics.

The mechanism by which opioids cause urinary retention is incompletely understood. Opioid effects on the lower urinary tract include disturbances of micturition characterized by urinary retention, especially after intrathecal opioid administration. Intrathecal administration of morphine and sufentanil caused dose-dependent suppression of detrusor contractility and decreased sensation of urge.<sup>348</sup> Mean times to recovery of normal lower urinary tract function were 5 and 8 hours after 10 or 30  $\mu$ g sufentanil and 14 and 20 hours after 0.1 or 0.3 mg morphine, respectively. Not all opioid agonists behave similarly, and morphine appears to be particularly potent with regard to producing urodynamic problems. Malinovsky et al. compared urodynamic effects of intravenously administered morphine (10 mg), buprenorphine (0.3 mg), fentanyl (0.35 mg), and

nalbuphine (20 mg).<sup>349</sup> It was shown that all of the opioids altered bladder sensations, but that detrusor contraction decreased only after administration of fentanyl and buprenorphine. Urinary retention induced by intravenous infusion of remifentanil, 0.15 µg/kg/min could be reversed by a single intravenous dose of methylnaltrexone 0.3 mg/kg or naloxone 0.01 mg/kg.<sup>350</sup> Reversal of urinary retention by methylnaltrexone indicates that peripheral mechanisms may play a role in opioid-induced bladder dysfunction.

A retrospective study for adult patients with chronic kidney disease undergoing orthopedic surgery estimated glomerular filtration rate during the postoperative period was significantly higher in the group in which remifentanil was used for anesthesia management than the group in which remifentanil was not used. This finding may suggest that anesthesia management using remifentanil may have a renal protective effect in adult patients with chronic kidney disease.<sup>351</sup>

## Effects of Opioids on Digestive Organs

### EFFECTS ON GASTROINTESTINAL TRACT

The adverse gastrointestinal effects of exogenous opioid treatment include nausea, vomiting, altered fluid dynamics, inhibited gastric emptying, inhibited intestinal coordinated propulsive activity, and increased transit time, all of which may contribute to postoperative ileus (Table 24.6).<sup>352</sup> Opioid-dependent mechanisms driving these effects are complex and those involving GI motility are believed to involve opioid receptors expressed throughout the myenteric plexus. Several opioid receptor types can be demonstrated on myenteric neurons, and both  $\kappa$ - and  $\mu$ -receptor agonists regulate cholinergic transmission in the myenteric plexus.  $\kappa$ -Agonists appear to modulate acetylcholine release more potently than  $\mu$ -agonists by inhibition of N-type voltage-sensitive  $\text{Ca}^{2+}$  channels via a pertussis toxin-sensitive G protein in guinea pig ileum.<sup>353</sup>

**TABLE 24.6** Effects of Opioids on the Gastrointestinal Tract

Pharmacologic Action	Clinical Effect
Decreased gastric motility and emptying	Decreased appetite; increased gastroesophageal reflux
Decreased pyloric tone	Nausea and vomiting
Decreased enzymatic secretion	Delayed digestion; hard, dry stools
Inhibition of small and large bowel propulsion	Delayed absorption of medication; straining; incomplete evacuation; bloating; abdominal distension; constipation
Increased fluid and electrolyte absorption	Hard, dry stools
Increased nonpropulsive segmental contractions	Spasms; abdominal cramps; pain
Increased anal sphincter tone	Incomplete evacuation

From Viscusi ER, Gan TJ, Leslie JB, et al. Peripherally acting mu-opioid receptor antagonists and postoperative ileus: mechanisms of action and clinical applicability. *Anesth Analg*. 2009;108:1811–1822.

The effect of morphine on esophageal motility has been little explored. Morphine (80 µg/kg) increased the velocity but did not alter the amplitude or duration of primary peristalsis of the esophagus, and it decreased the duration and magnitude of swallow-induced lower esophageal sphincter relaxation.<sup>354</sup> Gastric emptying is delayed by opioids, via supraspinal (vagus nerve-mediated) and spinal, as well as peripheral, mechanisms. Intrathecal morphine (0.4 mg) significantly decreased the gastroduodenal propagation velocity and acetaminophen absorption, and intramuscular morphine (4 mg) gave additional effects.<sup>355</sup> Tramadol (1.25 mg/kg IV) has a measurable but smaller inhibitory effect on gastric emptying compared with codeine (1 mg/kg IV) or morphine (0.125 mg/kg IV).<sup>356</sup> Opioids administered epidurally as well as intrathecally reduce gastrointestinal motility.<sup>355</sup> It was reported that translocation of enteric microorganisms from the intestinal tract to extraintestinal sites is promoted by reduction of gut propulsion after morphine treatment in rats.<sup>357</sup> Propofol (0.3 mg/kg bolus and 1.0 mg/kg/h) abolished the decrease of gastric tone induced by morphine (0.1 mg/kg intravenously), but did not abolish morphine-induced delay of gastric emptying.<sup>358</sup>

Naloxone reverses opioid-induced delays in gastric emptying. Methylnaltrexone, a quaternary naloxone derivative that does not cross the blood-brain barrier, can attenuate morphine-induced delays in gastric emptying, suggesting that a peripheral mechanism is involved in the opioid effect on gastrointestinal tract.<sup>359</sup> Naloxone (0.7 mg/kg) significantly inhibited gastric emptying of saline and milk in rats.<sup>360</sup> This observation might suggest that opioids can affect the gastrointestinal tract by a mechanism independent from the opioid receptors. Intravenous, but not intramuscular, metoclopramide (10 mg) also can reverse morphine-induced delays in gastric emptying.<sup>361</sup>

Opioid effects on the intestine are complex. Transit time from mouth to ileum may not be significantly altered by morphine, because morphine enhances ileal propulsion before decreasing motility. Opioids increase tone and decrease propulsive activity in most of the intestine. Constipation is the frequent side effect in patients who are administered opioids. Naloxonazine attenuated the fentanyl-induced inhibition of gastrointestinal transit more potently than the inhibition induced by morphine or oxycodone. Naloxone methiodide suppressed the oxycodone-induced inhibition of gastrointestinal transit more potently than the inhibition induced by morphine.<sup>362</sup> Thus,  $\mu$ -opioid receptor agonists induce the inhibition of gastrointestinal transit and drive constipation through different mechanisms.

### BILIARY AND HEPATIC EFFECTS

Opioid agonists increase biliary duct pressure and sphincter of Oddi (choledochoduodenal sphincter) tone in a dose- and drug-dependent manner through opioid receptor-mediated mechanisms. However, the clinical consequences of opioid-induced biliary tract actions are usually minimal. Although traditional teaching dictates that morphine induces “spasm” in the sphincter of Oddi and should not be used in acute pancreatitis, no studies or evidence exist to indicate morphine is contraindicated for use in acute pancreatitis.<sup>363</sup> Increases in biliary pressure caused by opioids are, with the exception of meperidine, reversible with naloxone.

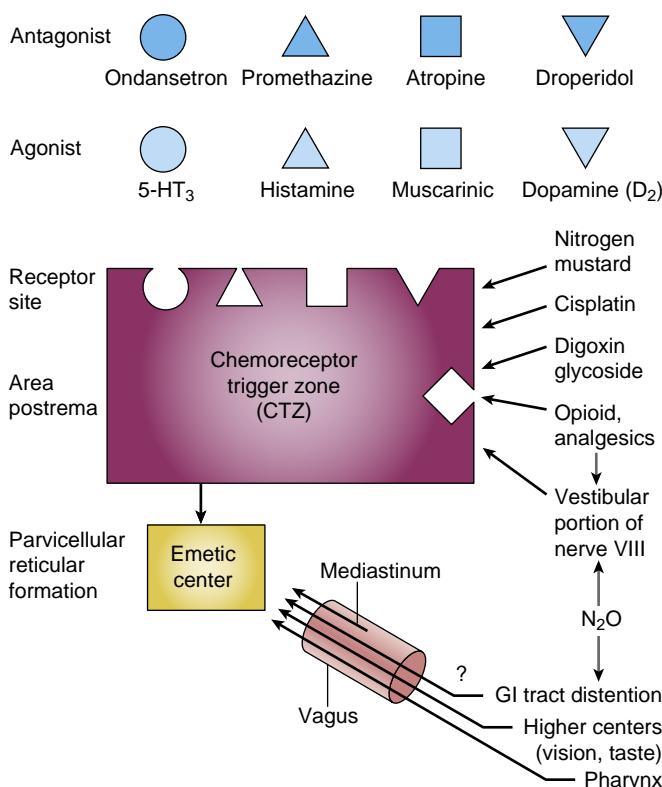
Oddi's sphincter manometry via choledochoscopy demonstrated that the regular dose of morphine could increase common bile duct pressure, whereas pethidine had no effect on Oddi's sphincter motility and tramadol shows inhibited motility of the sphincter of Oddi.<sup>364</sup> Fragen et al. studied the effect of remifentanil (0.1 mg/kg/min) on the flow of dye from the gall bladder into the duodenum, and showed that remifentanil delays the drainage of dye from the gall bladder into the duodenum, but the delay is shorter than that reported after morphine or meperidine.<sup>365</sup>

Opioids produce minimal effects on liver function during anesthesia and surgery but can affect ischemia-reperfusion injury. Remifentanil pretreatment can attenuate liver injury induced by ischemia-reperfusion, which was shown to be mediated by inducible NO synthase expression and exhausting reactive oxygen species but does not involve opioid receptors.<sup>366</sup> Morphine administered either intravenously or intrathecally 10 minutes before 1 hour of ischemia protects against ischemia-reperfusion injury after 6 hours of reperfusion in both normal and cirrhotic rat liver by a mechanism involving the opioid receptor.<sup>367</sup> Remifentanil significantly attenuated increases in serum aminotransferase levels and the liver histological changes induced by ischemia-reperfusion injury of the liver in rats, by a mechanism possibly involving hepatic interleukin-18.<sup>368</sup> These reports might suggest the beneficial effects of opioids in anesthetic management of liver surgery.

## NAUSEA AND VOMITING

Postoperative nausea and vomiting are serious problems which often embarrass anesthesiologists. Etiology, treatment, and prevention of PONV have been extensively investigated (Fig. 24.15).<sup>369</sup> Intraoperative use of opioids is a well-known risk factor for PONV.<sup>370</sup> Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla possibly through  $\delta$ -receptors, leading to nausea and vomiting. Alfentanil, compared with approximately equipotent doses of fentanyl and sufentanil, was found in one study to be associated with a lower incidence of PONV.<sup>371</sup>

The use of propofol in balanced or total IV anesthesia (TIVA) significantly reduces the incidence of opioid-induced nausea and vomiting. When opioids are employed, antiemetic prophylaxis should be considered, which includes drugs with anticholinergic activity, butyrophenones, dopamine antagonists, serotonin antagonists and acupressure. Ondansetron, a serotonin type 3 (5-HT<sub>3</sub>) receptor antagonist, was proved to be effective for postoperative opioid-induced nausea and vomiting.<sup>372</sup> A meta-analysis concluded that prophylactic use of 5-HT<sub>3</sub> receptor antagonists significantly reduced the incidence of PONV and the need of rescue antiemetic therapy in parturients who received intrathecal morphine for cesarean delivery.<sup>204</sup> Nausea and vomiting after epidural morphine (3 mg) for postcesarean section analgesia could be prevented by dexamethasone (8 mg IV) as efficiently as droperidol (1.25 mg IV).<sup>373</sup> Cannabinoid receptor agonists have been demonstrated to be effective antiemetics in some clinical settings. Animal experiments have shown that the cannabinoid agonist suppresses opioid-induced retching and vomiting by activation of the cannabinoid CB1 receptor.<sup>374</sup> A continuous low-dose naloxone infusion (0.25  $\mu$ g/kg/h) ameliorates some



**Fig. 24.15** The chemoreceptor trigger zone and the emetic center with the agonist and antagonist sites of action of various anesthetic-related agents and stimuli. GI, Gastrointestinal. (From Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. *Anesthesiology*. 1992;77:162–184.)

of the opioid-induced side effects, including nausea, vomiting, and pruritus, in many but not all patients without adversely affecting analgesia.<sup>375</sup> Transdermal scopolamine was shown to be effective for prophylactic use in parturients receiving intrathecal morphine while undergoing cesarean delivery but was associated with higher incidence of side effects such as dry mouth and blurry vision.<sup>376</sup>

Taken together, the prevention and/or treatment of opioid-induced nausea and vomiting continues to be a clinical challenge. Strategies that include the administration of 5-HT<sub>3</sub> receptor antagonists and/or the steroid dexamethasone show efficacy in well controlled trials. However, such approaches require exposure to additional medications that, in themselves, may carry additional risks of side effects.

## Other Opioid Effects

### OBSTETRICS

The parenteral administration of opioids for oocyte retrieval and prior to delivery remains a commonly used method of analgesia.

Alfentanil and pethidine have been safely used as analgesics during the harvesting of human oocytes for subsequent *in vitro* fertilization.<sup>377</sup> Teratogenic actions of opioids, including fentanyl, sufentanil, and alfentanil, at least in animal models, appear to be minimal. Nociception due to uterine cervical distension could be suppressed by  $\mu$ - and

$\kappa$ -agonists in rats,<sup>378</sup> but the analgesic effect of  $\mu$ -agonist but not  $\kappa$ -agonist was reduced by estrogen.<sup>379</sup> Aortocaval compression and associated hypotension may be exacerbated by parenteral opioids, especially following morphine or meperidine. Fetal manifestations of maternal opioid administration include decreases in heart rate variability. Adverse neonatal effects can occur after either morphine or meperidine administration to mothers. Fetal acidosis increases opioid transfer from the mother. Attempts to minimize neonatal effects of opioids include restricting opioid administration to the first stage of labor. The short-acting opioid alfentanil administered before cesarean delivery attenuated the maternal stress response, but led to slightly reduced Apgar score.<sup>380</sup> In a randomized, double-blind, controlled study, it was shown that a single bolus of 1  $\mu$ g/kg remifentanil administered to patients undergoing elective cesarean delivery effectively attenuated hemodynamic changes after induction and tracheal intubation, but remifentanil crosses the placenta and may cause mild neonatal depression.<sup>381</sup>

Because the fetus is capable of pain perception after the 26th week of gestation, adequate postoperative fetal pain management is essential after fetal surgery. It was shown that the sheep fetus absorbs sufentanil after intraamniotic instillation, and that significantly greater plasma concentrations were obtained in the fetal lamb as compared with the mother sheep.<sup>382</sup>

Morphine and meperidine have been found in the breast milk of mothers receiving intravenous opioid analgesia.<sup>383,384</sup> Although both fentanyl and morphine are concentrated in breast milk in milk-to-plasma ratios of 2 to 3:1, newborn exposure is reported to be insignificant. Newborns of mothers with OUD or taking prescription opioids can exhibit opioid withdrawal often referred to as neonatal abstinence syndrome (NAS) and require appropriate treatment and observation.<sup>385,386</sup>

## ANAPHYLACTOID REACTIONS

True allergic reactions and systemic anaphylactoid reactions to opioids are rare. More commonly, local reactions caused by preservatives or histamine may occur. In 32% of heroin addicts dying suddenly after injection, the concentration of tryptase was elevated ( $>10$   $\mu$ g/L), but no correlation was found between the IgE levels and tryptase, supporting the hypothesis that mast cell degranulation was not mediated by allergic reaction.<sup>387</sup> This report suggests that heroin fatalities may be in part driven by anaphylactoid reaction.

## OCULAR EFFECTS

The use of fentanyl, sufentanil, and alfentanil during induction of anesthesia can help to prevent increases in intraocular pressure. Fentanyl, alfentanil, and sufentanil doses as small as 2.5, 10, and 0.1  $\mu$ g/kg, respectively, may be sufficient as long as appropriate anesthetic depth is achieved prior to tracheal intubation. Remifentanil (1  $\mu$ g/kg) combined with propofol (2 mg/kg) or thiopental (5 mg/kg) was reported to be effective for prevention of intraocular pressure change after succinylcholine and tracheal intubation.<sup>388,389</sup>

## IMMUNE EFFECTS

Opioids can affect immune function through adaptive immunity, innate immunity, and neuroendocrine system (Box 24.4).<sup>390</sup> The literature investigating the function of classical opioid receptors ( $\mu$ ,  $\delta$ , and  $\kappa$ ) present on immune cells suggest a complex relationship between clinically used opioids and immune function, including through indirect mechanisms. However, because the  $\mu$ -opioid receptor knockout mice showed no immune modulatory effects after central administration of opioids, the central immune modulatory effect of opioids is mediated by  $\mu$ -opioid receptors.<sup>391</sup>

It was shown that the maximal suppression of natural killer (NK) cell activity, proliferation of splenic T and B cells, and interferon- $\gamma$  production are observed 0.5 to 1 hour after 15 mg/kg morphine injection in rats.<sup>392</sup> The time course

### BOX 24.4 Opioid Effects on Immunity

#### Adaptive Immunity

- ↓ Splenic and thymic weight (rodents)
- ↓ T cell viability and proliferative response
- ↓ T-helper cell function
- ↓ CD4/CD8 population *in vivo*
- ↓ IL1 $\beta$ , IL-2, TNF- $\alpha$ , and IFN- $\gamma$  (mouse splenocytes)
- ↓ Th1/Th2 ratio of T-helper cell population (PBMCs)
- ↓ NK cell activity
- ↓ Primary antibody response (B cells)
- ↓ B cells mitogenic response to bacterial LPS
- ↓ Macrophage activity
- ↓ TGF- $\beta$ 1 and IL-10 (antiinflammatory cytokines)
- ↑ T cell apoptosis (NF- $\kappa$ B and AP-1/NFAT pathways)
- Inhibition of CD3/28 mAb induced IL-2 transcripts

#### Innate Immunity

- ↓ Number of macrophages available to fight infections
- ↓ Leucocyte migration
- ↓ Peritoneal macrophages phagocytosis
- ↓ Respiratory burst activity and chemotaxis
- Inhibition of Fc  $\gamma$  receptor mediated phagocytosis
- ↓ Superoxide production from neutrophils and macrophages
- Alteration of IL-8 induced neutrophil chemotaxis
- ↓ Neutrophil cytokines involved in wound healing
- ↑ Apoptosis of macrophages impairing host defense barrier
- ↓ Leucocytes endothelial adhesion (intracellular adhesion molecules expression)

#### Neuroendocrine System

- ↑ Growth hormone, prolactin, and thyroid stimulating hormone secretion in humans
- May affect the function of the HPA axis (ACTH and CRH) with risk of adrenal insufficiency
- ↓ Sex hormones [LH and testosterone (hypogonadism)], oxytocin, and estradiol

ACTH, Adrenocortotropic hormone; AP-1, activator protein 1; CRH, corticotropin releasing hormone; Fc, fragment crystallizable region; HPA, hypothalamic pituitary adrenal axis; IL, interleukin; IFN- $\gamma$ , interferon-gamma; LH, luteinizing hormone; LPS, lipopolysaccharides; NF- $\kappa$ B, nuclear factor kappa beta; NFAT, nuclear factor of activated T-cells; NK, natural killer; PBMC, peripheral blood mononuclear cell; TGF- $\beta$ , transforming growth factor beta; TNF- $\alpha$ , tumor necrosis factor-alpha.

From Al-Hashimi M, Scott SW, Thompson JP, Lambert DG. Opioids and immune modulation: more questions than answers. *Br J Anaesth*. 2013;111:80-88.

was nearly concordant with the antinociceptive effect of morphine. Postoperative administration of morphine (10 mg IM) did not significantly affect the NK cell activity, while tramadol (100 mg IM) enhanced NK cell activity.<sup>393</sup> It was reported that intravenously administered fentanyl causes a rapid increase in NK cell cytotoxicity, which was coincident with an increase in the percentage of CD16<sup>+</sup> and CD8<sup>+</sup> cells in peripheral blood.<sup>394</sup> Compared with fentanyl (1000 µg), administration of morphine (40 mg) as part of balanced anesthetic technique suppressed several components of the inflammatory response (IL-6, CD11b, CD18, postoperative hyperthermia) to cardiac surgery and cardiopulmonary bypass.<sup>395</sup>

As a potential mechanism for the immunosuppressive effects of morphine, it was demonstrated that NF-κB activation induced by an inflammatory stimulus was inhibited by morphine-induced activation of  $\mu_3$ -opioid receptors in a NO-dependent manner.<sup>396</sup> Several investigators have independently reported direct effects of morphine on apoptosis in cultured human peripheral blood lymphocytes, which may result in compromising immune functions.<sup>397</sup> However, there is also a report that morphine has no effect on apoptosis-related molecules and does not promote apoptosis of human peripheral blood lymphocytes.<sup>398</sup>

With respect to the effects of opioids on neutrophils, it was reported that remifentanil, but not sufentanil, alfentanil, or fentanyl, could attenuate activation of human neutrophils exposed to lipopolysaccharides, and decreased activation of intracellular signaling pathways, including p38 and ERK1/2, and expression of proinflammatory cytokines, including TNF-α, IL-6, and IL-8, through a mechanism involving the κ-opioid receptor.<sup>399</sup> It was also reported that remifentanil attenuates lipopolysaccharide-induced acute lung injury by inhibition of proinflammatory cytokine production by downregulating the NF-κB pathway, suggesting a beneficial effect of remifentanil in acute lung injury or acute respiratory distress syndrome in sepsis.<sup>400</sup>

A prospective study for adult patients who underwent elective colorectal surgery demonstrated that the number of patients who developed surgical site infection was higher after remifentanil-based anesthesia (11.6%) compared with fentanyl-based anesthesia (3.4%).<sup>401</sup> A possible reason for this finding may be opioid-induced immunosuppression or opioid withdrawal-induced immunosuppression.

## CANCER PROGRESSION

Epidemiological studies have suggested that patients who receive general anesthesia with opioids have a greater rate of cancer recurrence than patients who receive local or regional anesthetics,<sup>402</sup> although there is no direct evidence to support altering anesthetic technique in cancer patients. Opioids may directly stimulate proliferation and invasion of tumor cells and inhibit apoptosis of tumor cells, or indirectly affect cancer recurrence by immunosuppression.<sup>403</sup> Overexpression of the  $\mu$ -opioid receptor in human non-small cell lung cancer was suggested to promote tumor growth and progression.<sup>404</sup> Furthermore, it was reported that women with A118G genotype of the  $\mu$ -opioid receptor have decreased breast cancer-specific mortality, suggesting that opioid pathways may be involved in tumor growth.<sup>405</sup> Drawing from preclinical studies using animals or cultured cells

opioids may promote tumor growth and metastasis through multiple mechanisms, whereas it is also reported that opioids can direct various anticarcinogenic pathways (Fig. 24.16).<sup>406</sup> Preclinical data have also suggested that  $\mu$ -opioid receptor inhibition can reverse the adverse effect of  $\mu$ -opioid receptor signaling on cancer progression, when a combination of methylnaltrexone, which blocks peripheral but not central  $\mu$ -opioid receptor, and chemotherapy is tested.<sup>407</sup>

One of the mechanisms involved in the effects of opioids on cancer prognosis is their effects on angiogenesis. Morphine can stimulate angiogenesis by a variety of mechanisms involving NO, MAPK, VEGF, and Rho/Rho kinase.<sup>408</sup> Blebea et al. reported that activation of opioid receptors inhibited angiogenesis, via endogenous opioid ligands.<sup>409</sup> Although both pro- and anti-angiogenic actions of opioids have been reported, it is generally believed that the proangiogenic (or neo-vasculogenic) effects predominate.

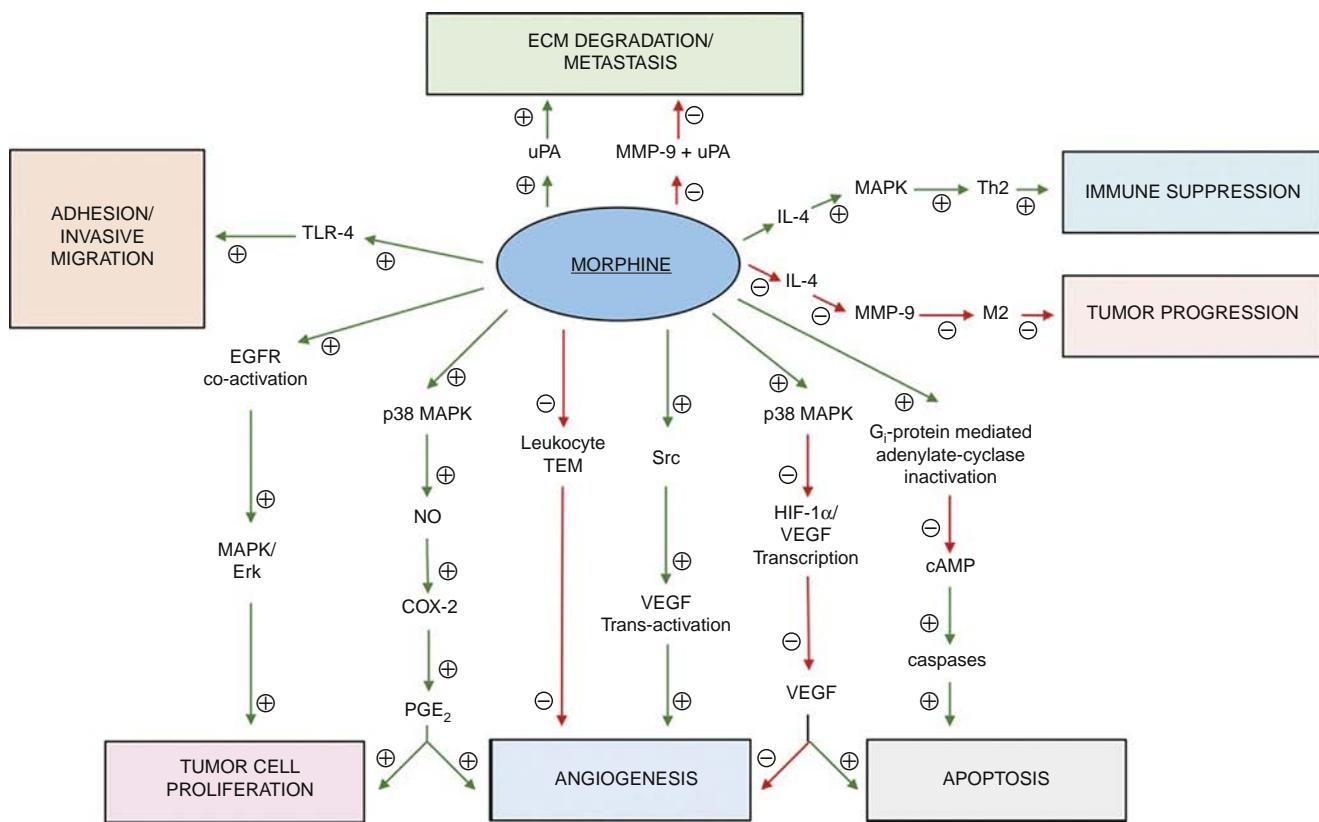
The opioid growth factor receptor (OGFR) is localized in both the nucleus and the cytoplasm and functions as a receptor for OGF, also known as methionine-enkephalin. OGFR is distinguished from classic opioid receptors ( $\mu$ ,  $\delta$ , and  $\kappa$ ) as not having any role in analgesia but functions as a negative regulator of cell proliferation. Morphine can also interact with OGFR expressed in lung cancer tissues and cell lines and may suppress lung cancer progression.<sup>410</sup>

## WOUND HEALING

Topical application of opioids has been explored as a strategy for reducing pain associated with cutaneous wounds. In addition to its analgesic functions, the peripheral opioid receptor system affects skin homeostasis by influencing cell differentiation, migration, and adhesion. Activation of peripheral opioid receptors on primary afferent neurons reduces the excitability of these neurons and suppresses the antidromic release of substance P and calcitonin gene-related peptide, which play an essential role in wound repair. It was shown that topical morphine application significantly reduced the number of myofibroblasts and macrophages in the closing wound.<sup>411</sup> These findings might limit the topical application of opioids as an analgesic therapeutic strategy in the treatment of painful cutaneous wounds. In contrast, it was shown that activation of the  $\delta$ -opioid receptors destabilizes intercellular adhesion and promotes the migratory keratinocyte phenotype, which is required for fast wound closure.<sup>412</sup> If these divergent findings can be resolved in favor of wound healing and enhanced localized analgesia, there is great potential for opioid applications in wound healing. Most clinical studies have not focused on opioid effects on the wound healing process but substantial analgesic effects without delaying wound closure were found. Larger clinical trials are required to examine whether opioids interfere with wound healing by inhibition of proinflammatory cytokine release or by development of hypertrophic scars, as shown in animal studies.<sup>413</sup>

## Pharmacokinetics and Pharmacodynamics of Opioids

With the advent of modern drug assay technology and the widespread availability of computers, it is now possible to



**Fig. 24.16 Effects of morphine on cancer cells.** It is important to note that the same pathway can have opposing end results, depending on the morphine doses, mode of administration, and animal models used. *cAMP*, Cyclic adenosine monophosphate; *COX-2*, cyclooxygenase-2; *ECM*, extracellular matrix; *EGFR*, epidermal growth factor receptor; *Erk*, extracellular-regulated kinase; *HIF-1 $\alpha$* , hypoxia inducible factor 1 alpha; *IL*, interleukin; *M2*, “alternative” activation of macrophages; *MAPK*, mitogen-activated protein kinase; *MMPs*, matrix metalloproteinases; *NO*, nitric oxide; *PGE<sub>2</sub>*, Prostaglandin E<sub>2</sub>; *Src*, non-receptor tyrosine kinase; *TLR-4*, toll-like receptor 4; *Th2*, T helper 2 cells; *uPA*, urokinase plasminogen activator; *VEGF*, vascular endothelial growth factor. (From Sekandarzad MW, van Zundert AAJ, Lirk PB, et al. Perioperative anesthesia care and tumor progression. *Anesth Analg*. 2017;124:1697–1708.)

analyze and model pharmacologic data which separates drug response into pharmacokinetic and pharmacodynamic components. Pharmacokinetic parameters govern the relationship between opioid dose and the opioid concentrations in the blood (or other body fluids). Pharmacodynamic parameters describe the relationship between opioid concentration in blood (or other fluids) and opioid effect.

Computer simulation techniques predict “context-sensitive half-times,” the time necessary to achieve a 50% decrease in drug concentration after termination of a variable-length continuous infusion to a steady-state drug level (see Chapter 26). Such simulations are intended to provide more clinically relevant meaning to pharmacokinetic parameters. The context-sensitive half-time and computer simulations have helped clinicians to select opioids in a more rational fashion. After 1-hour continuous infusion, the context-sensitive half-time of fentanyl is nearly six times that of alfentanil or sufentanil. Remifentanil’s context-sensitive half-time is independent of infusion duration.

## PHYSICOCHEMICAL PROPERTIES

Opioids are weak bases. When dissolved in solution, they are dissociated into protonated and free-base fractions, with the relative proportions depending on the pH and pKa. The free-base fraction is more lipid-soluble than the

protonated fraction. High lipid solubility facilitates opioid transport into the biophase or site of action. Therefore, highly lipid-soluble opioids have a more rapid onset of action. However, because the opioid receptor recognizes an opioid molecule in the protonated form, the intensity of opioid effects is closely related to the ionized concentration of drug in the biophase.

All opioids are to some extent bound to plasma proteins, including albumin and  $\alpha_1$ -acid glycoprotein. It is only the un-ionized, unbound fraction that constitutes the diffusible fraction and provides the concentration gradient that promotes diffusion of opioid from the blood to the tissue of interest. Thus, the speed of onset of opioid effect is affected by both the lipid solubility and the protein binding.

## PHARMACOKINETIC FEATURES OF INDIVIDUAL DRUGS

Representative pharmacokinetic parameters for the opioids commonly used in anesthesia are displayed in Table 24.7.

### Morphine

Morphine pharmacokinetics is notably different from that of the fentanyl congeners. This difference is in large part due to morphine’s comparatively low lipid solubility. There is relatively little transient first-pass uptake

**TABLE 24.7** Physicochemical and Pharmacokinetic Data of Commonly Used Opioid Agonists

	<b>Morphine</b>	<b>Fentanyl</b>	<b>Sufentanil</b>	<b>Alfentanil</b>	<b>Remifentanil</b>
pKa	8.0	8.4	8.0	6.5	7.1
% Un-ionized at pH 7.4	23	<10	20	90	67?
Octanol/H <sub>2</sub> O partition coefficient	1.4	813	1778	145	17.9
% Bound to plasma protein	20-40	84	93	92	80?
Diffusible fraction (%)	16.8	1.5	1.6	8.0	13.3?
t <sub>1/2α</sub> (min)	1-2.5	1-2	1-2	1-3	0.5-1.5
t <sub>1/2β</sub> (min)	10-20	10-30	15-20	4-17	5-8
t <sub>1/2γ</sub> (h)	2-4	2-4	2-3	1-2	0.7-1.2
Vd <sub>c</sub> (L/kg)	0.1-0.4	0.4-1.0	0.2	0.1-0.3	0.06-0.08
Vd <sub>ss</sub> (L/kg)	3-5	3-5	2.5-3.0	0.4-1.0	0.2-0.3
Clearance (mL/min/kg)	15-30	10-20	10-15	4-9	30-40
Hepatic extraction ratio	0.6-0.8	0.8-1.0	0.7-0.9	0.3-0.5	NA

NA, Not applicable; pKa, ion dissociation constant; t<sub>1/2</sub> α, β, γ, half-lives of a three-compartment model; Vd<sub>c</sub>, volume of distribution of the central compartment; Vd<sub>ss</sub>, volume of distribution at steady state.

From Bailey PL, Egan TD, Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia*. 8th ed. Philadelphia: Saunders; 2015. An imprint of Elsevier Inc., p. 887.

of morphine by the lung. The pKa of morphine (8.0) is greater than physiologic pH, and thus after intravenous injection only a small fraction (10%-20%) of morphine is un-ionized. Penetration of morphine into and out of the brain is presumably slower compared with that of other opioids. Approximately 20% to 40% of morphine is bound to plasma proteins, mostly albumin.

Morphine is principally metabolized by conjugation in the liver, but the kidney plays a key role in the extrahepatic metabolism of morphine. M3G is the major metabolite of morphine, but does not bind to opioid receptors and possesses little or no analgesic activity. M3G may actually antagonize morphine, and this effect may contribute to both variability in response and resistance to morphine analgesic therapy. M3G was reported to produce seizures in animals and cause allodynia in children.<sup>414</sup> M6G accounts for nearly 10% of morphine metabolite and is a more potent μ-receptor agonist than morphine with a similar duration of action. It was reported that M6G contributes substantially to morphine's analgesic effects even in patients with normal renal function.<sup>415</sup> A recent study reported that based on area under the concentration–time curve there was a major contribution of M6G to the overall analgesic effect; the mean contributions being estimated as 96.6%, 85.6%, 85.4%, and 91.3% after oral, subcutaneous, intravenous, and rectal administration of morphine, respectively.<sup>416</sup> In patients with renal insufficiency, 97.6% of the analgesic effect is caused by M6G when morphine is given orally. Especially in patients with renal dysfunction, the accumulation of M6G can lead to an increased incidence of adverse effects, including respiratory depression. Except for renal function, M6G accumulation was shown to be affected by transmembrane transporters inhibited by probenecid.<sup>417</sup> M6G can induce respiratory depression similarly as morphine, but the site of action in the ventilatory control system might be different between M6G and morphine.<sup>418</sup> It was suggested that SNP at the μ-opioid receptor affects the susceptibility to

M6G-related opioid toxicity.<sup>419</sup> Because the hepatic extraction ratio of morphine is high, the bioavailability of orally administered morphine is significantly lower (20%-30%) than after intramuscular or subcutaneous injection. It appears that M6G is in fact the primary active compound when morphine is administered orally (Fig. 24.17).<sup>420</sup> In contrast to the reports suggesting the high potency of M6G, there have been reports showing that short-term intravenous administration of M6G does not provide effective analgesia.<sup>421</sup>

### Fentanyl

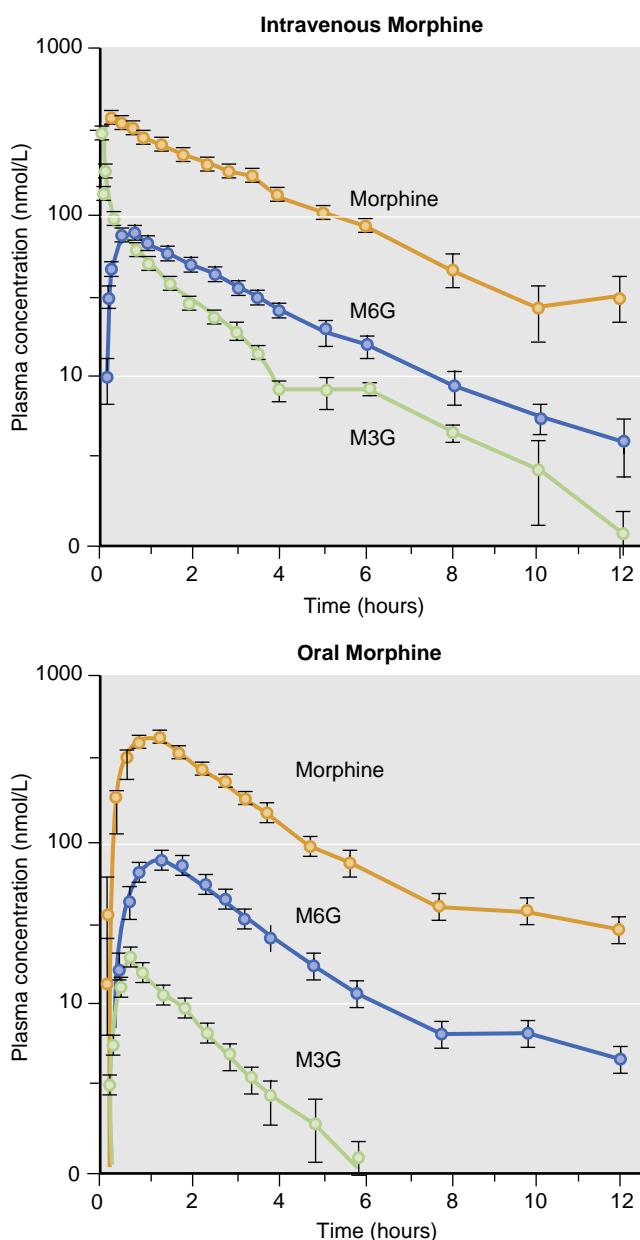
A three-compartment model is typically used to describe plasma fentanyl concentration decay. The lungs exert a significant first-pass effect and transiently take up approximately 75% of an injected dose of fentanyl. Approximately 80% of fentanyl is bound to plasma proteins, and significant amounts (40%) are taken up by red blood cells. Fentanyl is relatively long acting, in large part because of this widespread distribution in body tissues.

Fentanyl is primarily metabolized in the liver by N-dealkylation and hydroxylation. Metabolites begin to appear in the plasma as early as 1.5 minutes after injection. Norfentanyl, the primary metabolite, is detectable in the urine for up to 48 hours after intravenous fentanyl in humans.

### Alfentanil

Following IV injection, alfentanil plasma concentrations are described by either two-compartment or three-compartment model. Alfentanil is bound to plasma proteins (mostly glycoproteins) in higher proportions (92%) than fentanyl. At physiologic pH, it is mostly (90%) un-ionized because of its relatively low pKa (6.5). Thus, despite more intense protein binding, the diffusible fraction of alfentanil is higher than fentanyl. This explains, in part, its short latency to peak effect after intravenous injection.

The main metabolic pathways of alfentanil are similar to those of sufentanil and include oxidative N-dealkylation



**Fig. 24.17** Mean plasma concentrations ( $\pm$  standard error of means) of morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) after intravenous and oral administration of morphine. (From Osborne R, Joel S, Trew D, et al. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin Pharmacol Ther*. 1990;47:12-19.)

and O-demethylation, aromatic hydroxylation, and ether glucuronide formation. The degradation products of alfentanil have little, if any, opioid activity. Human alfentanil metabolism may be predominantly, if not exclusively, by cytochrome P-450 3A3/4 (CYP3A3/4).<sup>422</sup> This enzyme is known to display at least 8-fold difference in activity in humans. Alfentanil is also metabolized by human liver microsomal CYP3A5, which shows more than 20-fold pharmacogenetic variability in expression level leading to significant differences in human liver alfentanil metabolism.<sup>423</sup> In vitro study demonstrated that propofol in clinically relevant concentrations interferes with oxidative

metabolic degradation of alfentanil and sufentanil in the microsomal fraction of pig and human liver.<sup>424</sup>

### Sufentanil

The pharmacokinetic property of sufentanil is adequately described by a three-compartment model. After intravenous injection, first-pass pulmonary extraction, retention, and release are similar to those of fentanyl.<sup>425</sup> The pKa of sufentanil at physiologic pH is the same as that of morphine (8.0), and, therefore, only a small amount (20%) exists in the un-ionized form. Sufentanil is twice as lipid-soluble as fentanyl and is highly bound (93%) to plasma proteins including  $\alpha_1$ -acid glycoprotein.

The major metabolic pathways of sufentanil include N-dealkylation, oxidative O-demethylation, and aromatic hydroxylation. Major metabolites include N-phenylpropanamide.

### Remifentanil

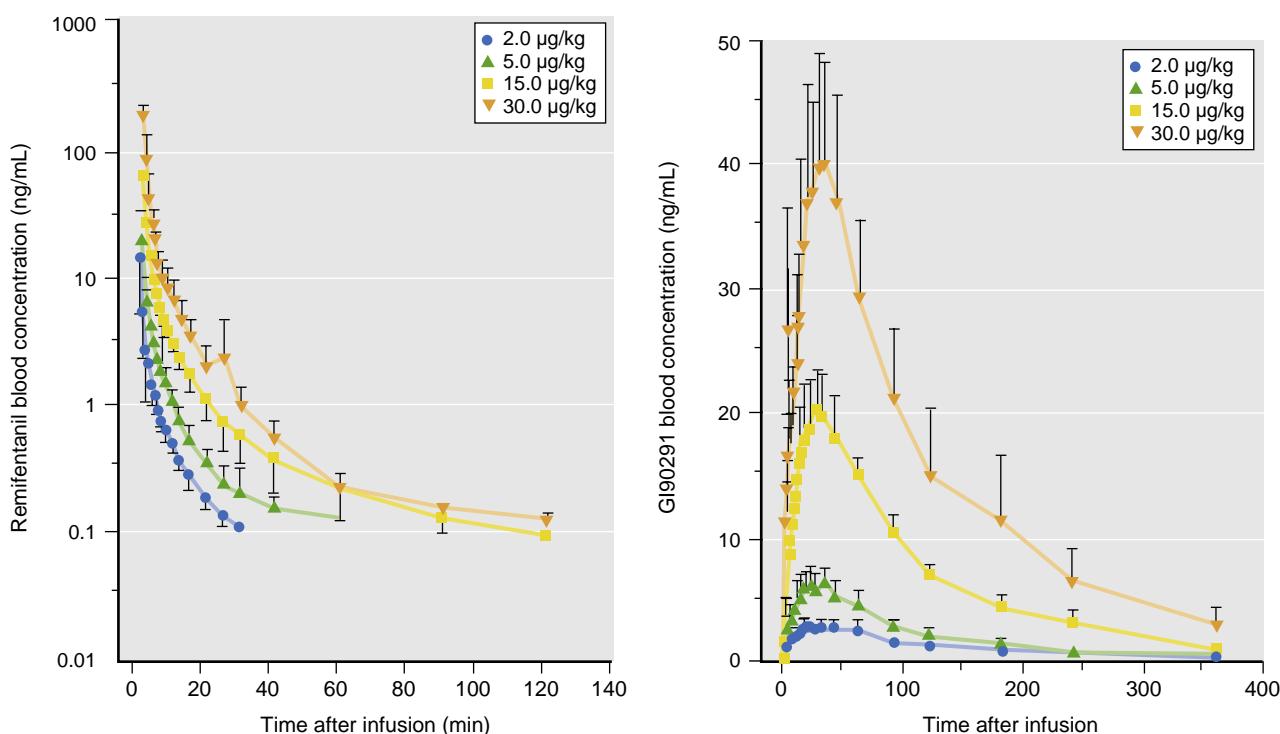
Although chemically related to the fentanyl congeners, remifentanil is structurally unique because of its ester linkages. Remifentanil's ester structure renders it susceptible to hydrolysis by blood- and tissue-nonspecific esterases, resulting in rapid metabolism and rapid reduction of blood concentration after an infusion has stopped (Fig. 24.18).<sup>426</sup> Remifentanil thus constitutes the first ultrashort-acting opioid for use as a supplement to general anesthesia.

Pharmacokinetic properties of remifentanil are best described by a three-compartment model. Its clearance is several times greater than normal hepatic blood flow, consistent with widespread extrahepatic metabolism. But, remifentanil is not significantly metabolized or sequestered in the lungs.<sup>427</sup> It is a weak base with a pKa of 7.07. It is highly lipid-soluble with an octanol/water partition coefficient of 19.9 at pH 7.4. Remifentanil is highly bound (= 70%) to plasma proteins (mostly  $\alpha_1$ -acid glycoprotein). The remifentanil free base is formulated with glycine. Because glycine has been shown to act as an inhibitory neurotransmitter that causes a reversible motor weakness when injected intrathecally in rodents, remifentanil is not approved for spinal or epidural use.<sup>428</sup>

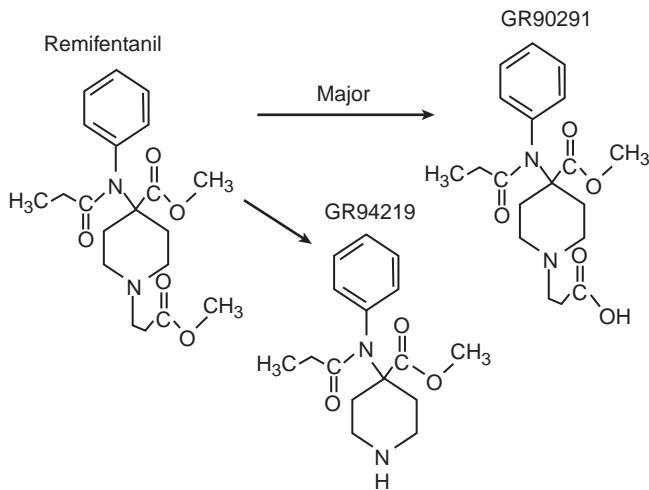
The primary metabolic pathway of remifentanil is de-esterification to form a carboxylic acid metabolite, GR-90291 (Fig. 24.19),<sup>429</sup> which is 0.003 to 0.001 times as potent as remifentanil. The low *in vivo* potency of GR90291 can be explained by its low affinity to the  $\mu$ -receptor in combination with a poor brain penetration.<sup>430</sup> Excretion of GR-90291 is dependent on renal clearance mechanisms. Evidence from dogs suggests that the remifentanil metabolites are, for practical purposes, completely inactive, even in the face of renal failure. Its pharmacokinetics is not appreciably influenced by renal or hepatic failure. In blood, remifentanil is metabolized primarily by enzymes within erythrocytes. Remifentanil is not a good substrate for pseudocholinesterase and, therefore, is not influenced by pseudocholinesterase deficiency.<sup>431</sup>

### SURROGATE MEASURES OF OPIOID POTENCY

Because a high-resolution measure of analgesia is not available, opioid potencies are usually estimated by some surrogate measures. Reduction of the MAC required to produce lack of movement to skin incision has been a



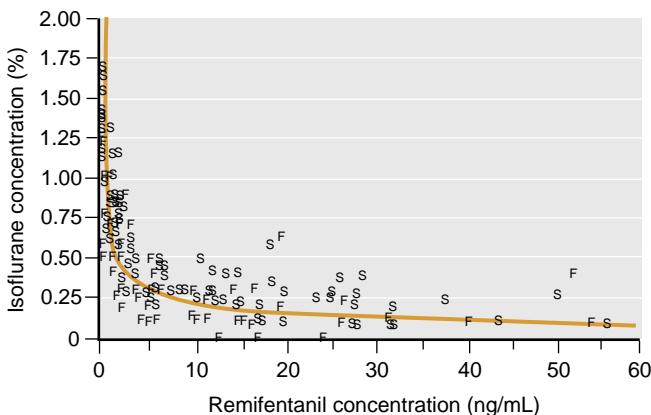
**Fig. 24.18** Mean ( $\pm$  standard deviation) blood concentration-time curves of remifentanil and its metabolite GI90291 after a 1-minute infusion of remifentanil of 2, 5, 15, and 30  $\mu\text{g}/\text{kg}$  ( $n = 6$  for each dose). (From Westmoreland CL, Hoke JF, Sebel PS, et al. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology*. 1993;79:893–903.)



**Fig. 24.19 Metabolic pathway of remifentanil.** Deesterification by nonspecific plasma and tissue esterases to form a carboxylic acid metabolite (GR90291) that has only 1/300 to 1/1000 the potency of the parent compound is the primary metabolic pathway. *N*-Dealkylation of remifentanil to GR94219 is a minor metabolic pathway. (From Egan TD, Lemmens HJ, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. *Anesthesiology*. 1993;79:881–892.)

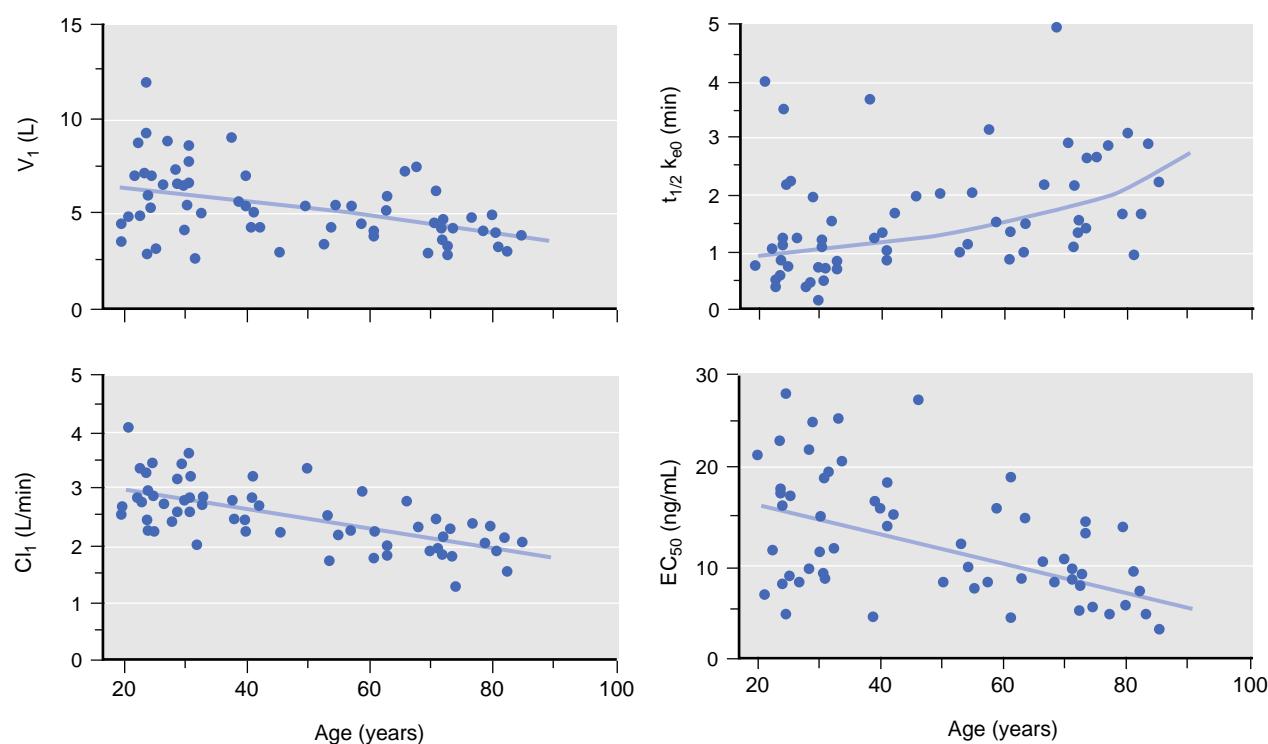
frequently utilized surrogate measure in the estimation of opioid potency (Fig. 24.20).<sup>125</sup> However, MAC is not useful as a surrogate measure of opioid potencies outside the operation rooms.

To guide the administration of opioids in anesthetized patients, indirect parameters that reflect the patient's



**Fig. 24.20** The reduction in isoflurane concentration to prevent movement at skin incision in 50% of patients by increasing measured remifentanil whole blood concentrations. *F* represents a patient who moved and *S* represents a patient who did not move. The solid line is the logistic regression solution for a 40-year-old patient. (From Lang E, Kapila A, Shlugman D, et al. Reduction of isoflurane minimal alveolar concentration by remifentanil. *Anesthesiology*. 1995;85:721–728.)

physiologic reaction to nociception like sweating, movement, heart rate, and blood pressure should be monitored. However, the low specificity of these signs can cause underdosage or overdosage of intraoperative analgesia. The Analgesia Nociception Index (ANI), derived from an electrocardiogram trace, has been proposed as a noninvasive guide to analgesia.<sup>432</sup> The ANI monitor calculates heart rate variation with respiration, a response mediated primarily by changes in the parasympathetic nervous system stimulation to the sinoatrial node of the heart. Patients receiving



**Fig. 24.21 Relationship between pharmacokinetic and pharmacodynamic parameters and age for remifentanil.** Volume of distribution ( $V_1$ ) and clearance ( $Cl_1$ ) are estimated using a three-compartment model.  $t_{1/2}k_{e0}$  is a half-life corresponding to  $k_{e0}$ , a first-order rate constant for elimination of drug from the effect compartment. (From Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. *Anesthesiology*. 1997;86:24–33.)

intraoperative ANI-guided fentanyl administration during sevoflurane anesthesia for lumbar discectomy and laminectomy demonstrated decreased pain in the recovery room, likely as a result of more objective intraoperative fentanyl administration.<sup>433</sup>

The EEG has been another widely utilized surrogate measure in estimating opioid potency. The EEG is advantageous, because it is noninvasive and can be used as an effect measure when an experimental subject is unconscious or apneic. When processed by Fourier spectral analysis, the raw EEG changes translate into a significant decrease in the value of the spectral edge, a parameter that quantitates the frequency below which a given percentage (usually 95%) of the power in the EEG signal is found. Although the clinical meaning of the EEG changes produced by opioids is unclear, the opioid potencies estimated using the EEG as a surrogate measure appear to be clinically reliable because they relate to clinically determined potencies in a proportional, reproducible fashion. However, because the surrogate measures do not always assess the drug effect of clinical interest (analgesia), estimations of potency based on surrogate measures must be interpreted with caution.

## FACTORS AFFECTING PHARMACOKINETICS AND PHARMACODYNAMICS OF OPIOIDS

### Age

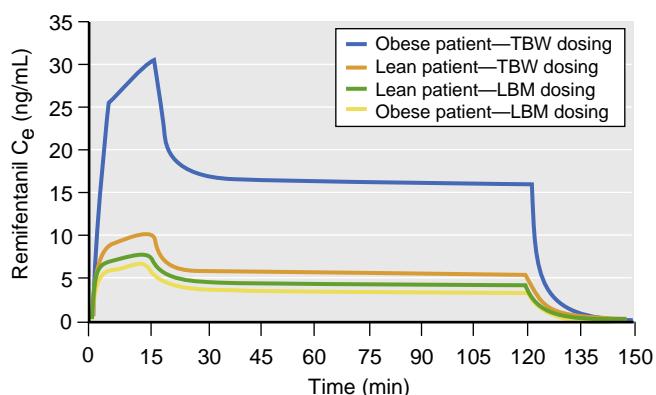
Pharmacokinetics and pharmacodynamics of opioids can be influenced by age. It is clear that neonates exhibit a reduced rate of elimination of essentially all opioids.<sup>434</sup> This is presumably due to immature metabolic mechanisms, including

the cytochrome P-450 system. The prolonged elimination of opioids observed in the neonatal period quickly normalizes toward adult values within the first year of life.<sup>434</sup>

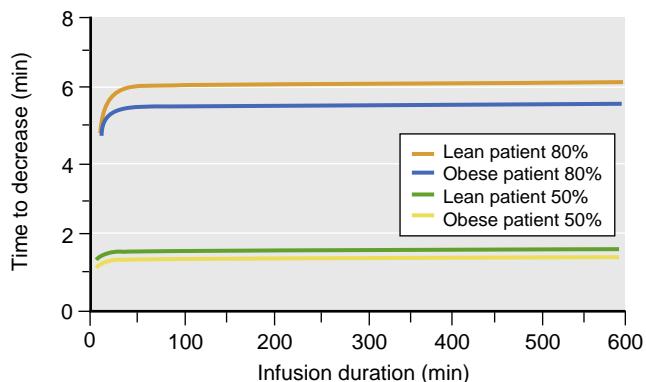
Intraoperative requirements of opioids are different between adults and children. The infusion rate of remifentanil to block somatic and autonomic response to skin incision was almost 2-fold higher in children (2–11 years) than adults (20–60 years).<sup>435,436</sup> With advanced age, although pharmacokinetic changes may play a minor role, pharmacodynamic differences are primarily responsible for the decreased dose requirement in the elderly. Age was inversely correlated with central volume of distribution, clearance, and potency of remifentanil (Fig. 24.21).<sup>437</sup> These combined pharmacokinetic and pharmacodynamic changes mandate a reduction in remifentanil dosage by at least 50% or more in the elderly.

### Body Weight

Many opioid pharmacokinetic parameters, especially clearance, appear to be more closely related to lean body mass. Total body weight-based dosing in an obese patient results in much higher remifentanil effect-site concentrations than does lean body mass-based dosing.<sup>438</sup> In contrast, for lean patients, the concentrations that result from total body weight-based dosing are not much greater than those based on body mass (Fig. 24.22). Clinically, context-sensitive half-times are not significantly different between obese and lean subjects (Fig. 24.23). There is mounting evidence to suggest that lean body mass is a better predictor of metabolic capacity than total body weight. Ideal body weight, a parameter closely related to lean body mass and one that



**Fig. 24.22** A computer simulation of the time course of remifentanil concentration change, when the dosage regimen is calculated based on lean body mass (LBM) or total body weight (TBW) for both obese and lean patients. Note that TBW-based dosing in an obese patient results in dramatically higher concentrations. (From Egan TD, Huizinga B, Gupta SK, et al. Remifentanil pharmacokinetics in obese versus lean patients. *Anesthesiology*. 1998;89:562–573.)



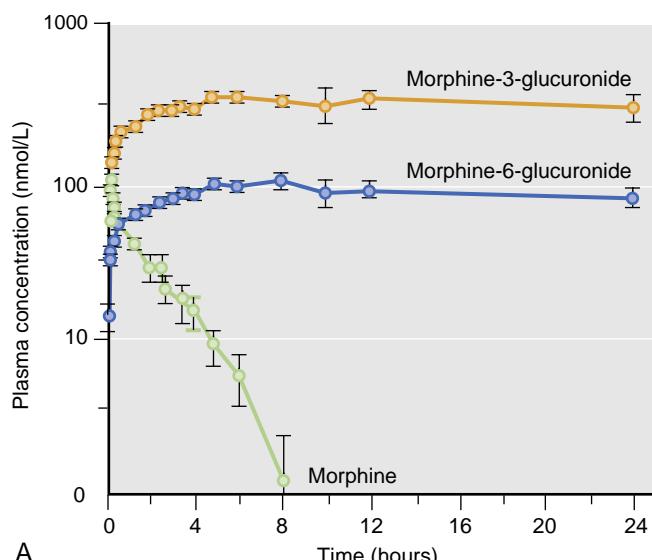
**Fig. 24.23** A computer simulation of the context-sensitive half-times (50% decrement times) and 80% decrement times of remifentanil in obese vs. lean subjects. In clinical terms, the curves are not grossly different in obese and lean subjects. (From Egan TD, Huizinga B, Gupta SK, et al. Remifentanil pharmacokinetics in obese versus lean patients. *Anesthesiology*. 1998;89:562–573.)

is perhaps more easily estimated by the clinician, is probably an acceptable alternative of lean body mass. Because obesity and obesity-associated disease have increased and continue to do so, obese patients will frequently present for anesthesia and operations. Understanding the influence of obesity on the disposition of opioids is an important question in contemporary anesthesia practice. In response, new pharmacokinetic models incorporating the influence of body mass have been recently reported.<sup>439,440</sup>

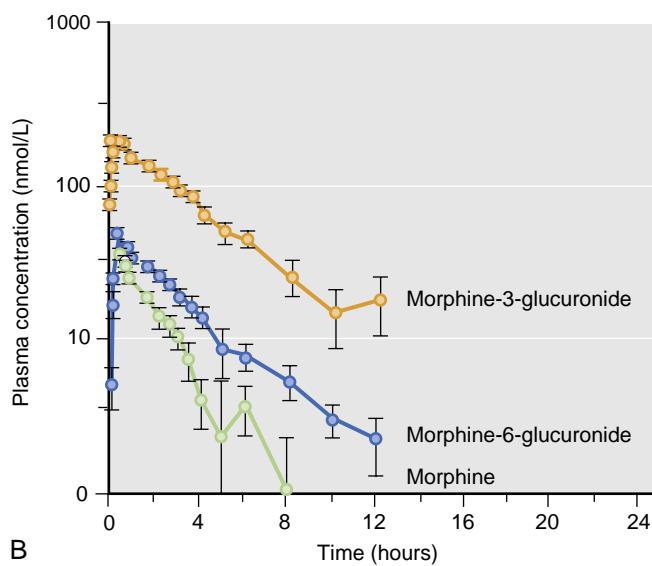
### Renal Failure

Renal failure has implications of major clinical importance with respect to morphine, hydromorphone, and meperidine. For the fentanyl congeners, the clinical importance of renal failure is less marked.

Morphine is an opioid with active metabolites that are dependent on renal clearance mechanisms for elimination. Morphine is principally metabolized by conjugation in the liver, and the water-soluble glucuronides (M3G and M6G) are excreted via kidney. The kidney also plays a role in the



A



B

**Fig. 24.24 Effect of renal failure on pharmacokinetics of morphine.** The graphs show the time-dependent change of the serum concentration of morphine and its metabolite in patients of renal failure (B) and in patients with normal renal function (A) who received 0.1 mg/kg morphine intravenously. (From Osborne R, Joel S, Grebenik K, et al. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther*. 1993;54:158–167.)

conjugation of morphine, accounting for nearly 40% of its metabolism.<sup>441</sup> Patients with renal failure can develop very high levels of M6G and life-threatening respiratory depression (Fig. 24.24).<sup>442</sup> In view of these changes induced by renal failure, morphine is not considered a good choice in patients with severely altered renal clearance mechanisms. There are similar concerns for the use of hydromorphone in the setting of renal dysfunction.

The clinical pharmacology of meperidine is also significantly altered by renal failure. Because normeperidine, the main metabolite of meperidine with analgesic and CNS excitatory effect, is subject to renal excretion, the potential CNS toxicity secondary to normeperidine accumulation is especially a concern in patients in renal failure.

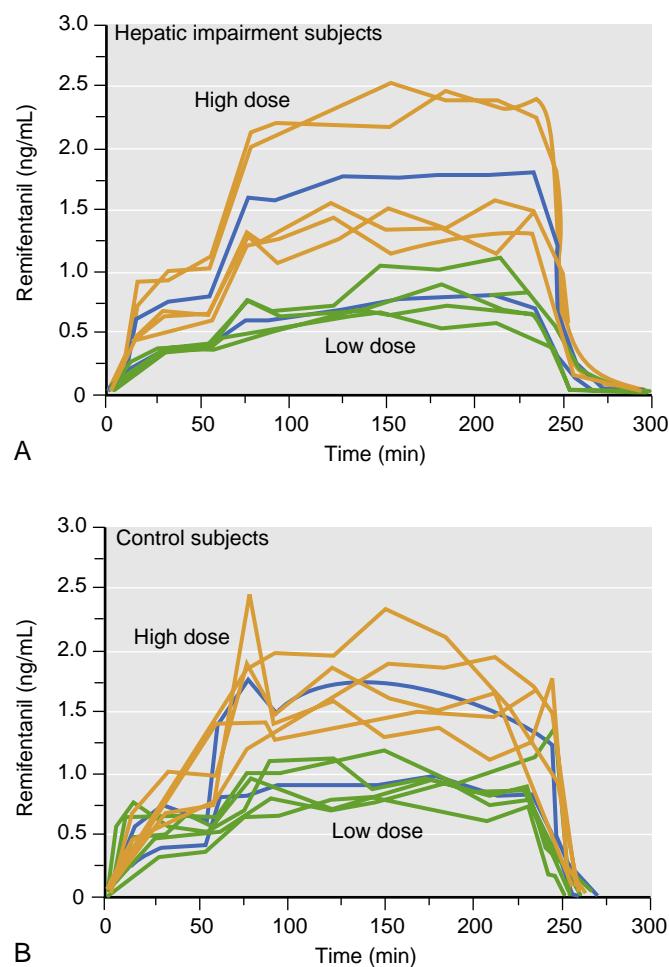
In contrast, the clinical pharmacology of the fentanyl congeners is not grossly altered by renal failure, although a decrease in plasma protein binding may potentially alter the free fraction of the fentanyl class of opioids. In the presence of renal impairment, none of fentanyl, alfentanil, sufentanil, and remifentanil deliver a high active metabolite load, or suffer from significantly prolonged clearance.<sup>443</sup> Neither the pharmacokinetics nor the pharmacodynamics of remifentanil is altered by impaired renal function. Levels of GI-90291 that develop during a remifentanil infusion in patients in renal failure are not likely to produce any clinically significant effects.

## HEPATIC FAILURE

Even though the liver is the metabolic organ primarily responsible for opioid biotransformation, the degree of liver failure typically observed in perioperative patients, with the exception of patients undergoing liver transplantation, does not have a major impact on the pharmacokinetics of most opioids. In addition to reduced metabolic capacity (i.e., cytochrome P-450 system and conjugation), liver disease may also lead to reductions in hepatic blood flow, hepatocellular mass, and plasma protein binding. The increase in total body water and the edema of advanced liver disease may alter the distribution characteristics of a drug. Enzyme induction such as observed in early alcoholism can actually increase metabolic capacity of the liver.

Morphine pharmacokinetics is relatively unchanged by developing liver disease, such as liver cirrhosis and hepatic carcinoma, because of the substantial compensatory extrahepatic metabolism of morphine. A reduction in hepatic blood flow would be expected to slow the decline of morphine plasma concentrations. After liver resection, M6G/morphine and M3G/morphine ratios were significantly reduced and circulating morphine concentration was increased mainly due to a lower morphine clearance.<sup>444</sup> In patients with cirrhosis, the metabolism of meperidine is decreased, leading to accumulation of the parent drug and possible CNS depressive effects similar to hepatic encephalopathy. Although the elimination of normeperidine is decreased as well in these patients, the ratio of normeperidine to meperidine is generally low, and the opioid effects of meperidine usually predominate.<sup>445</sup> The disposition of fentanyl and sufentanil appears to be unaffected in liver diseases.<sup>446</sup> Reductions in liver blood flow that result from either liver disease or some other disorder (e.g., shock) can affect the pharmacokinetic parameters of alfentanil, fentanyl, and sufentanil. It was demonstrated that there was a significant decrease in clearance of alfentanil in patients with mild to moderate cirrhosis compared with volunteers from the historical control group.<sup>447</sup> Remifentanil is an opioid whose pharmacokinetics is completely unchanged by liver disease (Fig. 24.25).<sup>448</sup> Its kinetics does not change during the anhepatic phase of orthotopic liver transplantation.<sup>449</sup> It was reported that 0.25 to 0.5  $\mu$ g/kg/min remifentanil could provide perioperative analgesia without neurological deterioration in a patient suffering from chronic hepatic failure with mild encephalopathy.<sup>450</sup>

In summary, a reduction in renal function may have the greatest effects on morphine due to a decrease in capacity for extrahepatic glucuronidation and clearance. Therefore, fentanyl may be a safer choice in renal failure patients due



**Fig. 24.25 Time-dependent changes of blood concentration of remifentanil in patients with liver disease (A) and in control subjects (B).** In the low-dose group, remifentanil was infused at 0.0125  $\mu$ g/kg/min for 1 hour and then 0.025  $\mu$ g/kg/min for 3 hours. In the high-dose group, the infusion rate of remifentanil was 0.025  $\mu$ g/kg/min for 1 hour and then 0.05  $\mu$ g/kg/min for 3 hours. (From Dershawitz M, Hoke JF, Rosow CE, et al. Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease. *Anesthesiology*. 1996;84:812–820.)

to their lack of active metabolites. In contrast, only under conditions of severe hepatic failure does one observe clinically significant changes in morphine or fentanyl clearance.

## Cardiopulmonary Bypass

CPB produces significant alterations in the pharmacokinetics of most opioids. These alterations are a result of CPB-induced modifications in distribution volumes (secondary to priming), changes in acid-base balance, organ blood flow, plasma protein concentrations, and body temperature. The binding of drugs to components of the bypass circuit can also alter opioid pharmacokinetics.

When morphine is given as a premedicant before cardiac anesthesia, its concentrations decline significantly on initiation of CPB. Miller et al. examined the effect of CPB on plasma fentanyl concentration and showed that total concentration of fentanyl in plasma was significantly decreased and the unbound fraction of fentanyl rose on initiation of CPB.<sup>451</sup> The total fentanyl concentration remained relatively stable during bypass until near the end of CPB when the mean total concentration increased, coinciding with

rewarming. Population pharmacokinetic modeling applied to concentration-versus-time data from patients undergoing coronary artery bypass grafting using CPB demonstrated that the effect of CPB on fentanyl pharmacokinetics is clinically insignificant, and that a simple three-compartment model accurately predicts fentanyl concentrations throughout surgery using CPB.<sup>452</sup> Elimination of alfentanil is prolonged by CPB primarily because of increased distribution. It was reported that the volume of distribution in steady state ( $Vd_{ss}$ ) and the volume of central compartment for alfentanil were significantly greater in the CPB groups, compared to the nonbypass group.<sup>453</sup> However, the elimination half-life ( $T1/2\beta$ ) of alfentanil did not differ significantly between the normothermic CPB, hypothermic CPB, and nonbypass groups. Between the normothermic and hypothermic CPB groups no significant differences in  $Vd_{ss}$ , clearance, or  $T1/2\beta$  were found. The free fraction of alfentanil during CPB remains constant despite complex changes in binding protein concentrations.<sup>454</sup> In adult patients undergoing elective myocardial revascularization with hypothermic CPB who received continuous infusions of remifentanil 1.0 to 2.0  $\mu\text{g}/\text{kg}/\text{min}$ , no evidence of accumulation or sequestration was found.<sup>427</sup> Russell et al. reported that normothermic CPB did not significantly affect the clearance of remifentanil, but hypothermic CPB reduced it by an average of 20%, and this was attributed to the effect of temperature on blood and tissue esterase activity.<sup>455</sup> In pediatric patients undergoing CPB for repair of atrial septal defect, there was no change in the  $Vd_{ss}$ , the volume of the central compartment,  $T1/2\alpha$ , and  $T1/2\beta$ , but clearance values of remifentanil increased 20% in the postbypass period.<sup>456</sup> In patients undergoing coronary artery bypass graft surgery with hypothermic CPB receiving continuous infusion of remifentanil, the volume of distribution increased by 86% with institution of CPB and remained increased after CPB, and elimination clearance decreased by 6.37% for each degree from 37°C.<sup>457</sup> Thus, although clearance of remifentanil reduces during CPB, remifentanil remains a very short-acting drug even during CPB.

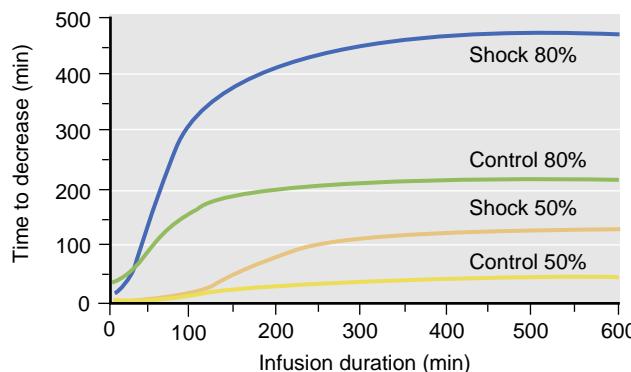
### Acid-Base Changes

It was demonstrated that pH changes influence the protein binding of fentanyl, sufentanil, and alfentanil, resulting in an increase in protein binding with alkalosis and a decrease with acidosis. These effects are greater for fentanyl than sufentanil and sufentanil than alfentanil. Relative changes in the free-drug fraction with pH variation from 7.4 to 7.0 were much higher for fentanyl (52%) when compared with sufentanil (29%) and alfentanil (6%). The pH dependence of plasma protein binding of the opioids significantly correlates with their partition between an organic and aqueous phase, suggesting the hydrophobic character of the interaction between plasma proteins and opioids. Increased ionization decreases the amount of fentanyl available for hepatic metabolism or renal excretion. Intraoperative hyperventilation during surgical procedures can significantly influence the pharmacokinetics of sufentanil resulting in an increased distribution volume and a prolonged elimination half-time.

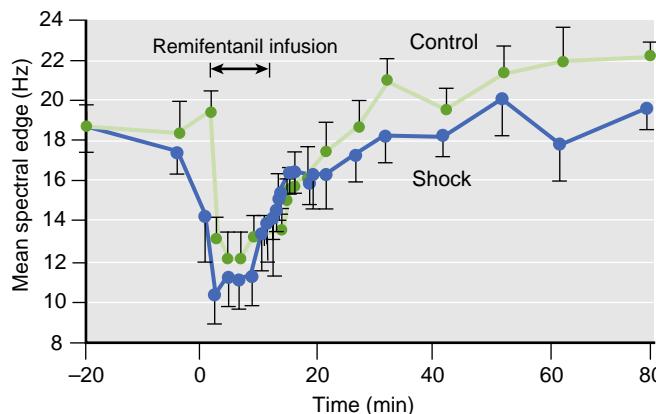
Thus, both intraoperative respiratory alkalosis and respiratory acidosis, especially in the immediate postoperative period, can prolong and exacerbate opioid-induced respiratory depression.

### Hemorrhagic Shock

It is a common practice to administer reduced doses of opioids to patients suffering from hemorrhagic shock to minimize adverse hemodynamic consequences and to prevent prolonged opioid effect. This is at least partially attributable to a pharmacokinetic mechanism. Analysis with pigs receiving fentanyl suggested that central clearance and central- and second-compartment distribution volumes were significantly reduced in hemorrhagic shock, resulting in higher fentanyl concentrations for any given dosages and prolonged context-sensitive half-time (Fig. 24.26).<sup>458</sup> Hemorrhagic shock also altered pharmacokinetics of remifentanil, suggesting that less remifentanil would be required to maintain a target plasma concentration (Fig. 24.27).<sup>459</sup> However, because of its rapid metabolism, changes in context-sensitive half-time are small. In a stepwise hemorrhage model of pigs receiving total intravenous anesthesia with remifentanil (0.5  $\mu\text{g}/\text{kg}/\text{min}$ ) and propofol (6 mg/kg/h after 2 mg/kg bolus), the plasma remifentanil concentration showed a threefold greater increase than that of propofol.<sup>460</sup> Thus, the remifentanil dose should be reduced substantially compared with propofol during total intravenous anesthesia for patients with significant blood loss.



**Fig. 24.26** A computer simulation of the context-sensitive half-times (50% decrement times) and 80% decrement times of fentanyl in shock versus control animals. (From Egan TD, Kuramkote S, Gong G, et al. Fentanyl pharmacokinetics in hemorrhagic shock: a porcine model. *Anesthesiology*. 1999;91:156–166.)



**Fig. 24.27** Mean spectral edge changes versus time during remifentanil infusion. The graph indicates spectral edge measurements for control animals and for animals with hemorrhagic shock, respectively. (From Johnson KB, Kern SE, Hamber EA, et al. Influence of hemorrhagic shock on remifentanil: a pharmacokinetic and pharmacodynamic analysis. *Anesthesiology*. 2001;94:322–332.)

## Genetic Variations in Opioid Metabolism

All opioid drugs are substantially metabolized mainly by cytochrome P450 (CYP) and to a lesser extent by UDP-glucuronosyltransferases (UGTs). Although CYP3A4 is involved in the metabolism of many of the opioids, it is the role of the highly polymorphic CYP2D6 that is of greater clinical interest with respect to the weaker opioids (codeine, dihydrocodeine, oxycodone, hydrocodone, and tramadol), because of the formation of their more potent hydroxyl metabolites (morphine, dihydromorphine, oxymorphone, and hydromorphone), which have about a 30-fold higher affinity for the  $\mu$ -receptor. The CYP2D6 gene is highly polymorphic, with 100 allelic variants identified, and enzymatic activity of some alleles may be either significantly high or low. In the case of a variant more rapidly producing metabolites of higher affinity there exists the possibility of administering an unintended opioid overdose. This has been especially of concern for the use of codeine-containing products in pediatric populations resulting in changes in prescribing practice. Alternately, variants leading to low production of potent metabolites may result in subtherapeutic outcomes.<sup>461</sup> Finally, UGTs mediate mainly the formation of glucuronides from buprenorphine, codeine, dihydrocodeine, dihydromorphine, hydromorphone, morphine, naloxone, naltrexone, and oxymorphone. UGT2B7 gene is polymorphic, and less than 20 allelic variants have been identified. It is possible that differences in metabolic activity among UGT alleles affect pharmacokinetics of opioids.<sup>461</sup>

## Anesthetic Techniques Using Opioids

### ANALGESIA

Opioids are frequently used to relieve pain during monitored anesthesia care and regional anesthesia. A single bolus administration of opioids can provide significant pain relief. Morphine is slow in onset and does not allow rapid titration to effect. Meperidine (50-100 mg IV) produces variable degrees of pain relief and is not always effective in patients with severe pain. IV boluses of fentanyl (1-3  $\mu$ g/kg), alfentanil (10-20  $\mu$ g/kg), or sufentanil (0.1-0.3  $\mu$ g/kg) can produce potent and short-lasting analgesia. Infusion rates range from 0.01 to 0.05  $\mu$ g/kg/min for fentanyl, 0.0015 to 0.01  $\mu$ g/kg/min for sufentanil, 0.25 to 0.75  $\mu$ g/kg/min for alfentanil, and 0.05 to 0.25  $\mu$ g/kg/min for remifentanil.

Plasma concentrations of opioids necessary for various purposes are listed in **Table 24.8**.

Changes in the excitability of central neurons play an important role in establishment of pain. In rats, low doses of fentanyl block the synaptic form of central sensitization in the rat spinal cord *in vivo*, suggesting the possibility of preemptive analgesia by fentanyl, but higher doses do not have this effect.<sup>462</sup> In fact, dose escalation of fentanyl or other potent opioids may produce a hyperalgesic state—mentioned previously. Reductions in postoperative pain and improved recovery have been attributed to preemptive analgesia with either epidural fentanyl or bupivacaine after radical prostatectomy.<sup>463</sup> In contrast, in patients undergoing transperitoneal tumor nephrectomy, preoperative intravenous administration of a combination of morphine, ketamine, and clonidine failed to exert a clinically relevant effect on postoperative pain.<sup>464</sup> Aida et al. reported that the effectiveness of preemptive analgesia varies according to the type of surgery, and preemptive analgesia with epidural morphine was reliably effective in limb and breast surgeries but ineffective in abdominal surgery.<sup>465</sup> A meta-analysis demonstrated that the results of preemptive analgesia with systemic administration of opioids are equivocal.<sup>466</sup> Thus, whether or not preemptive analgesia can be effectively achieved clinically by the early administration of opioids remains uncertain and may be highly context specific.

Patient-controlled analgesia (PCA) with opioids has become a widely accepted technique in which to provide postoperative analgesia, but pharmacokinetic optimization of opioid treatment in acute pain is a complex matter. Without considering effect-site drug concentrations over time, the choice of opioid and the amount, method, and frequency of its administration cannot be optimal. Morphine and fentanyl are often used for PCA therapy, and piritramide is also frequently used for PCA in European countries. A double-blind randomized study demonstrated that effect-site target-controlled remifentanil PCA with a slow and progressive adapted algorithm is feasible in young women undergoing uterine artery embolization.<sup>467</sup> Combination of opioid with other drugs might be a method for improvement of PCA. For thoracic surgery, addition of ketamine to opioid for intravenous PCA was superior to intravenous PCA opioid alone, whereas the effect of added ketamine was not significant for orthopedic or abdominal surgery.<sup>468</sup> Despite the utility of an opioid-based PCA, critical considerations must also be made as to an individual patient's relative risk of opioid-induced respiratory depression with appropriate oversight and monitoring.

**TABLE 24.8** Range of Approximate Plasma (or Whole Blood for Remifentanil) Opioid Concentration

	Fentanyl (ng/mL)	Sufentanil (ng/mL)	Alfentanil (ng/mL)	Remifentanil (ng/mL)
Predominant agent	15-30	5-10	400-800	—
Major surgery	4-10	1-3	200-400	2-4
Minor surgery	3-6	0.25-1	50-200	1-3
Spontaneous ventilation	1-3	<0.4	<200	0.3-0.6
Analgesia	1-2	0.2-0.4	50-150	0.2-0.4

## SEDATION

Critically ill subjects in the intensive care unit (ICU) often experience anxiety and agitation while being exposed to numerous stressful or noxious stimuli. ICU patients generally require a combination of analgesia and sedation to relieve their state of anxiety, improve adaptation to the endotracheal tube, and aid compliance with mechanical ventilation. Morphine, fentanyl, and sufentanil are frequently used intravenous analgesic agents in the ICU. A randomized double-blind study indicated that remifentanil (0.15 µg/kg/min) and morphine (0.75 µg/kg/min) could provide comparable levels of sedation, and the remifentanil-based regimen allowed a more rapid emergence from sedation and facilitated earlier extubation.<sup>469</sup> However, use of ultrapotent opioid agents such as remifentanil may also drive tolerance development and OIH—as discussed previously.

## BALANCED ANESTHESIA

Anesthesia with a single agent can often require doses that produce excessive hemodynamic depression. Alternately, “balanced anesthesia” with a balance of agents and techniques can be used to more selectively direct different components of anesthesia (i.e., analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance of homeostasis). For example, inclusion of an opioid as a component of balanced anesthesia can reduce preoperative pain and anxiety, decrease somatic and autonomic responses to airway manipulations, improve hemodynamic stability, lower requirements for inhaled anesthetics, and provide immediate postoperative analgesia. Opioids interact synergistically and markedly reduce the dose of propofol and other sedative-hypnotics required for loss of consciousness and during noxious stimulation such as skin incision (Fig. 24.28).<sup>470</sup> Although the intent of combining opioids with sedative-hypnotics and/or volatile anesthetics is to produce anesthetic conditions with stable hemodynamics

prior to as well as after noxious stimulation, this ideal is not always achieved.<sup>471,472</sup>

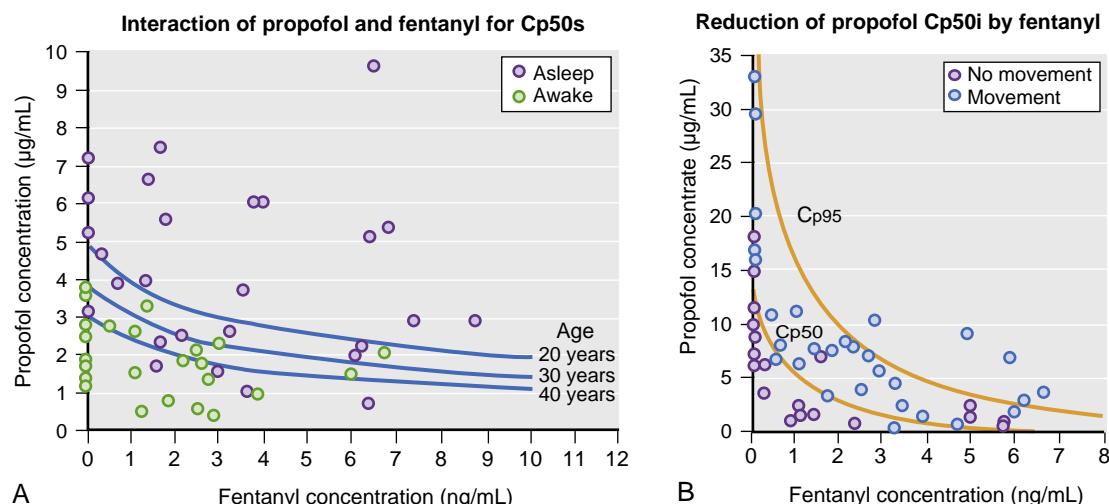
The timing, rate of administration, and dose of supplemental opioids should also be tailored to the specific condition of the patient and the expected duration of the operation in order to avoid problems. Giving a large dose of any opioid shortly before the end of surgery is very likely to result in postoperative respiratory depression. However, analgesic concentrations of opioids have little effect on the MAC awake of inhaled anesthetics.<sup>473</sup>

The ideal opioid would permit rapid titration, prevent unwanted responses to noxious stimuli, require little supplementation, not depress cardiovascular function, permit the return of adequate spontaneous ventilation in a timely manner, and produce effective postoperative analgesia with minimal side effects. Alfentanil and remifentanil provide the greatest ability to titrate opioids rapidly because of their extremely rapid time to onset (1-2 minutes) of peak effect. Sufentanil, alfentanil, and remifentanil are arguably superior to fentanyl in most respects. Antagonism of opioid action with naloxone for troublesome respiratory depression is required less frequently after alfentanil and sufentanil compared with fentanyl. Pharmacologic antagonism is not required after remifentanil administration because of its short half-life.

### Fentanyl

Anesthetic induction is usually achieved by combining a loading dose of fentanyl (2-6 µg/kg) with a sedative-hypnotic, most commonly thiopental or propofol, and a muscle relaxant. Maintenance of anesthesia can be achieved with low concentrations of potent inhaled anesthetics, and additional fentanyl (intermittent boluses of 25-50 µg every 15-30 minutes or a constant infusion of 0.5-5.0 µg/kg/h).

The plasma concentration of fentanyl required for postoperative analgesia was approximately 1.5 ng/mL.<sup>474</sup> MAC of isoflurane at skin incision can be reduced by 50% and 63%



**Fig. 24.28** (A) Measured arterial propofol and fentanyl concentrations at which patients did and did not respond to a verbal command at 10 minutes after the initiation of the infusion of these drugs. The solid lines represent the modeled concentration of propofol, according to decade of age when combined with the measured fentanyl concentrations, at which 50% of patients did not respond to verbal command (Cp50s). (B) Reduction by increasing concentration of fentanyl of propofol concentration at which 50% or 95% of patients did not move at skin incision (Cp50i and CP95i, respectively). The solid lines represent logistic regression solution. (From Smith C, McEwan Al, Jhaveri R, et al. The interaction of fentanyl on the Cp50 of propofol for loss of consciousness and skin incision. *Anesthesiology*. 1994;81:820-828.)

with plasma fentanyl concentrations of 1.67 and 3.0 ng/mL, respectively.<sup>121</sup> Increasing plasma fentanyl concentrations from 3.0 to 10 ng/mL only further reduced the MAC of isoflurane from 63% to 82%. Intraoperative requirement of propofol for hypnosis is also reduced by fentanyl. In patients undergoing spine fusion, to keep the mean arterial pressure within 15% of the control value when fentanyl was infused to keep the plasma concentration at 0, 1.5, 3.0, and 4.5 ng/mL, average propofol infusion rates were  $10.1 \pm 2.5$  (mean  $\pm$  SD),  $7.5 \pm 1.2$ ,  $5.7 \pm 1.1$ , and  $4.9 \pm 1.2$  mg/kg/h, respectively.<sup>475</sup>

Opioid pharmacokinetics and pharmacodynamics vary considerably among patients. It was reported that fentanyl dose based on total body weight may cause overdosing in obese patients.<sup>474</sup> As discussed previously, considerations for dosing based on lean body weight and/or ideal body weight may have merit in this context. Nevertheless, a balanced technique with fentanyl, titrating the opioid in anticipation of various stimuli and patient responses with pharmacokinetic guidelines in mind, will often result in a stable hemodynamic course and rapid awakening in a pain-free patient. Repeated doses or continuous infusions of fentanyl are most likely to result in significant depression of spontaneous ventilation.

### Alfentanil

Because alfentanil penetrates the brain so rapidly, equilibration of alfentanil between plasma and CNS can be achieved while plasma alfentanil levels are relatively low compared with sufentanil and fentanyl. This property explains how low doses (10-30  $\mu$ g/kg) of alfentanil, administered just before or simultaneously with a sedative-hypnotic, are effective.

Alfentanil (25-50  $\mu$ g/kg IV), followed by small titrated sleep doses of any sedative-hypnotic (e.g., 50-100 mg sodium thiopental), is usually successful in preventing significant hemodynamic stimulation from laryngoscopy and intubation. The optimum dose of alfentanil, coadministered with 2.5 mg/kg propofol, when inserting a classic laryngeal mask airway was 10  $\mu$ g/kg.<sup>476</sup> Further opioid supplementation can be achieved with an alfentanil infusion (0.5-2.0  $\mu$ g/kg/min) or intermittent boluses of alfentanil (5-10  $\mu$ g/kg) for shorter procedures. In balanced anesthetic techniques in which potent inhaled anesthetics are also employed, relatively low plasma alfentanil concentrations (e.g., 29 ng/mL) can reduce the MAC of isoflurane by approximately 50%.<sup>123</sup> The EC50 of alfentanil during propofol anesthesia, in which plasma concentration of propofol was kept at target concentrations of 3  $\mu$ g/mL, was 92 ng/mL for intubation, 55 ng/mL for skin incision, 84 ng/mL for the opening of the peritoneum, and  $66 \pm 38$  ng/mL for the intraabdominal part of surgery.<sup>477</sup> It was reported that hemodynamic changes induced by propofol might have an important influence on the pharmacokinetics of alfentanil. Propofol (target concentration, 1.5  $\mu$ g/mL) decreased the elimination clearance of alfentanil by 15%, rapid distribution clearance by 68%, slow distribution clearance by 51%, and lag time by 62%.<sup>478</sup> Alfentanil infusions or repeated doses should be minimized 15 to 30 minutes prior to the end of surgery in order to avoid problematic residual respiratory depression.

### Sufentanil

CP<sub>50</sub> for prevention of hemodynamic responses to laryngoscopy and tracheal intubation was 1.08 ng/mL with a

range of 0.73 to 2.55 ng/mL. In combination with propofol for induction of anesthesia in children, bolus administration of sufentanil 0.3  $\mu$ g/kg can completely abolish the cardiovascular response to tracheal intubation.<sup>479</sup> In healthy normotensive adult patients, a bolus sufentanil 0.1  $\mu$ g/kg followed by a continuous infusion at 0.08  $\mu$ g/kg/min for at least 5 minutes proved to be effective for blunting the cardiovascular response to intubation.<sup>480</sup> Maintenance of anesthesia can be achieved with sufentanil (intermittent boluses, 0.1-0.25  $\mu$ g/kg, or constant infusion, 0.5-1.5  $\mu$ g/kg/h). The CP<sub>50</sub> for sufentanil during skin incision (2.08  $\pm$  0.62 ng/mL) is twice as great as that for intubation in unpremedicated patients.<sup>481</sup> CP<sub>50</sub> value ratios at skin incision for sufentanil, fentanyl, and alfentanil are approximately 1:2:150 and represent different, and probably more accurate, potency ratios than those traditionally published based on drug dose. In patients undergoing coronary artery bypass grafting, sufentanil greater than  $1.25 \pm 0.21$  ng/mL reduced isoflurane requirements to less than 0.5% through the operation.<sup>482</sup>

### Remifentanil

Very short duration of action of remifentanil mandates that an infusion (0.1-1.0  $\mu$ g/kg/min) be started prior to or soon after a small bolus dose to ensure sustained opioid effect. Maintenance infusion rates of remifentanil range from 0.1 to 1.0  $\mu$ g/kg/min for balanced anesthesia. Remifentanil can reliably suppress automatic, hemodynamic, and somatic responses to noxious stimulation and allows the most predictable and rapid trouble-free emergence from anesthesia without postoperative respiratory depression. Infusion rates of  $0.1 \pm 0.05$   $\mu$ g/kg/min should permit the return of spontaneous ventilation and responsiveness with maintenance of analgesia. A randomized, double-blind, placebo-controlled study demonstrated that combination of 0.05-0.1  $\mu$ g/kg/min remifentanil and 2 mg midazolam provided effective sedation and analgesia during outpatient surgical procedures performed under local anesthesia.<sup>483</sup>

Associated with emergence from remifentanil anesthesia, the need for alternative analgesic therapies should be anticipated and administered in a timely fashion. Exposure to high doses of remifentanil may paradoxically reduce the pain threshold after its discontinuation, resulting in postoperative hyperalgesia, which is known to be associated with acute and persistent pain. It was reported that perioperative administration of morphine (0.15 or 0.25 mg/kg IV) or fentanyl (0.15 mg) did not provide entirely adequate immediate postoperative pain control after remifentanil-based anesthesia in major abdominal surgery.<sup>484,485</sup> Administration of ketamine (0.15 mg/kg followed by 2  $\mu$ g/kg/min) decreased intraoperative remifentanil use during abdominal surgery and postoperative morphine consumption without increasing the incidence of side effects.<sup>486</sup> In children undergoing strabismus surgery, combination of sevoflurane (2.5%) and remifentanil (1  $\mu$ g/kg followed by 0.1-0.2  $\mu$ g/kg/min) showed less frequent postoperative vomiting but higher postoperative pain scores compared with fentanyl (2  $\mu$ g/kg followed by 1  $\mu$ g/kg every 45 minutes).<sup>487</sup>

Postoperative pain relief with low-dose remifentanil infusion was also reported. After general anesthesia with propofol (75 mg/kg/min) and remifentanil (0.5-1.0 mg/kg/min)

for abdominal or thoracic surgery, continuous infusion of remifentanil (0.05 or 0.1 mg/kg/min) provided adequate analgesia.<sup>488</sup>

## TOTAL INTRAVENOUS ANESTHESIA

Many different IV anesthetic and analgesic compounds can be employed in a number of combinations to provide TIVA. Most commonly, an opioid is combined with another drug more likely to provide hypnosis and amnesia. For example, combination of alfentanil and propofol can produce desirable TIVA. Alfentanil provides analgesia and hemodynamic stability while blunting responses to noxious stimuli. On the other hand, propofol provides hypnosis and amnesia and is antiemetic. Anesthetic induction with alfentanil (25–50 µg/kg) and propofol (0.5–1.5 mg/kg) followed by infusions of 0.5 to 1.5 µg/kg/min of alfentanil and 80 to 120 µg/kg/min of propofol will produce complete anesthesia for a variety of procedures. It is proposed that alfentanil concentrations as low as 85 ng/mL, when combined with a blood propofol concentration of 3.5 µg/mL, can produce both optimal anesthetic conditions and speed of recovery.<sup>489</sup> Stanski and Shafer suggested that bolus doses and initial infusion rates would be 30 µg/kg and 0.35 µg/kg/min for alfentanil and 0.7 mg/kg and 180 µg/kg/min for propofol.<sup>490</sup> Recognizing that these calculations were based on EC<sub>50</sub> data in patients undergoing only moderately painful procedures, anesthesiologists should adjust these doses accordingly. In patients undergoing ear-nose-throat surgery, TIVA with remifentanil and propofol provided a more rapid respiratory recovery after brief surgical procedures, compared with TIVA with alfentanil and propofol.<sup>491</sup>

Maintenance infusions vary according to patient condition and surgical stimuli. Propofol (75–125 µg/kg/min) and alfentanil (1.0–2.0 µg/kg/min) were initially recommended. Propofol infusions should be terminated 5 to 10 minutes before anticipated patient awakening. Alfentanil infusion rates do not need to be less than 0.25 to 0.5 µg/kg/min until surgery is terminated. A multicenter evaluation demonstrated that in patients of elective inpatient surgery remifentanil 1 µg/kg IV followed by 1.0 µg/kg/min, when combined with propofol 75 µg/kg/min, effectively controlled responses to tracheal intubation.<sup>492</sup> Reduction of remifentanil infusion rate to 0.25–0.40 µg/kg/min after tracheal intubation was also recommended. Although midazolam-opioid combinations can also provide complete anesthesia, midazolam-alfentanil TIVA has not been found to compare favorably to propofol-alfentanil TIVA even with flumazenil reversal of benzodiazepine actions.<sup>493</sup>

TIVA techniques are especially useful when delivery of inhaled agents is compromised. By keeping the goals of balanced anesthesia in mind, combining modern opioids and other drugs, utilizing infusion pumps, and employing an increased understanding of pharmacokinetics, clinicians can successfully perform a variety of TIVA techniques. Approximate opioid doses and infusion rates for TIVA are listed in Table 24.9.

## OPIOID-BASED (HIGH-DOSE OPIOID) ANESTHESIA FOR CARDIAC SURGERY

Opioids can be administered as the primary anesthetic in opioid-based anesthetic techniques. High-dose

**TABLE 24.9** Approximate Opioid Loading (Bolus) Doses, Maintenance Infusion Rates, and Additional Maintenance Doses for Total Intravenous Anesthesia

	Loading Dose (µg/kg)	Maintenance Infusion Rate	Additional Boluses
Alfentanil	25-100	0.5–2 µg/kg/min	5–10 µg/kg
Sufentanil	0.25–2	0.5–1.5 µg/kg/h	2.5–10 µg
Fentanyl	4–20	2–10 µg/kg/h	25–100 µg
Remifentanil	1–2	0.1–1.0 µg/kg/min	0.1–1.0 µg/kg

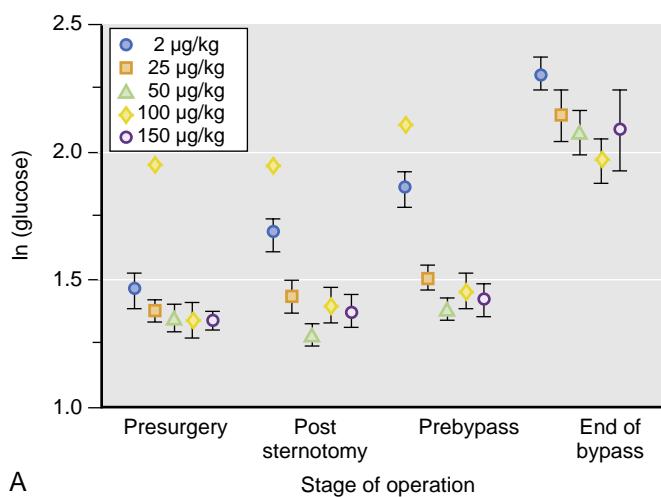
From Bailey PL, Egan TD, Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia*. 8th ed. Philadelphia: Saunders; 2015. An imprint of Elsevier Inc., p. 897.

opioid anesthesia was introduced as a stress-free anesthetic method for cardiac surgery. High-dose opioid anesthesia was first performed by the use of morphine, and fentanyl and sufentanil have been recommended later. However, several factors have diminished the popularity of high-dose opioid anesthesia, even in cardiac anesthesia. These include the lack of evidence substantiating any significant outcome benefit associated with the use of large doses of opioids, the added drug costs, and the trend toward “fast-track” approaches to the cardiac patient that can be impeded by large doses of opioids. However, opioids, particularly when administered by continuous infusion, are still among the most effective anesthetics for patients undergoing cardiac or other extensive operations.

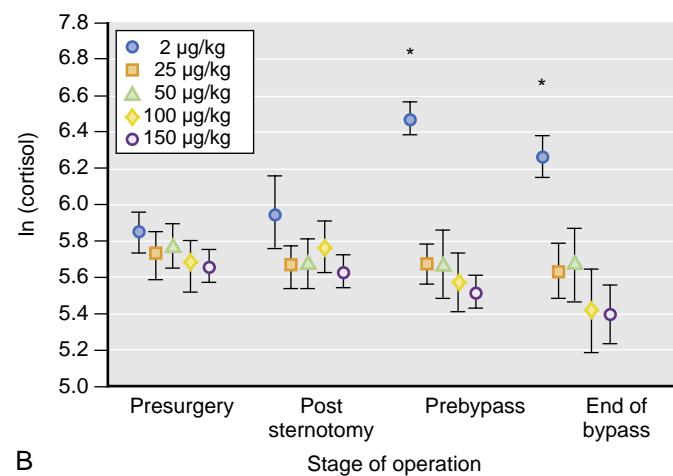
In an attempt to decrease the costs of cardiac surgery, fast-track programs have become popular. Engoren et al. reported that the more expensive but shorter-acting opioids, sufentanil and remifentanil, produced equally rapid extubation, similar stays, and similar costs to fentanyl, indicating that any of these opioids can be recommended for fast-track cardiac surgery.<sup>494</sup>

## Fentanyl

Many different techniques have been used to achieve anesthesia with fentanyl.<sup>495,496</sup> Rapid or slow bolus injections of fentanyl ranging from 5 to 75 µg/kg will establish plasma fentanyl concentrations (10–30 ng/mL) that are often sufficient to provide stable hemodynamics throughout the induction/intubation sequence. Continuous infusions of fentanyl for cardiac surgery range from 0.1 to 1.0 µg/kg/min up to or continuing through CPB. High-dose fentanyl anesthesia has also proved effective and safe for pediatric heart surgery. It was indicated that fentanyl 25 to 50 µg/kg combined with isoflurane 0.2% to 0.4% was sufficient to obtund hemodynamic and stress responses in the pre-CPB phase of open heart surgery in infants and young children (Fig. 24.29).<sup>497</sup> It was reported that 57 out of 59 eligible patients were successfully extubated at  $34 \pm 14$  minutes after termination of fentanyl (total dose,  $127 \pm 64$  µg/kg) with naloxone (total bolus,  $3.4 \pm 2.6$  µg/kg), and recovered fully without ventilatory support under the naloxone infusion, which was terminated at  $11 \pm 7$  hours.<sup>498</sup> These results suggest that naloxone infusion with individual dose titration can facilitate the use of high-dose opioid anesthesia, maintaining the advantage of this anesthesia. It was shown that high-dose fentanyl (50 µg/kg) is not associated



A Stage of operation



**Fig. 24.29 Suppression of stress responses in the prebypass phase of open heart surgery in infants and young children by fentanyl combined with low concentration (0.2%-0.4%) of isoflurane.** Mean ( $\pm$  SE) natural logarithm (ln) for glucose (A) or ln for cortisol (B) versus stage of surgery for each dose of fentanyl. The values for the 2  $\mu$ g/kg group indicated by asterisks were significantly higher ( $P < .01$ ) than in the other groups. (From Duncan HP, Cloote A, Weir PIM, et al. Reducing stress responses in the pre-bypass phase of open heart surgery in infants and young children: a comparison of different fentanyl doses. *Br J Anaesth.* 2000;84:556-564.)

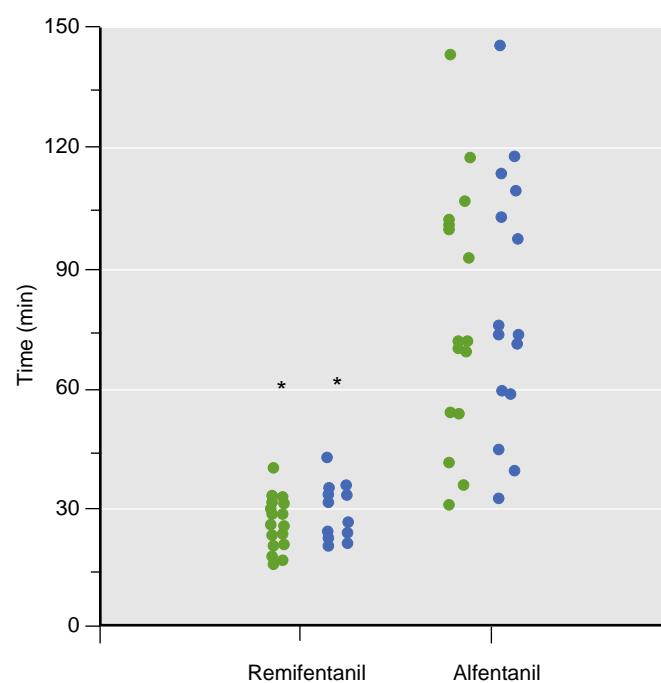
with a difference in the incidence of postoperative cognitive dysfunction at 3 or 12 months after coronary artery bypass surgery in the elderly, whereas low-dose fentanyl (10  $\mu$ g/kg) leads to shorter postoperative ventilation times and may be associated with a greater incidence of postoperative cognitive dysfunction 1 week after surgery.<sup>499</sup>

### Sufentanil

Advantages of high-dose sufentanil include more rapid induction, better blunting or elimination of hypertensive episodes, greater reduction in left ventricular stroke work, with higher cardiac outputs and more stable hemodynamics intraoperatively and/or postoperatively. Induction doses of sufentanil range from 2 to 20  $\mu$ g/kg administered as a bolus or infused over 2 to 10 minutes. Total doses of sufentanil employed in high-dose techniques usually range from 15 to 30  $\mu$ g/kg. However, no additional benefit could be demonstrated in terms of hemodynamic control or EEG signs by increasing the dose of sufentanil from 3 to 15  $\mu$ g/kg for the induction of anesthesia in patients premedicated with lorazepam.<sup>500</sup> The amount of sufentanil required can be markedly influenced by the supplements employed concomitantly. For patients undergoing coronary artery surgery, induction ( $0.4 \pm 0.2 \mu$ g/kg) and total maintenance ( $2.4 \pm 0.8 \mu$ g/kg) doses of sufentanil were used in combination with propofol ( $1.5 \pm 1$  mg/kg for induction and  $32 \pm 12$  mg/kg total). Interestingly, sufentanil requirements tripled when midazolam was employed instead of propofol.<sup>501</sup> Maintenance of anesthesia, utilizing infusion of sufentanil (1.0-2.0  $\mu$ g/kg/h), in a balanced anesthetic technique, achieves the advantages of opioid-based anesthesia and avoids prolonged opioid action into the postoperative period.

### Remifentanil

Remifentanil has been employed in cardiac anesthesia.<sup>455</sup> It was shown that induction with remifentanil 2  $\mu$ g/kg with propofol and maintenance with remifentanil at 0.25 or 0.5  $\mu$ g/kg/min provided appropriate anesthesia for



**Fig. 24.30** Times to awakening (green circles) and tracheal extubation (blue circles) in patients who underwent minimally invasive direct coronary artery bypass surgery after intravenous anesthesia with remifentanil and propofol or alfentanil and propofol. (From Ahonen J, Olkkola KT, Verkkala K, et al. A comparison of remifentanil and alfentanil for use with propofol in patients undergoing minimally invasive coronary artery bypass surgery. *Anesth Analg.* 2000;90:1269-1274.)

minimally invasive coronary artery bypass surgery with rapid awakening and tracheal extubation (Fig. 24.30).<sup>502</sup> Kazmaier et al. compared high-dose remifentanil (2.0  $\mu$ g/kg/min) and remifentanil 0.5  $\mu$ g/kg/min combined with propofol (target-controlled infusion aiming at a plasma concentration of 2.0  $\mu$ g/mL) in patients undergoing elective coronary artery bypass grafting.<sup>503</sup> It was demonstrated that high-dose remifentanil reduces stroke volume index,

heart rate, mean arterial pressure, myocardial blood flow, and myocardial oxygen uptake and its effects do not differ from those of remifentanil/propofol anesthesia. Geisler et al. examined efficacy and safety of high-dose remifentanil anesthesia in patients undergoing coronary artery bypass graft surgery.<sup>504</sup> It was demonstrated that continuous infusions of remifentanil 1.0 to 2.0  $\mu\text{g}/\text{kg}/\text{min}$  in combination with propofol 3  $\text{mg}/\text{kg}/\text{h}$  provided profound suppression of responses to surgical stimuli in the majority of patients, but there was a high incidence of muscle rigidity when remifentanil was used to induce anesthesia. They concluded that there was no apparent advantage in starting the remifentanil infusion rate above 1.0  $\mu\text{g}/\text{kg}/\text{min}$  and remifentanil is not suitable for use as a sole induction agent.

## OTHER APPLICATIONS OF OPIOIDS

### Transdermal Therapeutic System

Transdermal drug delivery generally requires high solubility in both water and oil, low molecular weight, high potency, and little or no skin irritation. Fentanyl is available in a transdermal therapeutic system (TTS). Potential advantages of delivering fentanyl transdermally include no first-pass drug metabolism by the liver, improved patient compliance, convenience and comfort, and consistent analgesia. Doses of TTS fentanyl include 25, 50, 75, and 100  $\mu\text{g}/\text{h}$  and achieve blood levels ranging from less than 1.0 to 2.0  $\text{ng}/\text{mL}$ , although significant variability exists. Pharmacokinetics of transdermally-delivered fentanyl (50  $\mu\text{g}/\text{h}$ ) was compared in 10 young adult (25–38 years) and eight elderly (64–82 years) patients.<sup>505</sup> It was shown that the mean half-time (time for plasma concentrations to double after patch application) was 4.2 hours and 11.1 hours and mean maximum plasma concentrations were 1.9  $\text{ng}/\text{mL}$  and 1.5  $\text{ng}/\text{mL}$ , in the younger and elderly groups, respectively. There were no differences in the time at which maximum plasma concentrations occurred nor elimination half-life after patch removal. Elevated body temperature and/or application of external warming devices can accelerate either the release of fentanyl from the patch or increase the vascular bed distribution from the subcutaneous tissues. Portenoy et al. demonstrated that steady state serum concentration was obtained by repeated application of TTS fentanyl and the apparent half-life following system removal after repeated application was relatively long presumably due to ongoing absorption from a subcutaneous depot.<sup>506</sup>

Results of clinical trials utilizing TTS fentanyl for postoperative analgesia have demonstrated a high incidence of significant respiratory depression, and this application is not recommended and is contraindicated.<sup>507</sup> In cancer pain, TTS fentanyl offers an interesting alternative to oral morphine, and its effectiveness and tolerability in this indication has been demonstrated by a number of trials.<sup>508</sup> Its usefulness in chronic pain of nonmalignant origin remains to be confirmed in controlled trials just as there is a lack of evidence for the efficacy of chronic oral opioid administration in the treatment of nonmalignant pain. In general, TTS fentanyl produces the same adverse effects as other opioids, mainly sedation, nausea, vomiting, and constipation. In comparison with oral morphine, TTS fentanyl causes fewer gastrointestinal adverse events.

Buprenorphine is suitable for transdermal application because of its properties that facilitate transdermal absorption such as low molecular weight, high lipophilicity, and high potency. Beyond its application in the management of OUD, buprenorphine TDS may be effective for moderate and possibly severe cancer pain.<sup>509</sup> Studies on the use of buprenorphine TTS for severe noncancer pain that is refractory to nonopioid analgesia are emerging. Poulain et al. studied the effect of buprenorphine TDS in patients with cancer pain and demonstrated a reduction in mild–moderate pain scores (from  $3.5 \pm 2.2$  to  $1.5 \pm 1.5$ ) in the group that received buprenorphine TDS, with worsening of pain scores (from  $1.5 \pm 1.5$  to  $2.7 \pm 1.9$ ) in the placebo group.<sup>510</sup> The transdermal formulation of buprenorphine in the United States is currently available in 5 dosage strengths: 5, 7.5, 10, 15, and 20  $\mu\text{g}/\text{h}$ , and the bioavailability decreases to 15% after a 7-day application.

### Iontophoresis

Iontophoresis is a technique by which drug passage through the skin is augmented by an external electric current. Clinically significant doses of morphine and fentanyl can be delivered iontophoretically. The fentanyl hydrochloride iontophoretic transdermal system (fentanyl ITS) is a novel PCA system that has been approved in the USA and Europe for the management of acute, moderate-to-severe postoperative pain.<sup>511</sup> This system allows patients to self-administer preprogrammed doses of fentanyl noninvasively through the use of iontophoretic technology. To assess the efficacy and safety of patient-controlled ITS using fentanyl hydrochloride (40- $\mu\text{g}$  infusion over 10 minutes) compared with a standard intravenous morphine PCA (1-mg bolus every 5 minutes; maximum of 10 mg/h), a prospective randomized controlled parallel-group trial was performed.<sup>512</sup> The results indicated that the fentanyl ITS can provide pain control equivalent to a standard morphine PCA, with a similar incidence of opioid-related adverse events. The fentanyl ITS may offer a number of clinical advantages over existing PCA modalities.<sup>511</sup> Its method of drug delivery avoids the risk of complications from needle-related injuries and infection, and its preprogrammed electronics eliminate the potential for manual programming errors and excessive dosing. In addition, the compact size of the system could enable greater patient mobility following surgery. The patient-controlled ITS with fentanyl has the potential to become a valuable option in the management of acute postoperative pain. Panchal and associates reported that fentanyl ITS was associated with a significantly lower incidence of analgesic gaps, which are defined as periods during which the patient does not have access to analgesia thus contributing to ineffective postoperative pain management, relative to morphine intravenous PCA.<sup>513</sup> Nevertheless, given potential variability in dose delivery and other factors, ITS systems may be restricted to monitored in-hospital facilities.

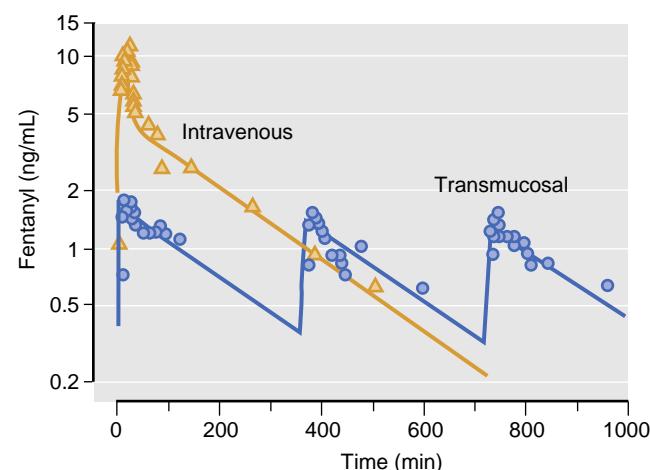
### Transmucosal Drug Delivery

Similar to transdermal drug delivery, transmucosal delivery through the oropharynx and nasopharynx eliminates hepatic first-pass metabolism (drugs are absorbed directly into the systemic circulation) and improves patient comfort, convenience, and compliance.

Buprenorphine, a potent, synthetic morphine analogue with mixed opioid agonist-antagonist properties and a long half-time, is readily absorbed from sublingual mucosal tissues. The portion of the drug that is swallowed is almost completely metabolized by the liver, and only a small fraction can reach the systemic circulation when swallowed. Systemic bioavailability after sublingual buprenorphine is approximately 50% of that following intravenous administration. Sublingual buprenorphine (0.3 mg) was compared with transdermal buprenorphine (5, 10 and 20  $\mu$ g/h) for osteoarthritis pain in the hips and/or knees and found to provide comparable analgesia.<sup>514</sup> Buccal buprenorphine was introduced and approved by the Food and Drug Administration in 2015 for the management of chronic pain. It is composed of flexible, water-soluble polymeric films that stick to the buccal mucosa and dissolve within a few minutes. The bioavailability of this formulation is 46%–65%, and it is useful in patients who are taking over 80 mg oral morphine sulfate equivalent per day for pain management.<sup>515</sup>

Initial experience with buccal morphine for postoperative analgesia had been promising. However, in female patients undergoing lower abdominal surgical procedures, buccal morphine did not significantly reduce postoperative pethidine consumption, compared with placebo, and all patients receiving buccal morphine reported a taste which reduced its acceptability.<sup>516</sup> Low lipid solubility of morphine makes it an unlikely candidate for effective transmucosal absorption. Opioids with high lipid solubility, such as buprenorphine, fentanyl, and methadone are more effectively absorbed sublingually than those with low lipid solubility such as morphine.

Oral transmucosal fentanyl citrate (OTFC) is a solid dosage form of fentanyl that consists of fentanyl incorporated into a sweetened lozenge on a stick. A portion of fentanyl is absorbed through the oral mucosa, and the rest is swallowed and absorbed through the gastrointestinal tract. The recommended doses range from 5 to 20  $\mu$ g/kg.<sup>517</sup> OTFC should be administered approximately 30 minutes before surgery (or painful procedure) to obtain peak effect. Plasma concentrations after OTFC administration peak at  $2.0 \pm 0.5$  ng/mL, 15 to 30 minutes after OTFC administration, then decline to less than 1 ng/mL an hour later.<sup>518</sup> Unlike transdermal fentanyl, OTFC leaves no significant depot in the mucosal tissues after it is removed. The systemic bioavailability of OTFC is 50% and reflects both buccal and gastrointestinal absorption. OTFC bioavailability is similar to that of buprenorphine (55%), but much greater than buccal morphine and other opioids with low lipid solubility. Egan et al. demonstrated that the pharmacokinetics of OTFC did not change with repeated dosing and the decline of plasma concentration was as rapid as when administered intravenously (Fig. 24.31).<sup>519</sup> Furthermore, Kharasch et al. reported that the pharmacokinetics of OTFC were not altered in older volunteers ( $67 \pm 6$  years), and no change in OTFC dosing in the elderly would appear necessary.<sup>520</sup> Peak fentanyl concentration and clinical effects after OTFC were minimally affected by hepatic/intestinal CYP3A induction by rifampicin and intestinal CYP3A inhibition by grapefruit juice, suggesting that first-pass metabolism minimally influences OTFC bioavailability.<sup>521</sup> Preoperative OTFC was reported to be effective for postoperative analgesia in pediatric tonsillectomy patients.<sup>522</sup> However, OTFC can induce



**Fig. 24.31** A typical result of time-dependent change in plasma concentration of fentanyl after oral transmucosal fentanyl citrate (OTFC) application and intravenous administration. Three 800- $\mu$ g doses of OTFC were administered with 6-hour intervals between doses, and fentanyl was infused at a constant rate of 50  $\mu$ g/minute to a total of 15  $\mu$ g/kg. (From Egan TD, Sharma A, Ashburn MA, et al. Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers. *Anesthesiology*. 2000;92:665–673.)

perioperative emesis and respiratory depression. OTFC has also been introduced for treatment of breakthrough cancer pain.<sup>523</sup> OTFC may be ideally suited to treat breakthrough cancer pain because fentanyl is rapidly absorbed from OTFC and patients can easily self-administer OTFC.

Delivery of opioids through the nasal mucosa has also been investigated. Side effects of intranasal sufentanil in children include reduced ventilatory compliance (chest wall rigidity), hypoxemia, impaired manual ventilation, nausea, and vomiting.<sup>524</sup> Pharmacokinetic studies in volunteers are reported for fentanyl, alfentanil, sufentanil, butorphanol, oxycodone, and buprenorphine.<sup>525</sup> Mean times for achieving maximum serum concentrations vary from 5 to 50 minutes, while bioavailability varies from 46% to 71%. Fentanyl, pethidine, and butorphanol have been studied for postoperative pain. Mean onset times vary from 12 to 22 minutes and times to peak effect from 24 to 60 minutes. Transnasal butorphanol provides superior and more prolonged analgesia than similar doses given IV for postoperative pain after cesarean section. PCA with intranasal fentanyl was demonstrated to be effective for postoperative pain management.<sup>526</sup> There was no difference in the efficacy of intranasal fentanyl (2  $\mu$ g/kg), intramuscular morphine (0.1 mg/kg), and intravenous morphine (0.1 mg/kg) in controlling postoperative pain and emergence delirium in children undergoing bilateral myringotomy and placement of ventilating tubes.<sup>527</sup> A novel intranasal morphine formulation composed of morphine monohydrate and chitosan, a nontoxic naturally occurring mucoadherent derived from shellfish, was shown to offer a noninvasive alternative to intravenous morphine for postoperative analgesia in patients after third molar extraction.<sup>528</sup> Intranasal administration of remifentanil (4  $\mu$ g/kg) produces good intubating conditions in 2 to 3 minutes after induction of anesthesia with sevoflurane in children.<sup>529</sup>

Fentanyl (300  $\mu$ g) inhalation produces low plasma drug level (0.1 ng/mL) after 15 minutes and analgesia that may

be disproportionately greater than expected.<sup>530</sup> Inhaled liposome-encapsulated fentanyl was also demonstrated to be a noninvasive route of administration with a rapid increase and prolonged maintenance of plasma fentanyl concentration.<sup>531</sup> Inhalation of nebulized fentanyl citrate significantly improved patient perception of breathing, respiratory rate, and oxygen saturation in terminally ill cancer patients.<sup>532</sup> This inexpensive and readily available treatment may offer substantial relief of end-of-life dyspnea. The advent of specialized and efficient pulmonary drug delivery systems has facilitated the evaluation of inhaled opioids, such as morphine and fentanyl, for management of severe pain associated with surgery or malignant disease.<sup>533</sup> It was shown that remifentanil delivered by inhalation is rapidly absorbed, pharmacologically active, rapidly cleared, and noninjurious to respiratory tissues in rodents.<sup>534</sup>

The rectal mucosa is another site for transmucosal drug delivery. The bioavailability of 30-mg morphine sulfate controlled-release suppository formulation was significantly greater than that of 30-mg oral controlled-release morphine sulfate tablets, which may be the result of partial avoidance of hepatic biotransformation with rectal administration.<sup>535</sup> The hydrogel formulation of rectal morphine may also be useful for premedication and analgesia in pediatric patients.<sup>536</sup>

### Oral Controlled-Release Medications

Despite the high first-pass metabolism of opioid analgesics, morphine has been formulated into an oral, sustained-release tablet (MST) and has been evaluated for premedication, postoperative analgesia, and as an analgesic for chronic cancer pain. MST provides unreliable preoperative anxiolysis and postoperative pain relief, possibly because of delayed time to onset of peak effects (3–5 hours), which can be increased by impaired gastric emptying and absorption from the small intestine. In addition, growing evidence has associated chronic use of sustained release formulation of opioids for noncancer pain to increase the risk of fatal overdose without significant benefit over other non-opioid modalities of analgesia. As an analgesic for chronic cancer pain, MST was shown to be an excellent formula.<sup>537</sup>

The relative analgesic potency of single doses of oral controlled-release oxycodone (20 or 40 mg) and oral controlled-release morphine (45 or 90 mg) was compared in a randomized, double-blind trial in women with moderate-to-severe pain following abdominal hysterectomy.<sup>538</sup> Controlled-release oxycodone at doses of 20 mg or 40 mg was comparable with controlled-release morphine at doses of 45 mg or 90 mg, respectively, for total and peak analgesic effects, indicating that oral controlled-release oxycodone was at least twice as potent as oral controlled-release morphine. A randomized, double-blind, crossover trial indicated that controlled-release oxycodone was as safe and effective as controlled-release morphine in the treatment of cancer pain.<sup>539</sup>

### Extended-Release Epidural Morphine (DepoDur)

DepoDur is a novel drug that delivers morphine by using DepoFoam technology, a drug-delivery system composed of multivesicular lipid particles containing nonconcentric aqueous chambers that encapsulate the active drug. When the plasma morphine concentration after epidural

administration of 5 mg of standard morphine was compared with those of 5 mg of DepoDur, the terminal half-life was comparable, but the peak concentration was significantly smaller and the peak systemic absorption occurs later with DepoDur. Randomized controlled studies demonstrated that 5–15 mg of DepoDur can be a potentially beneficial analgesic after elective cesarean delivery with no significant increases in adverse events for the period from 24 to 48 hours after surgery.<sup>540,541</sup> When compared to single-shot plain epidural morphine, DepoDur has been shown to provide a longer duration of postoperative pain control, and a decrease in the use of postoperative opioid in lower abdominal surgery,<sup>542</sup> total hip arthroplasty,<sup>543</sup> and total knee arthroplasty.<sup>544</sup> The adverse effect profile of DepoDur is similar to plain epidural morphine and includes nausea, vomiting, pruritus, and hypotension. It was reported that a large dose of epidural lidocaine before DepoDur administration alters the pharmacokinetics and drug effects of DepoDur.<sup>545</sup>

## Other Opioid Agonists

### CODEINE

Codeine (methylmorphine) is 6–7 fold less potent as morphine, has a high oral-parenteral potency ratio (2:3), and a plasma half-life of 2 to 3 hours. Codeine has mild to moderate analgesic but strong cough-suppressant properties after oral administration. Cytochrome P450 2D6 (CYP2D6) is the enzyme responsible for *O*-demethylation of codeine to morphine, and has genetic variants capable of rapid conversion of codeine to morphine in affected children and adults.<sup>546</sup> IV codeine produces profound hypotension and is neither approved nor recommended.

### OXYCODONE

Although oxycodone has been widely used in pain management for more than 90 years, its pharmacokinetic properties are still poorly known. Oxycodone is extensively metabolized in humans mainly by hepatic cytochrome P450, and only 10% of oxycodone is excreted in unchanged form in urine. Rifampin, a strong inducer of several drug-metabolizing enzymes, induces cytochrome P450, reduces the plasma concentration of intravenous and oral oxycodone, and modestly attenuates pharmacologic effects of oxycodone.<sup>547</sup> The role of several metabolites in its analgesic activity is still not fully understood.<sup>548</sup> Oxycodone is a potent analgesic after systemic administration, but its analgesic potency is poor after intrathecal administration.<sup>549</sup> It was shown that oxycodone is more potent than morphine for visceral pain relief in intravenous patient-controlled postoperative analgesia after laparoscopic hysterectomy.<sup>550</sup> With respect to pharmacologic effects other than analgesic effects, it was reported that the extent and speed of onset of oxycodone-induced respiratory depression was dose-dependent and greater than an equivalent dose of morphine.<sup>551</sup>

### MEPERIDINE (PETHIDINE)

Meperidine is predominantly a  $\mu$ -opioid receptor agonist that produces pharmacologic effects similar, but not identical, to

those of morphine. Meperidine sometimes causes excitation of the CNS, characterized by tremors, muscle twitches and seizures, that are largely due to accumulation of a metabolite, normeperidine. Meperidine has well-known local anesthetic properties.

Unlike morphine, after intravenous injection, first-pass uptake of meperidine by the lungs is approximately 65%. Meperidine is more highly bound to plasma proteins than is morphine, principally (70%) to  $\alpha_1$ -acid glycoprotein. As with morphine, a relatively high hepatic extraction ratio results in biotransformation that depends on hepatic blood flow. The major metabolite normeperidine has analgesic activity and is roughly twice as potent as meperidine in producing seizures in animals. The elimination half-life of normeperidine is considerably greater than that of meperidine, and thus repeated doses can easily produce accumulation of this toxic metabolite in patients with renal disease, with the potential for inducing seizures.

Meperidine is frequently used for postoperative pain management. A comparative study demonstrated that morphine, meperidine, and tramadol resulted in equivalent pain scores in intravenous PCA after abdominal hysterectomy.<sup>552</sup> Meperidine is also used to relieve pain and distress in women in labor. Intravenous meperidine (50 mg) and butorphanol (1 mg) significantly reduced pain intensity 15 minutes after injection in women with moderate to severe labor pain, but the analgesia was often inadequate.<sup>553</sup> Meperidine can be administered as PCA in labor.<sup>554</sup> Meperidine (12.5 to 35 mg) is also effective for prevention and treatment of postoperative shivering.<sup>197,555</sup>

## HYDROMORPHONE

Hydromorphone is structurally related to morphine but is approximately 5 to 10 times as potent. Because hydromorphone contains a keto-group in position 6 of the benzol ring, an active 6-glucuronate metabolite is not formed like morphine.<sup>556</sup> However, hydromorphone continues to represent an increased risk under conditions of renal insufficiency and failure due to a reduction in clearance and potential accumulation of hydromorphone-3-glucuronate. A bolus administration of hydromorphone reaches its peak effect in approximately 10-20 minutes, whereas an equivalent morphine bolus will require 20 minutes to reach peak. Analgesia after hydromorphone lasts 4 to 5 hours. Hydromorphone has been used for both acute and chronic pain conditions in adults and children.<sup>557</sup> It was reported that hydromorphone PCA provided adequate postoperative analgesia in gynecological surgery patients and there was no systematic difference between morphine and hydromorphone in opioid-related side effects.<sup>558</sup>

## LEVORPHANOL

Levorphanol is the only available semisynthetic opioid agonist of the morphinan series with a long half-life. It is 5 times as potent as morphine with an IM/oral potency ratio of 1:2. Levorphanol may have particular utility in patients with chronic pain and who demonstrate morphine tolerance, perhaps because of differences in opioid receptor activity. Analgesia produced by levorphanol is mediated via its interactions with  $\mu$ -,  $\delta$ -, and  $\kappa$ -opioid receptors. Levorphanol is

also an NMDA receptor antagonist. The long half-life of the drug increases the potential for drug accumulation.<sup>559</sup>

## METHADONE

Methadone is a potent  $\mu$ -opioid receptor agonist, with the longest half-life among the clinically used opioids. By virtue of one of methadone's isomers, it also exerts an inhibitory effect on NMDA receptors, which are implicated in the development of opioid tolerance, hyperalgesia, and chronic pain. Furthermore, methadone inhibits the reuptake of serotonin and norepinephrine, which may play a role in antinociception and mood elevation. Methadone itself is associated with less abuse potential than either morphine or heroin, and treatment with methadone has been considered to be the "gold standard" by which medication-assisted treatment (MAT) approaches are measured, as part of a comprehensive treatment program for OUD.

Methadone (IV) has an equivalent potency but longer duration of action than morphine. The plasma half-life of methadone is very long and variable (13-100 hours). Despite this property, many patients require dosing every 4 to 8 hours to maintain analgesic effects. Its major clinical applications are in the prevention of opioid withdrawal symptoms and in the treatment of chronic pain. It was shown that the same dose of IV methadone (20 mg) that is effective for postoperative pain is also suitable for the induction of anesthesia in combination with etomidate, and that methadone may have the potential for producing histamine release.<sup>560</sup> In patients undergoing posterior spinal fusion surgery, methadone 0.2 mg/kg at the start of surgery reduced postoperative opioid requirements, decreased pain scores, and improved patient satisfaction.<sup>561</sup> However, perioperative use of methadone represents a major clinical challenge, given the tremendous interpatient half-life variability which could contribute to unexpected postoperative respiratory depression.

## OXYMORPHONE

Oxymorphone is a semisynthetic opioid agonist that is specific for the  $\mu$ -opioid receptor and approved to treat both acute and chronic pain. Due to extensive liver metabolism, oral oxymorphone is contraindicated in patients with moderate-to-severe hepatic impairment.<sup>562</sup> Oxymorphone, structurally related to morphine, is almost 10 times as potent, but has a similar duration of action. It was shown that in patients with acute moderate-to-severe postsurgical pain, oral immediate-release oxymorphone 10, 20, or 30 mg provided significant dose-related pain relief compared with placebo, and this relief was maintained over several days with a safety profile comparable to that of immediate-release oxycodone.<sup>563</sup>

## PIRITRAMIDE

Piritramide, a synthetic opioid structurally related to meperidine acting on the  $\mu$ -opioid receptor, is often used for postoperative analgesia in several European<sup>564</sup> countries. Lack of hemodynamic effects and less side effects reported in early work made piritramide more suitable for postoperative pain control compared with other potent opioids.

Its relative analgesic potency compared with morphine is approximately 0.7. Intramuscular bolus injections of 7.5 to 15 mg were considered to be adequate for approximately 4 to 6 hours.<sup>564</sup> Pharmacokinetic analysis showed that piritramide is distributed extensively and eliminated slowly, and recommended for intermittent bolus administration.<sup>565</sup> A randomized controlled trial showed that intravenous PCA with piritramide can produce pain management as satisfactory as oral oxycodone after cesarean section.<sup>566</sup> It was also demonstrated that piritramide is at least as effective and as well tolerated as morphine for postoperative analgesia via a PCA system after hysterectomy.<sup>567</sup>

## TRAMADOL

Tramadol is a prodrug that is metabolized by CYP2D6 and CYP3A4 to its more potent opioid analgesic metabolites, particularly the *O*-demethylation product M1. There is a significant variability in the efficiency and amount of CYP2D6 enzymes among individuals. Therefore, the large phenotypic variation affects the speed of metabolism and the rate of accumulation or elimination of tramadol.<sup>568</sup>

The action of tramadol to induce analgesia represents the combination of two predominant mechanisms, reuptake inhibition of the noradrenergic serotonergic system and activation of the  $\mu$ -opioid receptor and to a lesser extent the  $\delta$ - and  $\kappa$ -opioid receptors.<sup>569</sup> It was suggested that tramadol may also have a direct serotonin-releasing action.<sup>570</sup> Given the analgesic effect of tramadol is only partially reversed by naloxone, its serotonergic and noradrenergic effects likely represent its predominant analgesic action.

Tramadol is onefifth to onetenth as potent as morphine. In rats, tramadol could reduce MAC of isoflurane in a naloxone-sensitive manner.<sup>571</sup> It was shown that intravenously administered tramadol was effective for postthoracotomy pain relief.<sup>572</sup> Analgesic doses of tramadol may produce less respiratory depression in part because of its non-opioid receptor-mediated actions, and have minimal effects on gastrointestinal motor function.<sup>573</sup> Nevertheless, tramadol used as a sole drug cannot be considered the drug of choice after moderately severe painful surgery. The doses needed to relieve pain in 80% of patients are much larger than the usual dose of 50 to 100 mg.<sup>574</sup>

Tramadol added to lidocaine for intravenous regional anesthesia provided a shorter onset time of sensory block.<sup>575</sup> Tramadol added to 1.5% mepivacaine for brachial plexus block enhances the duration of analgesia in a dose-dependent manner with acceptable side effects.<sup>576</sup> Intraarticular tramadol was also used for management and prevention of pain after arthroscopic knee surgery. It was shown that the intraarticular admixture of tramadol 100 mg with 0.25% bupivacaine provides a pronounced prolongation of analgesia compared with either drug alone in patients undergoing arthroscopic knee surgery.<sup>577</sup>

Tramadol has dose- and time-dependent bactericidal activity against *Escherichia coli* and *Staphylococcus epidermidis*, as well as antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The antibacterial properties of tramadol might be useful for reduction of bacterial infection after regional anesthesia.<sup>578</sup>

Coadministration of tramadol with proserotonergic medications can result in a hyperserotonergic state, serotonin

syndrome, which can be subacute or chronic, and range from mild to severe. In mild cases, patients are afebrile and may report symptoms of diarrhea, tremor, tachycardia, shivering, diaphoresis, or mydriasis.<sup>579</sup> In severe cases, neuromuscular hyperactivity, autonomic hyperactivity, altered mental state, gastrointestinal symptoms, and even death have been reported. Serotonergic medications that can interact with tramadol include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, triptans (e.g., sumatriptan), antipsychotics, anticonvulsants, antiparkinsonian agents, cough and cold medications containing dextromethorphan, herbal products containing St. John's wort, and medications that inhibit the metabolism of serotonin, such as monoamine oxidase inhibitors. Because symptoms of serotonergic and norepinephrine withdrawal are possible upon abrupt cessation of tramadol, gradual tapering or symptomatic support are necessary when tramadol administration is stopped.<sup>580</sup>

## MORPHINE-6-GLUCURONIDE

Morphine-6-glucuronide (M6G) is a potent metabolite of morphine. In contrast to morphine, M6G is not metabolized but excreted via the kidneys and exhibits enterohepatic cycling, as it is a substrate for multidrug resistance transporter proteins in the liver and intestines.<sup>580</sup> M6G exhibits a delay in its analgesic effect (blood–effect-site equilibration half-life 4–8 hours), which is partly related to slow passage through the blood–brain barrier and distribution within the brain compartment. M6G can be used as an analgesic in humans. Osborne et al. reported that 0.5 to 4 mg IV of M6G was effective for cancer pain for 2 to 24 hours without nausea and vomiting.<sup>581</sup> M6G 100  $\mu$ g and 125  $\mu$ g given intrathecally provided excellent analgesia after total hip replacement, as did intrathecal morphine sulfate 500  $\mu$ g.<sup>582</sup> In a randomized double-blind study it was shown that M6G has an analgesic effect similar to that of morphine over the first 24 hours postoperatively. However, initial onset of M6G effect may be slower than morphine.<sup>583</sup> M6G has also paradoxically been observed to increase pain sensitivity in mice and humans. The pronociceptive effect of M6G can be shown in knockout mice lacking  $\mu$ -,  $\kappa$ -, and  $\delta$ -opioid receptors, and might be due to activation of the NMDA receptors.<sup>584</sup>

## Agonist-Antagonist Opioid Compounds

Nalorphine, the first agonist-antagonist opioid, was successfully synthesized by Weijland and Erickson in 1942 and was found to be strongly antagonistic to almost all the properties of morphine. Although nalorphine was found to possess strong analgesic actions, it was unsuitable for clinical uses because of its psychotomimetic effects. Nalorphine was used in lower doses as an opioid antagonist.

Agonist-antagonist opioids are usually produced by alkylation of the piperidine nitrogen and addition of a three-carbon side chain such as a propyl, allyl, or methyl allyl to morphine. Buprenorphine is a partial agonist at the  $\mu$ -receptor and an antagonist at the  $\kappa$ -receptor.

The other compounds are  $\mu$ -antagonists and full or partial agonists at the  $\kappa$ -receptors. Agonist-antagonist opioids are less prone (but not immune) to abuse because they have analgesic ceiling effects, cause less euphoria, and are associated with less drug-seeking behavior and physical dependence.

Dosing data of these compounds are shown in Table 24.10. The agonist-antagonists depress respiration similarly as morphine, but ceiling effects exist (Table 24.11). Effects on the cardiovascular system differ among these compounds (Table 24.12).

**TABLE 24.10** Dosing Data for Agonist-Antagonist Opioids and Morphine

	Equianalgesic IM Dose (mg)	Duration of Analgesia (h)	Oral: IM Efficacy Ratio
Morphine	10	4-5	1:6
Buprenorphine	0.3-0.4	>6	1:2*
Butorphanol	2	3-4	—
Nalbuphine	10	3-6	1:4-5
Pentazocine	40	3	1:3

\*Sublingual:IM ratio.

IM, Intramuscular.

**TABLE 24.11** Respiratory Depressant Effects of Agonist-Antagonists Compared With Morphine\*

Drug	Correlation of Respiratory Depression with Dose
Morphine	Increases proportionally with dose
Buprenorphine	Ceiling effect at 0.15-1.2 mg in adults
Butorphanol	Ceiling effect at 30-60 $\mu$ g/kg
Nalbuphine	Ceiling effect at 30 mg in adults
Pentazocine	Ceiling effect suggested, but difficult to study because of psychotomimetic effects

\*Low or moderate naloxone doses readily reverse the respiratory depressant effects produced by therapeutic doses of all drugs listed, except buprenorphine.

From Zola EM, McLeod DC. Comparative effects and analgesic efficacy of the agonist-antagonist opioids. *Drug Intell Clin Pharm*. 1983;17:411.

**TABLE 24.12** Hemodynamic Effects of Agonist-Antagonist Compounds Compared With Morphine

Drug	Cardiac Workload	Blood Pressure	Heart Rate	Pulmonary Artery Pressure
Morphine	↓	↓	=↓	=↓
Buprenorphine	↓	↓	↓	?
Butorphanol	↑	=↑	=	↑
Nalbuphine	↓	=	=↓	=
Pentazocine	↑	↑	↑	↑

From Zola EM, McLeod DC. Comparative effects of analgesic efficacy of the agonist-antagonist opioids. *Drug Intell Clin Pharm*. 1983;17:411.

## PENTAZOCINE

Analgesia produced by pentazocine is primarily related to  $\kappa$ -receptor stimulation. Pentazocine is onehalf to onefourth as potent as morphine. Ceilings to both analgesia and respiratory depression occur after 30 to 70 mg of pentazocine. Although the potential for abuse is less than with morphine, prolonged use of pentazocine can lead to physical dependence. Nalorphine-like dysphoric side effects are common, especially after high doses (>60 mg) of pentazocine in the elderly. The dysphoric effects of pentazocine can be reversed with naloxone. Pentazocine depresses myocardial contractility and increases arterial blood pressure, heart rate, systemic vascular resistance, pulmonary artery pressure, and left ventricular work index. Pentazocine also increases blood catecholamine levels. Pentazocine inhibits gastric emptying and gastrointestinal transit in rats, whereas U50488H, a pure  $\kappa$ -agonist, did not significantly inhibit either.<sup>585</sup> Therefore, it might be speculated that pentazocine affects gastrointestinal function through a mechanism other than the opioid receptors.

Pentazocine has been shown to be an effective treatment for pruritus after cesarean delivery under spinal anesthesia with opioids, the incidence of which is ranging from 50% to 100%. A single 15-mg dose of IV pentazocine after delivery was shown to reduce both the incidence and severity of pruritus in women who have received subarachnoid opioids during cesarean delivery.<sup>586</sup> Pentazocine has limited application, because it is associated with a high incidence of PONV, it provides limited analgesia, it partially antagonizes other opioids, and it can produce undesirable cardiovascular and psychotomimetic effects.

## BUTORPHANOL

Butorphanol is an agonist at  $\kappa$ -receptors. Its activity at  $\mu$ -receptors is either antagonistic or partially agonistic. It is 5 to 8 times as potent as morphine and is only available in parenteral form. After IM injection, onset of effect is rapid, and peak analgesia occurs within 1 hour. Whereas duration of action of butorphanol is similar to that of morphine, its plasma half-life is only 2 to 3 hours. Although butorphanol (10 mg IM) causes as much respiratory depression as the same dose of morphine, higher doses reach a ceiling. Side effects after butorphanol include drowsiness, sweating, nausea, and CNS stimulation. In healthy volunteers, butorphanol (0.03 or 0.06 mg/kg IV) produces no or minimal cardiovascular changes. However, in patients with cardiac disease, butorphanol causes significant increases in cardiac index, left ventricular end-diastolic pressure, and pulmonary artery pressure.

Because butorphanol decreases the MAC for enflurane by only a small fraction, it cannot serve like the fentanyl congeners as an anesthetic agent. Butorphanol is subject to less abuse and has less addictive potential than morphine or fentanyl. Acute biliary spasm can occur after butorphanol, but increases in biliary pressure are less than after equipotent doses of fentanyl or morphine. Transnasal butorphanol is effective in relieving migraine and postoperative pain.<sup>587</sup>

## BUPRENORPHINE

Buprenorphine is a thebaine derivative,  $\mu$ -receptor partial agonist, and similar in structure to morphine but

approximately 33 times more potent. Whereas fentanyl dissociates rapidly from  $\mu$ -receptors (half-life of 6.8 minutes), buprenorphine has a higher affinity and takes much longer (half-life of 166 minutes) to dissociate. Onset of action of buprenorphine is slow, its peak effect may not occur until 3 hours, and duration of effect is prolonged (<10 hours). Volume of distribution of buprenorphine is 2.8 L/kg and its clearance is 20 mL/kg/min. Plasma concentrations of the metabolites of buprenorphine, norbuprenorphine, buprenorphine-3-glucuronide, and norbuprenorphine-3-glucuronide may approximate or exceed those of the parent drug. Both glucuronide metabolites are biologically active and may contribute to the overall pharmacology of buprenorphine.<sup>588</sup>

Subjective effects (e.g., euphoria) of buprenorphine are similar to morphine. Buprenorphine produces depression of minute ventilation which leveled off at doses higher than 3.0  $\mu$ g/kg to about 50% of baseline, in contrast to the case of fentanyl, in which dose-dependent respiratory depression results in apnea at doses higher than 2.9  $\mu$ g/kg (Fig. 24.32).<sup>589</sup> Buprenorphine has been successfully used for premedication (0.3 mg IM), as the analgesic component in balanced anesthesia (4.5–12  $\mu$ g/kg), and for postoperative pain control (0.3 mg IM). Buprenorphine, like the other agonist-antagonist compounds, is not acceptable as a sole anesthetic, and its receptor kinetic profile restricts its usefulness if other  $\mu$ -agonists are used. Opioid withdrawal symptoms develop slowly (5–10 days) after buprenorphine is discontinued following long-term use.

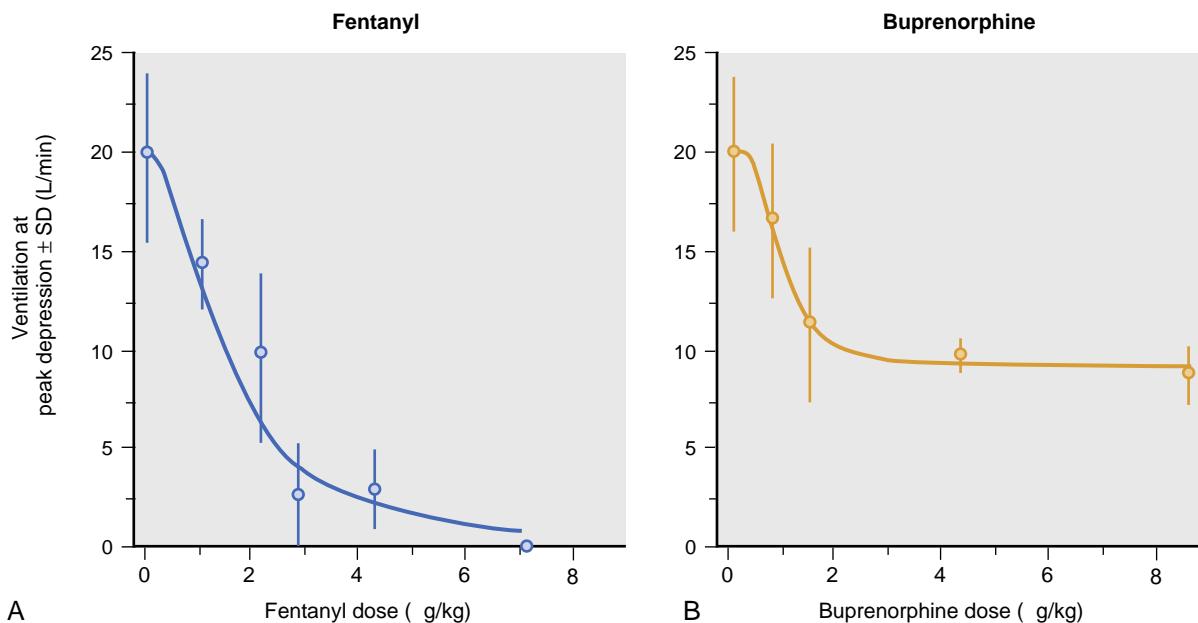
A sublingual combination tablet composed of buprenorphine and naloxone in a fixed 4:1 ratio may provide pain relief in patients with chronic pain with OUD. However, the unique pharmacological profile of buprenorphine/naloxone confers it to be a weak analgesic relative to full  $\mu$ -receptor agonists. Studies investigating the efficacy of

buprenorphine/naloxone or buprenorphine alone for the management of non-malignant pain are ongoing. Possible mechanisms of pain relief by buprenorphine/naloxone therapy in opioid-dependent patients with chronic pain may include reversal of opioid-induced hyperalgesia and improvement in opioid tolerance and OUD.<sup>590</sup>

Acute administration of  $\kappa$ -opioid receptor agonists and antagonists has been shown to produce effects characterized as prodepressive or antidepressant, respectively, in rodent behavioral tests, encouraging further investigation of  $\kappa$ -opioid receptor antagonists as potential anti-depressant treatments in humans.<sup>591</sup> In a preliminary clinical study, low doses of buprenorphine, which possess  $\kappa$ -receptor antagonist activity, produced impressive alleviation of depressive symptoms in patients that were considered treatment-resistant within 1 week of initiating administration.<sup>592</sup>

## NALBUPHINE

Nalbuphine is an agonist-antagonist opioid that is structurally related to oxymorphone and naloxone, and binds to  $\mu$ -receptors as well as to  $\kappa$ - and  $\delta$ -receptors. Nalbuphine acts as an antagonist at the  $\mu$ -receptor and an agonist at the  $\kappa$ -receptor. Activation of supraspinal and spinal  $\kappa$ -receptors results in limited analgesia, respiratory depression, and sedation. Nalbuphine, like other agonist-antagonist compounds, interferes with the analgesia produced by pure  $\mu$ -agonists. In rats, coadministration of nalbuphine with morphine dose-dependently blocked the development of morphine tolerance and dependence, without attenuation of antinociceptive effect of morphine.<sup>593</sup> Nalbuphine is only available for parenteral use. Onset of effects is rapid (5–10 minutes), and duration is long (3–6 hours) because of a long plasma elimination half-life (5 hours).



**Fig. 24.32 Dose-response relationships for reduction of minute ventilation induced by fentanyl (A) and buprenorphine (B).** The response is the peak ventilatory depression at each dose. The line through the data is the fit to the Hill equation. Placebo is 0  $\mu$ g/kg. Data are mean  $\pm$  standard deviation. (From Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth*. 2005;94:825–834.)

Nalbuphine has been administered as an analgesic supplement for conscious sedation or balanced anesthesia, and as an analgesic for postoperative and chronic pain problems. In patients undergoing myocardial revascularization, continuous infusion of nalbuphine (0.05-0.1 mg/kg/min) and fentanyl (0.15-0.3 µg/kg/min) was compared.<sup>594</sup> It was shown that nalbuphine lacks the ability to attenuate cardiovascular and hormonal responses to tracheal intubation and surgical procedures, and was concluded that continuous infusion of nalbuphine cannot be recommended for anesthesia in patients undergoing myocardial revascularization. For postoperative patient-controlled epidural analgesia, the combination of hydromorphone 0.075 mg/mL and nalbuphine 0.04 mg/mL resulted in lower incidence of nausea and decreased need of bladder catheterization compared with hydromorphone alone.<sup>595</sup> A randomized double-blind controlled study in patients undergoing gynecological operations demonstrated that interaction between morphine and nalbuphine in intravenous PCA admixture is additive, and combination of the two drugs can decrease the incidence of pruritus.<sup>596</sup>

A prospective randomized double-blinded study demonstrated that nalbuphine (4 mg IV) was as effective as ondansetron (4-8 mg IV) for prevention of intrathecal morphine-induced pruritus after cesarean delivery.<sup>597</sup> Some reports showed that nalbuphine provides a rapid and potent antishivering effect similarly as meperidine.<sup>598</sup> However, a quantitative systematic review of randomized controlled trials did not support the conclusion.<sup>197</sup>

## DEZOCINE

Desocine is slightly more potent and acts faster than morphine, with a similar duration. Although no longer used clinically in Western countries, dezocine is gaining popularity in China as an alternative medication for perioperative pain management. A pharmacologic study showed the unique molecular pharmacologic profile of dezocine as a partial µ-receptor agonist, a κ-receptor antagonist, and a norepinephrine and serotonin reuptake inhibitor (*via* norepinephrine transporter and serotonin transporter).<sup>368</sup> Although dezocine was shown to be an effective alternative to fentanyl when administered during outpatient laparoscopy with propofol and N<sub>2</sub>O, dezocine was associated with a high incidence of postoperative nausea and a delayed discharge time.<sup>599</sup> In adult patients who had arthroscopic surgery under general anesthesia, dezocine (5 mg IV) and morphine (5 mg IV) were similarly effective for postoperative analgesia and showed similar side effects.<sup>600</sup> A recent report showed that intravenous dezocine 0.1 mg/kg can effectively suppress cough induced by 5 µg/kg fentanyl.<sup>601</sup>

## MEPTAZINOL

Meptazinol has been reported to cause minimal respiratory depression because of its selectivity for µ<sub>1</sub>-receptors. In patients receiving meptazinol (2.5 mg/kg) with a barbiturate, no cardiovascular changes were observed at tracheal intubation, whereas blood pressure and heart rate were significantly increased in patients receiving fentanyl (5 µg/kg).<sup>602</sup> Side effects (nausea and vomiting) limit its use to relieve severe pain.

# Opioid Antagonists

## NALOXONE

Clinically, opioid antagonists are used to restore spontaneous ventilation in patients who breathe inadequately after opioid overdoses or opioid anesthesia. In addition, opioid antagonists can reduce or reverse opioid-induced nausea and vomiting, pruritus, urinary retention, rigidity, and biliary spasm associated with numerous therapies employing opioids, such as neuraxial analgesic techniques. It was reported that the potency ratio for naloxone:nalbuphine for antagonism of pruritic effects of epidural morphine was approximately 40:1.<sup>603</sup>

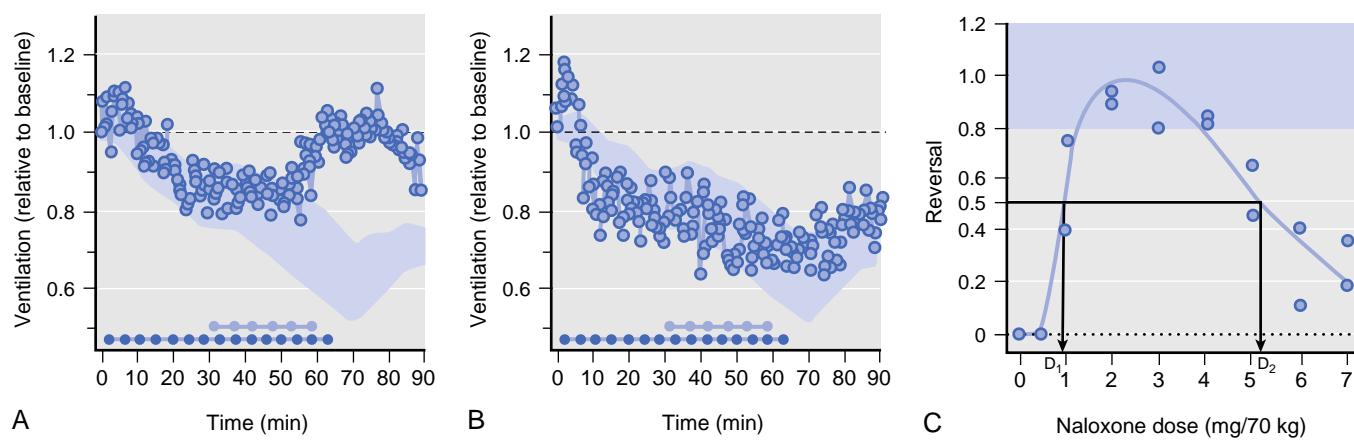
Morphine requirements were significantly less in patients receiving naloxone, suggesting that naloxone enhanced analgesia.<sup>604</sup> Proposed possible mechanisms for this apparent paradoxical effect of naloxone include enhanced release of endogenous opioids and opioid receptor upregulation.

Although naloxone is generally considered to be a pure opioid receptor antagonist, it delays gastric emptying of saline or milk, as does morphine in the rat.<sup>360</sup> Furthermore, high-dose naloxone possesses partial agonistic activity on the µ- and κ-opioid receptors in the cultured cells.<sup>605</sup>

## Reversal of Respiratory Depression by Naloxone

In the early 1950s, nalorphine and levallorphan were evaluated as opioid antagonists. They were often found unacceptable because of a high incidence of side effects, as well as incomplete reversal. Naloxone was introduced into clinical practice in the late 1960s. There have been reports of side effects (increases in heart rate and blood pressure) and more serious complications (e.g., pulmonary edema). Initial naloxone dose recommendations ranged from 0.4 to 0.8 mg. Onset of action of IV naloxone is rapid (1-2 minutes), and half-life and duration of effect are short, approximately 30 to 60 minutes. If IV access is not available, naloxone, in doses similar to those given IV, is effectively absorbed after intratracheal administration. Reversal with naloxone is limited by high affinity for and slow dissociation from the µ-opioid receptor of buprenorphine, and depends on the buprenorphine dose and the correct naloxone dose window (Fig. 24.33).<sup>606</sup> Because respiratory depression from buprenorphine may outlast the effects of naloxone boluses or short infusions, a continuous infusion of naloxone may be required to maintain reversal of respiratory depression.<sup>606</sup>

Several mechanisms produce increases in arterial blood pressure, heart rate, and other significant hemodynamic alterations after naloxone reversal of opioids. These include pain, rapid awakening, and sympathetic activation not necessarily due to pain. When patients receiving naloxone for opioid agonist reversal are hypothermic due to intraoperative heat loss, O<sub>2</sub> consumption and minute ventilation can increase two- to threefold.<sup>607</sup> Such metabolic demands also stress the cardiovascular system, increasing cardiac output. In addition, greater degrees of hypercapnia at the time of opioid antagonism will result in greater degrees of cardiovascular stimulation because of associated sympathetic stimulation. Opioid reversal may be particularly hazardous in patients with pheochromocytoma or chromaffin tissue tumors. However, it was also reported that



**Fig. 24.33 Reversal of buprenorphine-induced respiratory depression with naloxone depends on the correct naloxone dose window.** Respiratory depression induced by 0.2 mg buprenorphine was reversed by naloxone 2 mg (A) and 6 mg (B) given over 30 minutes in one subject. Gray field in the background is the result of the placebo group in which saline was infused instead of naloxone. Light gray dots and dark gray dots represent buprenorphine and naloxone infusion, respectively. (C) Influence of 0 (placebo) and 0.5-7 mg naloxone on 0.2 mg intravenous buprenorphine-induced respiratory depression. Reversal was calculated from the naloxone-induced change in ventilation, and it ranges from 0 (effect not different from placebo) to 1 (reversal to predrug baseline level). (From van Dorp E, Yassen A, Sarton E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology*. 2006;105:51-57.)

IV administration of 10 mg naloxone did not significantly change plasma catecholamine concentration and blood pressure in pheochromocytoma patients.<sup>608</sup>

Recurrence of respiratory depression after naloxone is due to the short half-life of naloxone. “Renarcotization” occurs more frequently after the use of naloxone to reverse longer-acting opioids such as morphine. This is commonly not seen in clinical practice because opioid concentrations are often just above the threshold for respiratory depression, and treatment with a single or just a few effective bolus doses of naloxone is sufficient to reverse the respiratory depression induced by most opioids for the short time that the agonist concentration exceeds the respiratory depression threshold.<sup>251</sup> Short-acting opioids such as alfentanil rarely pose a danger of renarcotization, because of a rapid plasma decay curve and weak opioid receptor binding compared with fentanyl and sufentanil. Naloxone, although active at  $\mu$ -,  $\delta$ -, and  $\kappa$ -receptors, has greatest affinity for  $\mu$ -receptors, which mediate most potent opioid effects, including respiratory depression and analgesia. Careful titration of naloxone often can restore adequate spontaneous ventilation without reversal of adequate analgesia.

### Other Applications of Naloxone

Low-dose naloxone not only has been shown to block the development of acute opioid tolerance but also to ameliorate undesired opioid-induced side effects. Naloxone infusion 0.25  $\mu$ g/kg/h prevented the acute opioid tolerance induced by a large dose of remifentanil at 0.30  $\mu$ g/kg/min, provided a quicker recovery of bowel function, and reduced the length of hospital stay after open colorectal surgery.<sup>609</sup>

Reversal of effects of alcohol, barbiturates, and benzodiazepines by naloxone has been reported. However, it was also reported that naloxone potentiates anxiolytic-like action of benzodiazepines and barbiturates in the rat.<sup>610</sup> It is not advisable to try to reverse the effects of overdose of benzodiazepines and barbiturates by naloxone. Although it was suggested that the  $\mu$ -opioid receptor is involved in the antinociceptive action of ketamine in mice,<sup>74</sup> naloxone did

not affect the action of ketamine on secondary hyperalgesia induced by burn injury in humans.<sup>611</sup>

Evidence indicates that endogenous opioid peptides participate in the control of cardiovascular regulation during hemorrhagic shock. In patients with documented septic shock and resistance to a one-liter fluid challenge, administration of naloxone by initial bolus of 0.03 mg/kg followed by infusion at a rate of 0.2 mg/kg/h significantly increased mean arterial pressure, but did not affect survival.<sup>612</sup> This effect may be due to centrally mediated increases in sympathetic tone and decreases in parasympathetic output and/or antagonism of endogenous opioids. However, the clinical usefulness of naloxone to treat shock remains to be determined and additional randomized clinical trials are needed to assess its usefulness.<sup>613</sup>

One study indicated that opioids can elicit excitatory as well as inhibitory modulation of the action potentials of sensory neurons, and ultra-low doses of naloxone could selectively block the excitatory effect of opioids.<sup>614</sup> A prospective randomized double-blind study demonstrated that addition of an ultra-low dose of naloxone (100 ng) to 34 mL of 1.5% lidocaine solution with or without fentanyl in axillary brachial plexus block prolongs the time to first postoperative pain and motor blockade but also lengthens the onset time.<sup>615</sup>

It has been reported that naloxone may ameliorate the neurologic deficit following an ischemic or traumatic neurologic insult in animals.<sup>616</sup> In humans, a randomized controlled trial demonstrated that naloxone (a bolus of 5.4 mg/kg, followed by infusion at 4.0 mg/kg/h for 23 hours) does not improve neurologic recovery after acute spinal cord injury.<sup>617</sup> However, it was reported that combined use of cerebrospinal fluid drainage and naloxone reduces the risk of paraplegia in thoracoabdominal aneurysm repair.<sup>618</sup> Naloxone may also have a therapeutic role in heat stroke disorders<sup>619</sup> and cholestasis-induced pruritus.<sup>620</sup> Although intravenous naloxone has been claimed to produce pain relief in opioid-resistant central post-stroke pain, a double-blind trial concluded that intravenous naloxone was of no value in alleviating central post-stroke pain.<sup>621</sup>

## NALTREXONE

Naltrexone is a  $\mu$ -,  $\delta$ -, and  $\kappa$ -opioid receptor antagonist. It is longer acting than naloxone (plasma half-life of 8–12 vs. 0.5–1.5 hours), and it is active when taken orally. A double-blind, placebo-controlled study for patients undergoing cesarean section indicated that naltrexone (6 mg) was an effective oral prophylactic against the pruritus and vomiting associated with intrathecal morphine, but was associated with shorter duration of analgesia.<sup>622</sup>

As a prescribed treatment for opioid dependence, extended-release naltrexone hydrochloride was compared directly with opioid medication treatment, which includes daily buprenorphine hydrochloride with naloxone hydrochloride. It was shown that extended-release naltrexone, administered 380 mg as monthly intramuscular injections, was as effective as buprenorphine–naloxone in maintaining short-term abstinence from heroin and other illicit substances and should be considered as a treatment option for opioid-dependent individuals.<sup>343</sup> Importantly, naltrexone induction requires individuals to be completely off opioids due to the likelihood of severe opioid withdrawal.

## NALMEFENE

Nalmefene has a greater preference for  $\mu$ - than  $\delta$ - or  $\kappa$ -receptors. Nalmefene is equipotent to naloxone. Nalmefene is long-acting after oral (0.5–3.0 mg/kg) and parenteral (0.2–2.0 mg/kg) administration. Bioavailability after oral administration is 40% to 50%, and peak plasma concentrations are reached in 1 to 2 hours. The mean terminal elimination half-life of nalmefene is 8.5 hours, compared with 1 hour for naloxone. Prophylactic administration of nalmefene significantly decreased the need for antiemetics and antipruritic medications in patients receiving intravenous PCA with morphine.<sup>623</sup>

## METHYLNALTREXONE

Methylnaltrexone is the first quaternary ammonium opioid receptor antagonist that does not cross the blood–brain barrier.<sup>352</sup> It can reverse adverse effects of opioid medications mediated by peripheral opioid receptors, while the opioid effects mediated by opioid receptors in the central nervous system, such as analgesia, are not affected. Delayed gastric emptying induced by 0.09 mg/kg morphine could be attenuated by 0.3 mg/kg methylnaltrexone in healthy volunteers.<sup>359</sup> Methylnaltrexone has been shown to be effective for management of opioid-induced constipation. It was reported that subcutaneous methylnaltrexone (0.15 mg/kg) rapidly induced laxation in patients who had received opioids for 2 or more weeks and who had received stable doses of opioids and laxatives for 3 or more days without relief of opioid-induced constipation.<sup>624</sup> It was also reported that methylnaltrexone (12 mg once daily) did not affect opioid-mediated analgesia in patients with chronic noncancer pain suffering from opioid-induced constipation who received more than 50 mg of oral morphine equivalents daily.<sup>625</sup> Because methylnaltrexone does not cross the dura, it might have potential to reverse peripherally mediated side effects of epidural opioids.<sup>626</sup> Randomized double-blind placebo-controlled studies have shown effectiveness

of methylnaltrexone and alvimopan, another peripherally acting opioid receptor antagonist, in management of postoperative ileus, a transient cessation of coordinate bowel function after surgery.<sup>352</sup>

## NALOXEGOL

Methylnaltrexone is restricted by the need for subcutaneous administration and is approved only for treatment of opioid-induced constipation in patients with advanced medical illness. Naloxegol, an oral peripherally acting  $\mu$ -opioid antagonist, is a pegylated derivative of naloxone. Pegylation confers substrate properties for P-glycoprotein transporter and thus limits the ability of naloxegol to cross the blood–brain barrier. A double-blind study in outpatients with noncancer pain and opioid-induced constipation demonstrated that a daily dose of 12.5 mg or 25 mg naloxegol improved bowel movement, as compared with placebo, without changing pain scores and daily opioid dose.<sup>627</sup>

## Drug Interactions With Opioids

### GENERAL PRINCIPLES

Opioids are frequently combined with other anesthetic agents to produce optimal anesthetic conditions. Many drugs concomitantly administered for anesthesia can interact each other. Although some of these interactions are intentionally sought, others are unwanted and adverse. There are three general types of mechanisms of drug interactions—pharmaceutical, pharmacokinetic, and pharmacodynamic.<sup>628</sup>

Pharmaceutical interactions are chemical in nature, as illustrated when an alkaline solution of thiopental and an acidic solution of nondepolarizing muscle relaxants precipitate when simultaneously administered via IV.

Pharmacokinetic interactions occur when the administration of one agent alters the pharmacokinetics or disposition of another. Hemodynamic changes induced by one agent can affect pharmacokinetic behavior of the other agent. Sufentanil, which has a greater hepatic extraction ratio than alfentanil, is more likely to be affected by decreases in hepatic blood flow. Cimetidine can prolong opioid effects by decreasing hepatic blood flow and/or diminishing hepatic metabolism. Opioid plasma levels also increase in the presence of propofol.<sup>629</sup> Decreased opioid metabolism, by the CYP 3A4 isoform of the cytochrome P-450 enzyme responsible for the oxidative metabolism of more than 50 drugs, may also underlie pharmacokinetic interactions. A wide range of chemical compounds, including many drugs, can interact with the cytochrome P-450 system, causing either an increased activity (enzyme induction) or enzyme inhibition (Box 24.5).<sup>628</sup> Alfentanil, but not sufentanil, may have its action prolonged as a result of impaired metabolism in patients receiving erythromycin.<sup>630,631</sup>

Pharmacodynamic interaction between opioids and inhaled anesthetics were assessed with classic MAC reduction evaluations in animals and humans. Although marked synergism between opioids and inhaled anesthetics occurs with analgesic doses of opioids, there is a ceiling effect to MAC reduction by opioids. The pharmacodynamic

### BOX 24.5 Drugs That Inhibit or Induce Cytochrome P-450 Enzymes

#### Inhibitors

- Antibiotics
  - Macrolides
  - Troleandomycin
  - Erythromycin
  - Fluoroquinolones
  - Isoniazid
- Aazole antifungal drugs
  - Ketoconazole
  - Itraconazole
- Calcium entry blockers
  - Diltiazem
  - Verapamil
- Omeprazole
- Cimetidine
- Propofol
- Grapefruit juice
- Inducers
- Barbiturates
- Antiepileptics
  - Carbamazepine
  - Phenytoin
  - Primidone
- Rifampicin
- Dichloralphenazone
- Ethanol
- Tobacco smoke

From Bovill JG. Adverse drug interactions in anesthesia. *J Clin Anesth.* 1997;9(Suppl):3S.

synergism between opioids and sedative-hypnotics such as propofol is profound. Choosing an opioid with a short context-sensitive half-life allows greater doses of that opioid to be administered, along with reduced doses of propofol, without compromising the time for recovery from anesthesia. Thus, the optimal plasma level of propofol is estimated to be approximately 30% less when it is combined with remifentanil instead of alfentanil.<sup>629</sup>

Drug dosing regimens and plasma concentration of opioid and sedative-hypnotics to provide optimal hemodynamic control during a range of noxious stimuli are necessary. However, complicating our understanding of drug interactions is the observation that the same degree of interaction does not apply across different types of stimuli.

### SEDATIVE-HYPNOTICS

#### Benzodiazepines

Alfentanil was found to reduce the midazolam ED<sub>50</sub> value for the induction of anesthesia in a dose-dependent fashion. On the contrary, concerning the antinociceptive effect, interaction between these two types of drugs may be less than additive.<sup>632</sup> Midazolam enhanced opioid-induced antinociception at the spinal level but inhibited it at the supraspinal level.<sup>633</sup> Many studies reveal benzodiazepine-opioid interactions for many properties other than analgesia to be synergistic (supra-additive). Both the cardiovascular and respiratory actions of opioids can be significantly altered by the concomitant administration of benzodiazepines.<sup>634</sup>

In anesthetized rabbits, fentanyl and midazolam synergistically caused depression of phrenic nerve activity.<sup>635</sup> Combinations of benzodiazepines and opioids, although occasionally preserving ventricular function, can cause significant and occasionally profound decreases in blood pressure, cardiac index, heart rates, and systemic vascular resistances. Fluid loading may attenuate circulatory depression that occurs when benzodiazepines and opioids are combined.

#### Barbiturates

Barbiturates can potentiate or produce hypotension if a large dose is administered with opioids. Hypotension after barbiturate-opioid combination is due to venodilatation, decreased cardiac filling, myocardial depression, and decreased sympathetic nervous system activity. Reducing induction doses of barbiturates administered concomitantly with opioids is recommended.

#### Propofol

Administration of propofol-opioid combinations provides unconsciousness and block responses to noxious stimuli. However, when given as an intravenous bolus for induction of anesthesia, propofol can create moderate to severe preintubation hypotension. Propofol-fentanyl and propofol-sufentanil anesthesia for coronary artery bypass surgery may provide acceptable conditions, but mean arterial pressure can decrease to levels that may jeopardize coronary perfusion, especially during the induction of anesthesia. In healthy volunteers, addition of alfentanil (effect-site concentration of 50 or 100 ng/mL) did not affect the changes in the BIS induced by propofol, but blocked BIS increase induced by painful stimuli.<sup>636</sup> In patients undergoing spine fusion, infusion of fentanyl (blood levels at 1.5-4.5 ng/mL) reduced the infusion rate of propofol necessary to keep mean arterial pressure, but delayed spontaneous eye opening and recovery of orientation.<sup>475</sup> In patients undergoing ambulatory gynecologic laparoscopy, administration of fentanyl (25-50 µg IV) at the time of anesthetic induction reduced maintenance propofol requirement, but failed to provide effective postoperative analgesia and increased the need of postoperative use of antiemetics.<sup>637</sup> Pharmacokinetic interaction as well as pharmacodynamic interaction between propofol and opioids has been reported. Target-controlled infusion of alfentanil (target concentration, 80 ng/ml) was shown to increase blood propofol concentration by 17%, and decrease the elimination clearance, the distribution clearance, and the peripheral volume of distribution of propofol.<sup>638</sup>

#### Etomidate

Etomidate can be combined in low doses with opioids with little loss of cardiovascular stability. In patients scheduled for coronary artery bypass grafting, etomidate (0.25 mg/kg) plus fentanyl (6 µg/kg) resulted in less hypotension after induction and intubation than propofol (1 mg/kg) plus fentanyl (6 µg/kg).<sup>639</sup>

#### Ketamine

Many studies on combinations of opioids and ketamine, an NMDA receptor antagonist, have been reported to optimize analgesic therapy to a variety of painful conditions. OIH

and subsequent opioid tolerance can be prevented by ketamine in rats, suggesting the usefulness of combination of ketamine and opioids for postoperative analgesia. A pharmacologic study suggested that endogenous opioids and  $\mu$ - and  $\delta$ -opioid receptors are also involved in ketamine-induced central antinociception but the  $\kappa$ -opioid receptor is not involved in this effect.<sup>640</sup>

In the acute perioperative setting, results vary depending on the clinical context. Combination of ketamine (2.5 or 10 mg IV) and alfentanil (0.25 or 1 mg IV) provided no advantage over a larger dose of either drug alone in relieving pain caused by intradermal capsaicin injection in healthy volunteers.<sup>641</sup> Furthermore, combination of ketamine 1 mg/mL and morphine 1 mg/mL for PCA did not provide benefit to patients undergoing major abdominal surgery.<sup>642</sup> In contrast, Lauretti et al. reported that oral ketamine and transdermal nitroglycerine effectively reduced daily consumption of oral morphine in patients with cancer pain.<sup>643</sup> A prospective randomized double-blind controlled study demonstrated that intraoperative and postoperative administration of ketamine for the first 48 hours after surgery (2  $\mu$ g/kg/min after a 0.5 mg/kg bolus) improved postoperative analgesia with a significant decrease of morphine consumption.<sup>644</sup> Furthermore, it was reported that a small dose of ketamine and memantine, a long-acting oral NMDA receptor antagonist, was effective in managing intractable pain in an opioid-tolerant patient.<sup>645</sup> Webb et al. reported that small-dose ketamine could be a useful addition to perioperative tramadol administration in patients undergoing abdominal surgery.<sup>646</sup>

## INHALED ANESTHETICS

Volatile anesthetics are frequently combined with opioids in order to ensure amnesia and to promote immobility and hemodynamic stability. Clinical trials of opioids supplemented with volatile anesthetics for cardiac surgery demonstrate well-preserved cardiac output and minimal decreases in mean arterial blood pressure.<sup>647</sup> Myocardial ischemia may not, however, always be ameliorated by approaches that combine opioids with potent inhaled agents in spite of apparent "good" hemodynamic control. Some of the potent inhaled anesthetics can increase sympathetic nervous system activity and may increase the risk of myocardial ischemia in the cardiac patient.<sup>648</sup> Prior administration of fentanyl, in doses as low as 1.5  $\mu$ g/kg, can markedly attenuate such responses. Alfentanil (10  $\mu$ g/kg) is also effective in attenuating these effects.

## MUSCLE RELAXANTS

Pancuronium bromide has been frequently used for muscle relaxation during high-dose opioid anesthesia. The vagolytic action of pancuronium can attenuate opioid-induced bradycardia and support blood pressure. In patients undergoing coronary artery bypass grafting administered with sufentanil (3-8  $\mu$ g/kg), pancuronium (120  $\mu$ g/kg) caused significant increase in mean arterial pressure, heart rate, and cardiac output but did not induce myocardial ischemia.<sup>649</sup> Pancuronium-induced tachycardia was easily and rapidly treated and caused no differences in ischemia or perioperative myocardial infarction. Many factors alter

the impact of pancuronium and other muscle relaxants on hemodynamics when combined with opioids: the dose, timing, and rate of administration of each relaxant as well as the premedication, intravascular volume, left ventricular function, and presence of other drugs with autonomic nervous system actions.

Combinations of vecuronium and high doses of opioids may produce negative chronotropic and inotropic effects resulting in decreases in heart rate, cardiac output, and blood pressure, and increases in the need for vasopressor support. In patients scheduled for coronary artery surgery administered with 40  $\mu$ g/kg sufentanil in combination with vecuronium (0.1 mg/kg), heart rate, mean arterial pressure, and systemic vascular resistance decreased from baseline values after tracheal intubation with neither significant change in cardiac output nor evidence of new myocardial ischemia.<sup>650</sup>

In patients anesthetized with fentanyl 50  $\mu$ g/kg and scheduled to undergo elective coronary artery bypass grafting, rocuronium 0.6 mg/kg (approximately equivalent to 2  $\times$  ED<sub>95</sub> dose) was associated with changes of only small magnitude in hemodynamic variables, including increases in stroke volume index (+15%) and cardiac index (+11%), and a decrease in pulmonary capillary wedge pressure (-25%).<sup>651</sup> In patients undergoing coronary artery bypass surgery under fentanyl anesthesia, mivacurium 0.15 or 0.2 mg/kg produced decreases in mean arterial pressure and systemic vascular resistance index possibly mediated by histamine release, whereas atracurium (0.5 mg/kg) produced no significant hemodynamic changes.<sup>652</sup>

## MONOAMINE OXIDASE INHIBITORS

MAOI can underlie the most serious and potentially fatal drug interaction with opioids. Combination of meperidine and MAOI can induce the serotonin syndrome which is caused by excess serotonin availability in the CNS at the 5-HT<sub>1A</sub> receptor and characterized by confusion, fever, shivering, diaphoresis, ataxia, hyperreflexia, myoclonus, or diarrhea. The phenylpiperidine series opioids, including meperidine, tramadol, and methadone, appear to be weak serotonin reuptake inhibitors and have all been involved in serotonin toxicity reactions with MAOIs, whereas morphine, codeine, oxycodone, and buprenorphine are known not to be serotonin reuptake inhibitors, and do not precipitate serotonin toxicity with MAOIs.<sup>653</sup> Alfentanil and remifentanil could be used with MAOIs without complications.<sup>654,655</sup>

## CALCIUM CHANNEL BLOCKERS

Because opioids can inhibit voltage-dependent Ca<sup>2+</sup> channel activity through the activation of G proteins, it may be possible that opioid action is potentiated by Ca<sup>2+</sup> channel blockers. Numerous animal studies and a few clinical studies have documented that opioid-induced analgesia is potentiated by L-type Ca<sup>2+</sup> channel blockers. However, there is also a report that L-type Ca<sup>2+</sup> channel blockers do not potentiate morphine analgesia at clinically relevant doses.<sup>656</sup> N-type Ca<sup>2+</sup> channels are involved in the release of neurotransmitters from sensory neurons in the spinal cord. It was reported that intrathecal administration of a blocker of this channel,

$\omega$ -conotoxin GVIA, produced antinociception, and interacts synergistically with opioids at the spinal cord level.<sup>657</sup>

## MAGNESIUM

Magnesium has been shown to have antinociceptive effects probably due to its antagonistic action on the NMDA receptor. Intravenous administration of magnesium sulfate 50 mg/kg preoperatively and 8 mg/kg/h intraoperatively significantly reduced intra- and postoperative fentanyl requirement.<sup>658</sup> However, passage of magnesium across the blood-brain barrier is limited. Intrathecal administration of fentanyl 25  $\mu$ g plus magnesium sulfate 50 mg provided significantly prolonged analgesia compared with fentanyl alone, in patients requesting analgesia for labor.<sup>659</sup> It is likely that magnesium can potentiate opioid analgesia by both central and peripheral mechanisms.<sup>660</sup> A randomized, double-blind, prospective study showed that a relatively high dose of remifentanil (0.2  $\mu$ g/kg/min) enhances perincisional hyperalgesia in patients undergoing thyroidectomy, and intraoperative magnesium sulfate (30 mg/kg at induction followed by 10 mg/kg/h) can prevent remifentanil-induced hyperalgesia.<sup>226</sup>

## NONSTEROIDAL ANTIINFLAMMATORY DRUGS

NSAIDs such as ibuprofen, diclofenac, or ketorolac have been perioperatively administered to reduce opioid requirement. It was reported that perioperative administration of diclofenac (75 mg twice daily) reduced morphine consumption and the incidence of adverse effects such as sedation and nausea after total abdominal hysterectomy.<sup>661</sup> In a randomized double-blind trial, 0.1 mg/kg morphine was shown to be superior to 30 mg ketorolac as postoperative pain relief, but adding ketorolac to morphine reduces postoperative opioid requirement and opioid-related side effects in the early postoperative period.<sup>662</sup> Through the reduction of opioid requirements, NSAIDs are thought to help prevent opioid-induced hyperalgesia and/or the development of acute opioid tolerance although direct NSAID-dependent mechanisms are under investigation. A randomized double-blind placebo-controlled study has shown that 8 mg of lornoxicam prevented increase in postoperative morphine consumption induced by intraoperative fentanyl in female patients undergoing abdominal hysterectomy with spinal anesthesia.<sup>663</sup>

## ACETAMINOPHEN

Acetaminophen has central analgesic and antipyretic effects that share similarity to those of NSAIDs, but has weak peripheral antiinflammatory action. Acetaminophen has been shown to have significant fentanyl-sparing effects and to reduce side effects when combined with fentanyl in intravenous parent- or nurse-controlled analgesia for postoperative pediatric pain management.<sup>664</sup> On the other hand, a randomized, placebo-controlled, double-blind study in children who received standard propofol-remifentanil anesthesia undergoing spine surgery showed that intravenously administered acetaminophen 90 mg/kg/day did improve analgesia, but did not diminish oxycodone consumption during 24 hours.<sup>665</sup>

## GABAPENTINOIDs

Gabapentinoids, such as gabapentin and pregabalin, structural analogs of  $\gamma$ -aminobutyric acid, bind to the  $\alpha_2\delta$  subunit of spinal voltage-gated calcium channel, and produce antihyperalgesic effects in neuropathic and other painful conditions. It was suggested that both pharmacodynamic and pharmacokinetic interaction between morphine and gabapentin leads to increased analgesic effects.<sup>666</sup> Furthermore, intrathecal administration of gabapentin was shown to prevent the development of opioid tolerance induced by repeated intrathecal injection of morphine.<sup>667</sup> It might be possible that systemic and intrathecal application of gabapentin prevents the development of OIH.<sup>668</sup> Preoperative administration of pregabalin is proposed as a promising way of enhancing postoperative pain control. A randomized, triple-blinded, placebo-controlled study demonstrated that preoperative administration of 300 mg pregabalin in patients undergoing transperitoneal nephrectomy reduces postoperative opioid consumption and decreases the area of mechanical hyperalgesia.<sup>669</sup>

## ANTIDEPRESSANTS

Antidepressants are widely used to treat various chronic inflammatory and neuropathic pain conditions. Results in clinical studies were not consistent with respect to interactions between opioids and antidepressants. An isobolographic analysis demonstrated that systemic amitriptyline and morphine synergistically inhibit cutaneous orofacial inflammatory pain in rats.<sup>670</sup> Tricyclic antidepressants may cause respiratory depression in patients with chronic obstructive pulmonary diseases, and reduced CO<sub>2</sub> sensitivity has also been reported in patients receiving tricyclic antidepressants. An animal study demonstrated that pretreatment with amitriptyline increases morphine-induced hypercarbia through pharmacodynamic processes, suggesting that morphine doses should be reduced with careful titration, if patients are receiving concomitant treatment with tricyclic antidepressants.<sup>671</sup> It was demonstrated that perioperative administration of duloxetine, a potent selective serotonin and norepinephrine reuptake inhibitor, can reduce morphine requirement after knee replacement surgery.<sup>672</sup>

## DIPHENHYDRAMINE

Diphenhydramine, a histamine H<sub>1</sub> receptor antagonist, is used as a sedative, an antipruritic, and an antiemetic agent. When administered alone, it modestly stimulates ventilation by augmenting the interaction of hypoxic and hypercarbic ventilatory drives. It was shown that diphenhydramine counteracts the alfentanil-induced decrease in the slope of the ventilatory response to CO<sub>2</sub>.<sup>673</sup>

## LOCAL ANESTHETICS

Systemic administration of local anesthetics can significantly reduce pain and perioperative systemic lidocaine can significantly reduce opioid requirements.<sup>674</sup> Curiously, previous evidence suggests that opioid-tolerant patients are less responsive to local anesthetics for postoperative pain

management. In a study examining the effect of systemic morphine (seven daily subcutaneous injections of morphine 10 mg/kg) on the potency of lidocaine-induced block of the compound action potential in isolated rat sciatic nerves, it was shown that lidocaine potency was decreased due to the intrinsic changes in the peripheral nerve, and the loss of lidocaine potency remained 35 days after the last morphine injection.<sup>675</sup> Because there may be a decrease in potency of local anesthetics even in patients on moderate doses of opioids, additional study is necessary to better guide the perioperative use of systemic lidocaine.

Complete references available online at [expertconsult.com](http://expertconsult.com).

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## KEY POINTS

- With a better understanding of pain pathways and mechanisms, it has been recognized that ion channels play an important role in the transduction, transmission, and modulation of nociceptive signals. This opens a new avenue of developing novel therapeutic agents for the treatment of acute or chronic pain, particularly neuropathic pain.
- Although the exact mechanism of action remains unclear for many drugs listed in this chapter, they often are a component of a multidrug treatment strategy that has been increasingly used for the management of chronic pain conditions.

## Introduction

Recent advances in our understanding of pain mechanisms have enabled us to treat acute and chronic pain conditions with a variety of nonopioid pain medications. The option of using nonopioid pain medications is particularly meaningful given the growing global concern over prescription opioid abuse and overdose. Besides acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), several new categories of nonopioid pain medications can be used for the management of acute or chronic pain and, in particular, neuropathic pain. Examples of these nonopioid pain medications include drugs that block voltage-sensitive sodium channels and voltage-sensitive calcium channels, facilitate opening of chloride channels, increase function of the endogenous  $\gamma$ -aminobutyric acid (GABA) system, and modulate the N-methyl-D-aspartate (NMDA) receptor activity. In particular, ion channel blockers possess the antihyperalgesic effect by targeting specific mechanisms of pathologic pain, although most analgesics in this category do not necessarily produce the typical analgesic effect (i.e., raising the pain threshold above the normal baseline).<sup>1</sup>

This chapter briefly discusses NSAIDs and acetaminophen and focuses on describing several ion channel blockers that are commonly used in the treatment of pain conditions, as listed in [Box 25.1](#). They are grouped into two categories: calcium channel blockers and sodium channel blockers.

## Nonsteroidal antiinflammatory drugs

NSAIDs include ibuprofen, naproxen, indomethacin, ketorolac, and diclofenac and are examples of a class of medication commonly used as analgesic to reduce myofascial pain, postoperative pain, and chronic pain conditions. In a recent

Cochrane review of 16 randomized, controlled clinical trials (2144 patients), pain relief and function restoration were compared in patients with acute soft tissue injury treated with oral NSAIDs and other oral analgesics including acetaminophen with or without opioids. The analgesic effect was similar between NSAIDs and acetaminophen or opioid, and there were no differences in functional restoration at 7 days,<sup>2</sup> but the patients who were taking opioids reported more adverse side effects.<sup>3</sup> Although acetaminophen, indomethacin, or diclofenac produced similar pain reduction, the combination of acetaminophen and diclofenac showed slightly better pain reduction.<sup>4</sup> Intravenous ketorolac (15 or 30 mg) is a common medication of choice during the early postoperative period if there are no contraindications, such as renal insufficiency.<sup>5</sup> Ketorolac has also been successfully used in pediatric surgical patients.<sup>6,7</sup> A recent metaanalysis also found that NSAIDs were equivalent to opioids or paracetamol in the relief of acute renal colic pain.<sup>8</sup>

The cyclooxygenase-2 (COX-2) inhibitors are considered an alternative to NSAIDs (mixed COX-1/COX-2 inhibitors) while possessing reduced gastrointestinal side effects. However, COX-2 inhibition is associated with increased risk of adverse cardiovascular events, although recent clinical studies, including the data from the PRECISION trial that examined long-term cardiovascular safety issues, support the notion that both NSAIDs and COX-2 carry a certain degree of cardiovascular risk.<sup>9</sup>

## Acetaminophen

For many decades, oral acetaminophen has been widely used as an analgesic to treat mild to moderate pain. Recently, intravenous acetaminophen has become available in the United States. Results of a randomized trial of patients who had colorectal surgery indicated that

## BOX 25.1 Ion Channel Blockers as Pain Medications (Recommended Dosing)

### Calcium Channel Blockers

Gabapentin: Starting dose 100–300 mg/day; titrating up to 1800–3600 mg/day  
 Pregabalin: Starting dose: 75–150 mg/day; titrating up to 450–600 mg/day  
 Zonisamide: Starting dose: 50–100 mg/day; titrating up to 450 mg/day  
 Ziconotide: Starting dose: 0.1 µg/h; titrating up to 0.4 µg/h  
 Levetiracetam: Starting dose: 250–500 mg/day; titrating up to 2000 mg/day

### Sodium Channel Blockers

Lidocaine: Used in a lidocaine test: 1 mg/kg via slow intravenous push or drip  
 Mexiletine: Starting dose: 150–300 mg/day; titrating up to 600 mg/day  
 Carbamazepine: Starting dose: 100 mg/day; titrating up to 600 mg/day  
 Oxcarbazepine: Starting dose: 150 mg/day; titrating up to 900 mg/day  
 Lamotrigine: Starting dose: 25–50 mg/day; titrating up to 250–500 mg/day  
 Topiramate: Starting dose: 50–100 mg/day; titrating up to 300–400 mg/day.

intravenous acetaminophen decreased postoperative opioid consumption, reduced hospital stay, improved pain control, shortened time to return of bowel function, and lowered the rate of postoperative ileus.<sup>10</sup> Similar results were found after procedures for posterior spinal fusion,<sup>11</sup> craniotomy,<sup>12</sup> vitrectomy,<sup>13</sup> esophagectomy,<sup>14,15</sup> and total joint arthroplasty.<sup>16</sup>

Compared with an opioids-only option for postoperative pain management in adolescents with idiopathic scoliosis, patients treated with intravenous acetaminophen plus ketorolac consumed less opioids and had less severe constipation.<sup>17</sup> A retrospective analysis of the results of the Premier Database of 61,017 cholecystectomy patients showed that 31,133 (51%) of the patients who received intravenous acetaminophen had experienced a shorter length of hospital stay, a decrease in hospitalization costs, a reduced average daily morphine-equivalent dose, and lower rates of respiratory depression, nausea, and vomiting.<sup>18</sup> However, several studies have failed to show that intravenous acetaminophen achieved the positive results as described here.<sup>19–21</sup> The hepatic side effect is a significant concern for those with long-term acetaminophen use, particularly with alcohol. A recent analysis of nine prospective cohort studies has also linked long-term acetaminophen use with an increased risk of adverse neurodevelopmental outcomes following prenatal acetaminophen exposure.<sup>22</sup>

## Calcium Channel Blockers

Opening of calcium channels is an important step of synaptic transmission because it facilitates release of neurotransmitters and neuromodulators from presynaptic sites. Changes in intracellular calcium concentration also modulate cell

membrane excitability and initiate a cascade of intracellular responses. Therefore blocking calcium channels can play a significant role in modulating both nociceptive and antinociceptive processes. Drugs that reduce calcium influx into the intracellular compartment of neuronal or glial cells may be used as adjunctive or alternative medications for the treatment of various pain conditions, particularly chronic neuropathic pain conditions. Most calcium channel blockers used as antihypertensive drugs may be suitable for chronic pain management because of their side effects and site of action. Gabapentin, pregabalin, zonisamide, ziconotide, and levetiracetam are examples of drugs that block calcium channels as a part of their mechanisms of action and have been used in pain management.

## GABAPENTIN

Gabapentin was initially approved by the U.S. Food and Drug Administration (FDA) as an anticonvulsant (partial seizure) and is currently extensively used for the treatment of neuropathic pain conditions. Although gabapentin's mechanism of action is unclear, it does block voltage-gated calcium channels by binding to the  $\alpha_2$ - $\delta$  subunit,<sup>23</sup> thereby reducing calcium influx. By blocking calcium influx, gabapentin reduces the release of glutamate and substance P from primary nociceptive afferents, thereby modulating nociceptive transmission. Gabapentin has been used to treat painful diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, complex regional pain syndrome, and painful peripheral neuropathies caused by human immunodeficiency virus (HIV), cancer, multiple sclerosis, and spinal cord injury.

Painful diabetic neuropathy is a debilitating condition commonly seen in patients with diabetes mellitus. Up to 25% of patients with diabetes may suffer from spontaneous pain, allodynia, hyperalgesia, paresthesias, and other pain symptoms.<sup>24</sup> Postherpetic neuralgia is another common neuropathic pain condition. The incidence of postherpetic neuralgia is estimated to be 9% to 34%, which increases significantly with age. Multiple classes of drugs have been tried to treat pain associated with painful diabetic neuralgia and postherpetic neuralgia, including tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, imipramine, and desipramine. Because of the significant side effects of TCAs, gabapentin has been increasingly used in the treatment of these pain conditions.

Gabapentin is effective in reducing several salient symptoms of neuropathic pain such as burning and shooting pain, allodynia, and hyperalgesia.<sup>25,26</sup> The number needed to achieve at least 50% pain relief with antidepressants and gabapentin are 3.4 and 2.7, respectively.<sup>27</sup> Although both antidepressants and gabapentin may provide moderate pain relief, antidepressants may have more major side effects.

The recommended gabapentin dose range is 1800 to 3600 mg/day, starting at 100 to 300 mg/day and increasing 100 to 300 mg every 1 to 3 days. Adverse effects are usually mild to moderate and typically subside within 7 to 10 days after the treatment is started; however, serious side effects can occur including mood swing, edema, and suicidality. In general, a slow titration process can significantly reduce some otherwise intolerable side effects, such

as dizziness. In addition to its use as a monotherapy, gabapentin has been extensively used in multimodal drug therapy in conjunction with TCAs and other anticonvulsants.<sup>1</sup> Multimodal drug therapy provides better pain control, requiring a smaller dose range for each drug included in the regimen. Gabapentin also can treat complex regional pain syndrome, phantom pain, trigeminal neuralgia, cancer-related neuropathic pain, multiple sclerosis, spinal cord injury, HIV-associated painful sensory neuropathy, and glossopharyngeal neuralgia.

The role of gabapentin in acute postoperative pain management remains unclear.

## PREGABALIN

Pregabalin is an anticonvulsant that has a high affinity to the  $\alpha_2$ - $\delta$  subunit of voltage-sensitive calcium channels. The mechanism of action of pregabalin is similar to that of gabapentin. Pregabalin decreases calcium influx, thereby reducing the release of excitatory neurotransmitters, including glutamate, substance P, and calcitonin gene-related peptide. Pregabalin has no activity on GABA or benzodiazepine receptors; therefore it has no significant drug-drug interactions with such agents.

Pregabalin has been used to treat painful diabetic neuropathy and postherpetic neuralgia, with a significant therapeutic effect.<sup>28,29</sup> It has a quick onset, and, in some cases, pain reduction can be expected on the first day of treatment with pregabalin (300 mg/day). Sustainable sleep improvement is also observed 1 week after the therapy is initiated. Common side effects are dizziness, somnolence, and mild to moderate peripheral edema.<sup>30</sup> Other concerns over pregabalin include behavioral changes such as mood swing and suicidality. Before starting pregabalin, it is recommended to check the baseline creatinine level. Moreover, pregabalin (at an average dose of 450 mg/day) is effective in patients with fibromyalgia, who often have clinical presentations including diffuse musculoskeletal pain, sleep disturbance, and fatigue.

## ZONISAMIDE

Zonisamide blocks both voltage-sensitive sodium channels and N-type calcium channels. Studies suggest that zonisamide may be used to treat mania, Parkinson disease, and poststroke central pain or to provide migraine prophylaxis.<sup>31,32</sup> Its possible mechanisms of action include modulation of monoamine neurotransmitter release and free radical scavenging. Zonisamide is effective for the treatment of painful diabetic neuropathy (540 mg/day). The tolerability of zonisamide is difficult to assess because it is often used in multimodal drug therapy. Thus the data on the effectiveness and side effects of zonisamide remain limited.

## ZICONOTIDE

Ziconotide is a synthetic peptide analogue of omega conotoxin derived from a marine snail, *Conus magus*. Ziconotide potently and selectively blocks N-type voltage-sensitive calcium channels. This drug is approved only for intrathecal use in patients with severe pain who are refractory to other treatment options, including intrathecal morphine.

In early clinical trials, ziconotide exhibited severe central nervous system and psychiatric adverse effects with an initial intrathecal infusion rate of 0.4  $\mu$ g/h and frequent dosing titration.<sup>33</sup> More recently, ziconotide has been shown to be effective for chronic pain conditions resulting from cancer, acquired immunodeficiency syndrome, and trigeminal neuralgia.<sup>34,35</sup> The role of ziconotide in postoperative pain management is less clear. Given ziconotide's significant side effects and restrictive delivery route, its routine use in acute postoperative pain management is not well justified.

The initial infusion rate of ziconotide should start at 0.1  $\mu$ g/h intrathecally, with a slow titration of no more than 2 to 3 times the initial dose per week. An implanted intrathecal infusion system is required for the long-term use of this therapy if the initial ziconotide trial is effective.<sup>36</sup> Patients with severe psychiatric disorders may not be proper candidates for this therapy. On the other hand, ziconotide may be advantageous over intrathecal morphine because patients do not develop tolerance after a prolonged use of ziconotide. However, adverse neurologic effects associated with ziconotide therapy will require careful patient selection and monitoring. Using a smaller dose increment may help to avoid systemic toxicity.

## LEVETIRACETAM

Levetiracetam is an anticonvulsant approved by the FDA for treatment of epilepsy.<sup>37</sup> Its mechanisms of action are less clear because it may have effects on several neurotransmitter systems, including dopaminergic, glutamatergic, and GABAergic systems. But at least one of its mechanisms of action is due to inhibition of N-type voltage-sensitive calcium channels. Levetiracetam improves neoplastic plexopathies, painful peripheral neuropathy, and postherpetic neuralgia. It also has been used in migraine headache prophylaxis. The dose range is 500 to 2000 mg/day. At this dose range, levetiracetam is well tolerated in clinical trials. Common adverse effects are dry eyes and dizziness.<sup>38</sup>

## Sodium Channel Blockers

Sodium channels are primarily involved in nerve conduction. Sodium channels can be divided into two general categories based on their sensitivity to tetrodotoxin (TTX): TTX-sensitive (TTX-S) and TTX-resistant (TTX-R) sodium channels. TTX-S sodium channels are expressed mainly in large and medium dorsal root ganglion neurons, whereas TTX-R sodium channels are expressed mainly in small-diameter dorsal root ganglion neurons, including C-afferent neurons. Expression of both TTX-S and TTX-R sodium channels is likely to be altered when peripheral nerves are injured or severed (axotomy), producing aberrant high-frequency spontaneous ectopic discharges. Sodium channel blockers at a proper dose range are believed to suppress ectopic discharges without blocking normal nerve conduction, which forms the basis of using sodium channel blockers in the treatment of chronic pain conditions, particularly neuropathic pain. Selective Nav 1.7 and Nav 1.8 sodium channel blockers are being investigated for possible clinical applications. Currently, several representative sodium

channel blockers include lidocaine, mexiletine, carbamazepine, oxcarbazepine, lamotrigine, and topiramate.<sup>39</sup>

## LIDOCAINE

Lidocaine is a local anesthetic and cardiac antiarrhythmic. Since the 1980s, intravenous administration of lidocaine has been used as a diagnostic tool and, in some cases, a therapeutic tool for intractable neuropathic pain.<sup>39</sup> This treatment modality has been shown to improve chronic pain conditions induced by neurologic diseases, including stroke, neurogenic facial pain, and myofascial pain.<sup>40,41</sup> Up to 78% of cases are associated with a positive outcome when intravenous lidocaine is used.<sup>42</sup> A major pitfall of intravenous lidocaine treatment is its short duration, which requires frequent treatment sessions.

Topical 5% lidocaine patch and over-the-counter topical lidocaine gel or cream provide a local analgesic effect with a minimum systemic effect. Lidocaine patch has been used in patients with neuropathic pain conditions such as painful diabetic neuropathy, postherpetic neuralgia, and peripheral neuropathies. It reduces allodynia and hyperalgesia associated with such conditions.<sup>43</sup> Although the evidence remains weak and unclear, lidocaine patch has been used to treat chronic lower back pain. In some cases, lidocaine patch has become a part of multimodal drug therapy, such as a combination of topical lidocaine patch and gabapentin.<sup>1</sup>

## MEXILETINE

Mexiletine is an oral lidocaine congener. It may be used to overcome the shortcoming of transient pain relief with intravenous lidocaine. In many cases, intravenous lidocaine is used as a test to determine whether the intended lidocaine treatment is effective. When a positive response is achieved, oral mexiletine is administered to maintain the therapeutic effect.<sup>44,45</sup> This treatment regimen reduces pain due to painful diabetic neuropathy refractory to other therapies.<sup>46</sup> Mexiletine alone has been used to treat phantom pain and pain after spinal cord injury.<sup>46</sup>

Fibromyalgia and myofascial pain are other clinical conditions that may be responsive to a lidocaine and mexiletine treatment regimen. In addition, anecdotal reports suggest that oral mexiletine may be used to treat primary erythromelalgia, metastasis bone pain, and headaches.

## CARBAMAZEPINE

A primary mechanism of action of carbamazepine is sodium channel blockade, which decreases spontaneous firing of A $\delta$ -fibers and C-fibers. Carbamazepine has been approved to treat trigeminal neuralgia, a neuropathic pain condition characterized by episodic lightning, lancinating, or shooting pain along the trigeminal nerve distribution.<sup>47</sup> Carbamazepine has been used for decades and was superior to placebo in a number of clinical trials. It was once considered a “gold standard” and remains a treatment of choice for trigeminal neuralgia, with a response rate of 89% within 5 to 14 days after the treatment is initiated. However, carbamazepine has significant drug-drug interactions and a long list of adverse effects, including central nervous system side

effects. In the United States the FDA has issued black box warnings about this drug, including aplastic anemia and agranulocytosis. Therefore its clinical utility is rather limited considering that newer anticonvulsants are available with fewer and less severe side effects.

## OXCARBAZEPINE

Oxcarbazepine is an analogue of carbamazepine, which acts as a sodium channel blocker and stabilizes neuronal membrane. In contrast to carbamazepine, oxcarbazepine has fewer drug-drug interactions and side effects, particularly severe blood dyscrasias. The most common side effects of oxcarbazepine are dizziness, drowsiness, hypotension, nausea, and asymptomatic mild hyponatremia. Oxcarbazepine has been used to treat intractable trigeminal neuralgia refractory to other anticonvulsants.<sup>48</sup> With a median dose of 750 mg/day, this novel drug appears to have the same efficacy as carbamazepine in the treatment of trigeminal neuralgia but a much lower incidence of side effects.

Oxcarbazepine also reduces pain associated with painful diabetic neuropathy and complex regional pain syndrome. For patients with postherpetic neuralgia that is unresponsive to carbamazepine and gabapentin, oxcarbazepine, starting at 150 mg/day and titrating up to a maintenance dose of 900 mg/day, may be a promising drug because it significantly reduces allodynia related to postherpetic neuralgia. Oxcarbazepine appears to be well tolerated and may serve as a reasonable alternative to other sodium channel blockers.

## LAMOTRIGINE

Lamotrigine has multiple mechanisms of action, although it also blocks both sodium and calcium channels.<sup>49</sup> Lamotrigine is effective in the treatment of trigeminal neuralgia, neuralgia after nerve section, and pain related to HIV neuropathy. With a daily lamotrigine dose of 75 to 300 mg, the intensity of burning and shooting pain is relieved by 33% to 100%, and the frequency of shooting pain attack is reduced by 80% to 100%. In patients with spinal cord injury, lamotrigine decreases overall pain sensation to less than the level of injury in patients with incomplete spinal cord injury but has little effect on spontaneous and evoked pain in patients with complete spinal cord injury.

A typical starting dose for lamotrigine is 25 to 50 mg/day, which can be slowly titrated up over 2 to 3 weeks to 250 to 500 mg/day in divided doses. Tolerability is usually low at high doses (>300 mg/day). Up to 10% of patients may have rashes after taking this medication, with a 3 in 1000 incidence of Stevens-Johnson syndrome. Other side effects are mild dizziness, somnolence, nausea, and constipation.

## TOPIRAMATE

Topiramate is another drug that has multiple mechanisms of action. However, at least one of its actions is to block voltage-sensitive sodium channels. It also may potentiate GABA inhibitory action, block voltage-sensitive calcium channels, and inhibit subtypes of glutamate receptors (non-NMDA receptors). Topiramate can cause significant weight loss (up to 7%), a side effect that could be beneficial for

certain patient populations with chronic pain conditions. Topiramate, at a daily dose of 400 mg or greater, attenuates neuropathic pain, improves sleep quality, and reduces body weight.<sup>48</sup> When used to treat chronic lumbar radicular pain, the effect of topiramate is inconclusive because of a high dropout rate and frequent side effects in clinical trials. However, topiramate 30 to 80 mg/day is superior to placebo for the treatment of chronic tension, migraine, and cluster headaches with a substantial tolerability.<sup>50</sup>

 Complete references available online at [expertconsult.com](http://expertconsult.com).

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## KEY POINTS

- The pharmacokinetics of anesthetic drugs are described by multicompartment models. Accurate intravenous drug delivery requires adjusting the maintenance infusion rates to take into account the accumulation of the drug in the peripheral tissues.
- *Biophase* is the site of action of a drug. Initiation, maintenance, and titration of intravenous anesthetics must account for the delay in equilibration between plasma and the site of drug effect.
- Some drug effects directly reflect the concentration of the drug in the biophase (direct-effect models). Other drug effects reflect the alteration of feedback systems by anesthetics (indirect-effect models). The influence of opioids on ventilation reflects the dynamic influence of opioids on the feedback between ventilation and carbon dioxide and is thus an example of an indirect drug effect.
- The target concentration in the effect site is the same as the target concentration in plasma at steady state. Effect-site requirements are influenced by patient physiologic characteristics, surgical stimulation, and concurrent drug administration. Ideally, target concentrations should be set for the hypnotic (volatile anesthetic or propofol) and the analgesic (opioid) that properly accounts for the synergy between them.
- To achieve an effective target concentration, the conventional teaching of administering an initial dose as calculated by the product of target concentration and volume of distribution, followed by a maintenance rate as calculated as the product of target concentration and clearance, is inaccurate. The initial dose may be calculated as the product of target concentration and volume of distribution at peak effect. Maintenance rates must initially account for the distribution of drug in peripheral tissues and should only be reduced to the product of target concentration and clearance after equilibration of plasma and peripheral tissue concentrations.
- The terminal half-life does not reflect the clinical time course of drug plasma concentration. The context-sensitive decrement time is the time for a given decrement in drug concentration, as a function of the duration of infusion that maintains a steady plasma concentration. Context-sensitive decrement times properly incorporate the multicompartment behavior of intravenous anesthetics. The context-sensitive half-time is the time for a 50% decrement in concentration.
- Alfentanil, fentanyl, sufentanil, remifentanil, propofol, thiopental, methohexitol, etomidate, ketamine, midazolam, and dexmedetomidine can all be administered as a continuous intravenous infusion. Specific caveats, infusion rates, and titration guidelines are presented in this text.
- Target-controlled infusions (TCIs) use pharmacokinetic models to determine intravenous anesthetic administration rates required to achieve specified plasma or effect-site drug concentrations. Various plasma and effect-site targeting TCI systems are commercially available worldwide (except within the United States) to administer hypnotics and opioids.
- Closed-loop drug delivery systems have used the median electroencephalographic frequency, bispectral index (BIS), or auditory-evoked potentials to control intravenous anesthetic delivery. Although these systems have generally performed well clinically, they remain under investigation.

## Introduction

Drugs must reach their site of action to be effective. In 1628, William Harvey proved in *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* that venous blood was transported to the arterial circulation and thus to body organs by the heart. That drugs injected into veins could be rapidly carried to the entire body was rapidly recognized.

Consequently, for intravenous drug delivery to be successful, predictable intravenous access is essential.

The development of intravenous methods of anesthetic drug delivery has been made possible by technologic advances. In the middle of the 17th century, Christopher Wren and his Oxford contemporaries applied a feather quill and animal bladder to inject drugs into dogs and humans and rendered them unconscious. The hollow hypodermic

needle and a functional syringe were developed by Frances Rynd (1801–1861) and Charles Pravaz (1791–1853), respectively. Contemporary needles, catheters, and syringes are descendants of these early devices. In the twentieth century, equipment began to be made of plastics, first polyvinyl chloride, then Teflon, and later, polyurethane. In 1950, Massa invented the Rochester needle (Fig. 26.1),<sup>1</sup> which led to the revolutionary concept of the “over-the-needle” catheter, which is still the gold standard for intravenous access for nearly all intravenous drug delivery today.<sup>2</sup>

Although fundamental principles of intravenously administering drugs were known in the 18th century, intravenous induction of anesthesia became common only in the 1930s after the discovery of barbiturates. Maintenance of anesthesia by intravenously administered anesthetics has become practical, safe, and popular in the past 2 decades. Intravenous drugs such as methohexitone and thiopental, although suitable for intravenous induction of anesthesia, are not suitable for use by infusion for the maintenance of anesthesia. In the case of thiopental, accumulation can lead to cardiovascular instability and delayed recovery, whereas methohexitone is associated with the excitatory phenomenon and epileptiform electroencephalographic (EEG) changes. Although the next

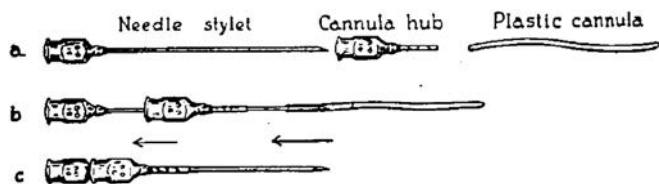


Fig. 26.1 Details of the assembly of the Massa plastic needle, sold by Rochester Products Company, Rochester, Minnesota. (From Massa DJ. A plastic needle. *Anesthesiology*. 1951;12:772–773. Used with permission.)

generation of intravenous drugs, such as ketamine, althesin, and etomidate, possessed desirable pharmacokinetic characteristics, their use has been limited as a result of other side effects, including hallucinations, anaphylaxis, and adrenal suppression, respectively. The discovery of propofol in 1977 provided the anesthetic practice an intravenous drug suitable for both induction and maintenance of anesthesia; currently, propofol is still one of the most frequently used drugs for this purpose.<sup>3</sup> Other drugs suitable for continuous infusion used today are some of the opioids such as alfentanil and sufentanil and certainly the short-acting opioid remifentanil. In addition, some of the nondepolarizing neuromuscular blocking agents are used as continuous infusions in specific situations.

Drugs are still predominantly injected as a bolus or continuous infusion using standard dosing guidelines, thereby ignoring the large interindividual variability in the dose-response relationship.<sup>4</sup> In contrast to inhaled anesthetics, for which the inspired and end-tidal concentrations can be continuously measured in real time (“online”), the actual plasma or effect organ concentration of an intravenously administered drug is not immediately measurable in clinical practice. Therefore manually adjusting the intravenous drug injection regimens to maintain an online measured plasma concentration is impossible. It becomes even more complex if a specific effect-site concentration is the target. Optimal patient-individual dosing may be achieved by the application of pharmacokinetic-pharmacodynamic principles. Additionally, recent findings suggest that the pharmacokinetic and pharmacodynamic interactions during intravenous administration of various drugs are important and, as such, should be taken into account when optimizing drug administration.<sup>5,6</sup> Computer technology can be used to assist the clinician in titrating intravenous drug administration by using the therapeutic end point as the feedback signal for dosing (Fig. 26.2).

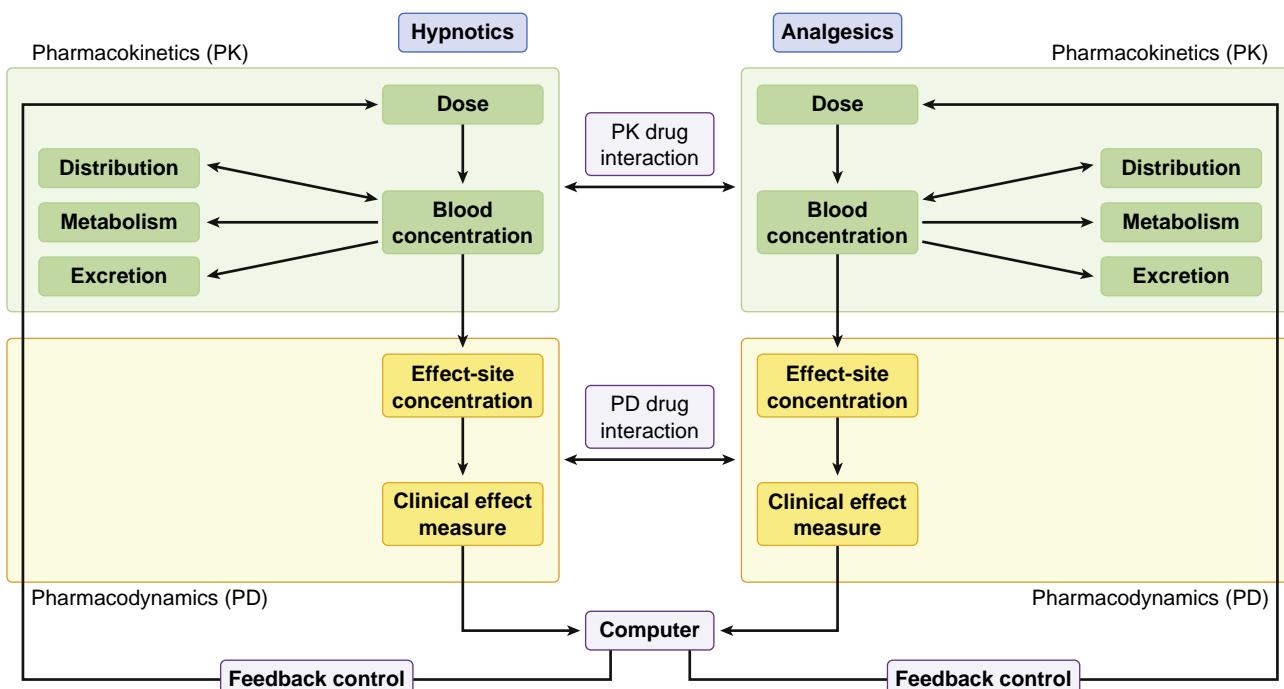


Fig. 26.2 Schematic representation of the dose-response relationship for both hypnotics and opioids. The pharmacokinetic (PK) (green area) and the pharmacodynamic (PD) (yellow area) parts of this relationship are shown. Closed-loop control of drug administration using the clinical measure is indicated as feedback control. PK and PD drug interactions are indicated. (From Sahinovic MM, Absalom AR, Struys MM. Administration and monitoring of intravenous anesthetics. *Curr Opin Anesthesiol*. 2010;23:734–734. Used with permission.)

The development of the first mechanical syringe pumps in the 1950s improved the quality of intravenous drug administration. A more recent technologic development in intravenous anesthesia is the introduction of computerized pharmacokinetic model–driven continuous-infusion devices, enabling the attainment of desired plasma levels of an intravenous anesthetic drug by using a computer-controlled infusion pump operated in accordance with the published pharmacokinetics of the drug.<sup>7</sup> These efforts have resulted in the release of the first commercial target-controlled infusion (TCI) device in Europe, developed by Zeneca specifically for the administration of propofol. Since that time, several countries (with the exception of the United States) have approved the use of TCI devices for the delivery of anesthetic drugs.<sup>8</sup>

The ultimate development in anesthetic delivery systems will be devices for closed-loop administration of intravenous drugs during anesthesia. Systems have been developed for closed-loop administration of various drugs such as neuromuscular blocking agents, hypnotics, and opioids. The control variables for these systems have included various pharmacodynamic measures derived from techniques such as acceleromyography, automated blood pressure measurement, and electroencephalography.

The dose-response relationship can be divided into three parts (see Fig. 26.2): (1) the time course of the relationship between the given dose and the plasma concentration is defined as pharmacokinetics, (2) the relationship between the plasma concentration and/or effect-organ concentration and the clinical effect is defined as pharmacodynamics, and (3) the coupling between pharmacokinetics and pharmacodynamics is required when the blood is not the site of drug effect.

Before reviewing delivery techniques and devices for intravenous anesthesia, this chapter presents some pharmacokinetic and pharmacodynamic principles as background for understanding how to administer intravenous drugs to their best advantage. Further discussion of the principles of pharmacokinetics and pharmacodynamics can be found in Chapter 23.

## Pharmacokinetic Considerations

The aim of optimal intravenous drug dosing is to reach and maintain a desired time course of therapeutic drug effect as accurately as possible, thereby preventing dose-related adverse drug effects. To be useful in anesthesia, this time course should include a rapid onset of clinical effects, smooth maintenance, and fast recovery after the termination of drug administration. The pharmacokinetics of many intravenous drugs can be described using mammillary multicompartment pharmacokinetic models. These models assume that the drug is directly given and mixed in the plasma, resulting in an immediate peak in its plasma concentration.

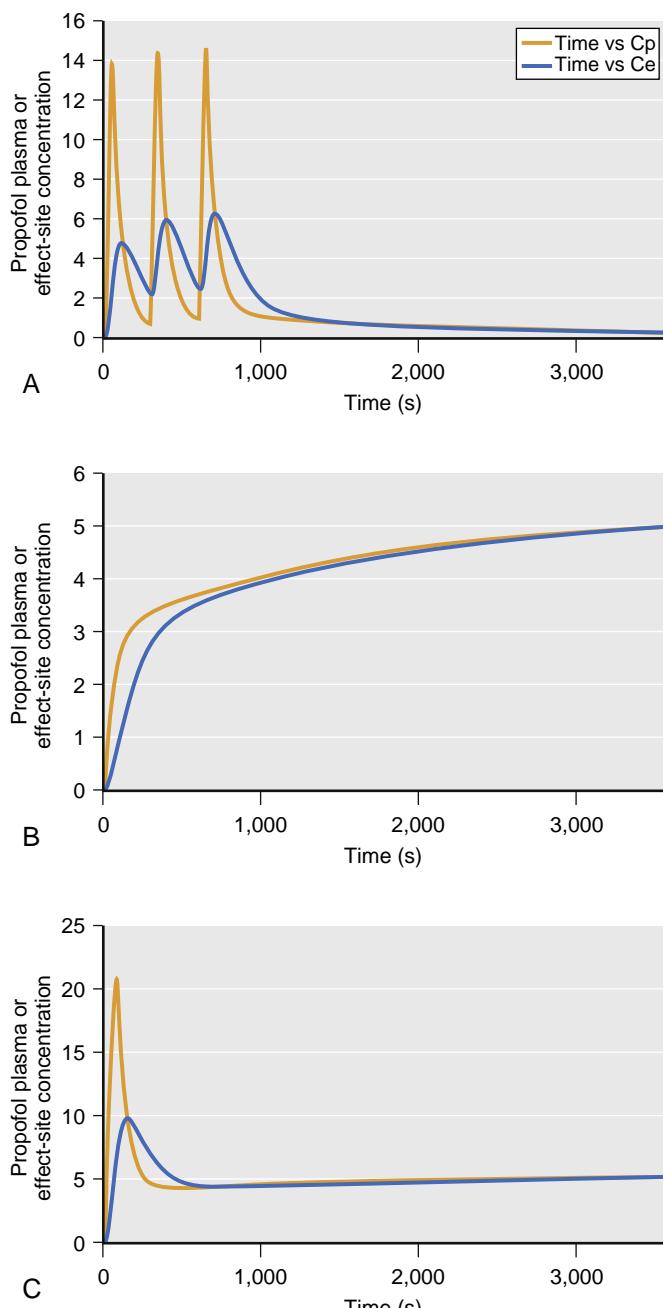
The easiest clinical technique is to administer a single dose, calculated to keep the plasma concentration above the therapeutic target concentration for the required time (Fig. 26.3). A constant concentration cannot be maintained, but it should not decrease to less than the therapeutic concentration. Unfortunately, when one single bolus is

used, the initial dose must be large enough to maintain a concentration above the lowest therapeutic concentration even at the end of surgery. However, this sometimes very large dose of drug may cause numerous side effects attributable to the initially high concentrations in the body. It might be less harmful to keep the drug concentration above the lowest therapeutic level without very high initial concentrations by repeatedly injecting smaller doses; even with this technique, however, maintaining a stable plasma concentration is still impossible.

To produce a time course of drug effect that follows the time course of anesthetic requirement, a continuous infusion titrated to the perceived anesthetic requirement should be used. Typically, just enough amount of drug is given to achieve the therapeutic blood or plasma drug concentration. Drug administration thereafter should be continuously titrated throughout surgery. Although such a regimen does not overshoot the required concentration (and therefore avoids the risk of concentration-related side effects), yet another difficulty exists. Whereas, the large bolus approach produces an effective concentration (EC) from the onset, albeit with an excessive overshoot, a continuous infusion takes a long time to become effective because of the slow increase in concentration. Reaching steady state (see Fig. 26.3) takes a very long time during which the increase in concentration is rapid at first but then slows down as equilibrium is approached. For example, it will take longer than 1 hour for the propofol infusion to generate a plasma concentration that is at least 95% of the steady-state concentration. Consequently, although simple infusions are obviously very effective for maintaining constant blood concentrations once steady state is reached and for avoiding overshoot, infusions do not offer a clinically realistic approach. Therefore a combination of an initial bolus followed by a stepwise decreasing continuous infusion is more useful.<sup>9,10</sup>

Pharmacokinetic models can be used to calculate the required drug-dosing regimen to reach and maintain a therapeutic drug concentration as fast as possible without overshooting or accumulation. In this chapter, an explanation of how pharmacokinetic models can be used to calculate accurate dosing schemes for use with intravenous drug delivery systems is offered.

Pharmacokinetic models are mathematical descriptions of how the body *disposes* of drugs. The parameters describing this process are estimated by administering a known dose of the drug and measuring the resulting plasma concentrations. A mathematical model then relates the input over time,  $I(t)$ , with the concentrations over time,  $C(t)$ . These models can take many forms. Fig. 26.4 shows concentrations in plasma and effect site over time after a single intravenous bolus of drug at time 0. Drug concentrations continuously decrease after the bolus, and the rate of decrease is approximately proportional to the amount of drug in plasma. Typically, this behavior can be described with the use of exponential models. The curve might have a single exponent, in which case the plasma concentrations over time might be described by the function  $C(t) = Ae^{-kt}$ , where  $A$  is the concentration at time 0 and  $k$  is a constant that describes the rate of decrease in concentration. The relationship appears to be a straight line when graphed as the log of concentration versus time. The pharmacokinetics



**Fig. 26.3** Predicted propofol plasma concentration ( $C_p$ ) and effect-site concentration ( $C_e$ ) for a repeated bolus dose (1 mg/kg given at time 0 and after 5 and 10 minutes) (A), continuous infusion (10 mg/kg/h) (B), and a bolus (2 mg/kg) followed by a continuous infusion (10 mg/kg/h) (C). Simulated patient is a man, 45 years of age, 80 kg, 175 cm; Schnider model.

of intravenous anesthetic drugs is more complex because after the bolus, a period of rapid decline is observed before the terminal *log-linear* portion (i.e., the part that is a straight line when described as log concentration vs. time). This process can be modeled by taking several monoexponential curves and adding them together. The result is a polyexponential curve. For example, the concentrations after an intravenous bolus might be described by an equation with two exponents,  $C(t) = Ae^{-\alpha t} + Be^{-\beta t}$ , or an equation with three exponents,  $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$ .

The aforementioned is applied to single bolus dosing, which is, of course, only one way of administering intravenous anesthetic drugs. A more general way to think of pharmacokinetics is to decompose the input into a series of small bits (boluses) and consider each bit of drug separately. The general pharmacokinetic model of drug disposition commonly used in anesthesia independently considers each bit of drug and analyzes its contribution by means of polyexponential decay over time. The formal mathematic description of each bit of drug in terms of polyexponential decay over time is the relationship (Eq. 26.1)

$$C(t) = I(t) * \sum_{i=1}^n A_i e^{-\lambda_i t} \quad (26.1)$$

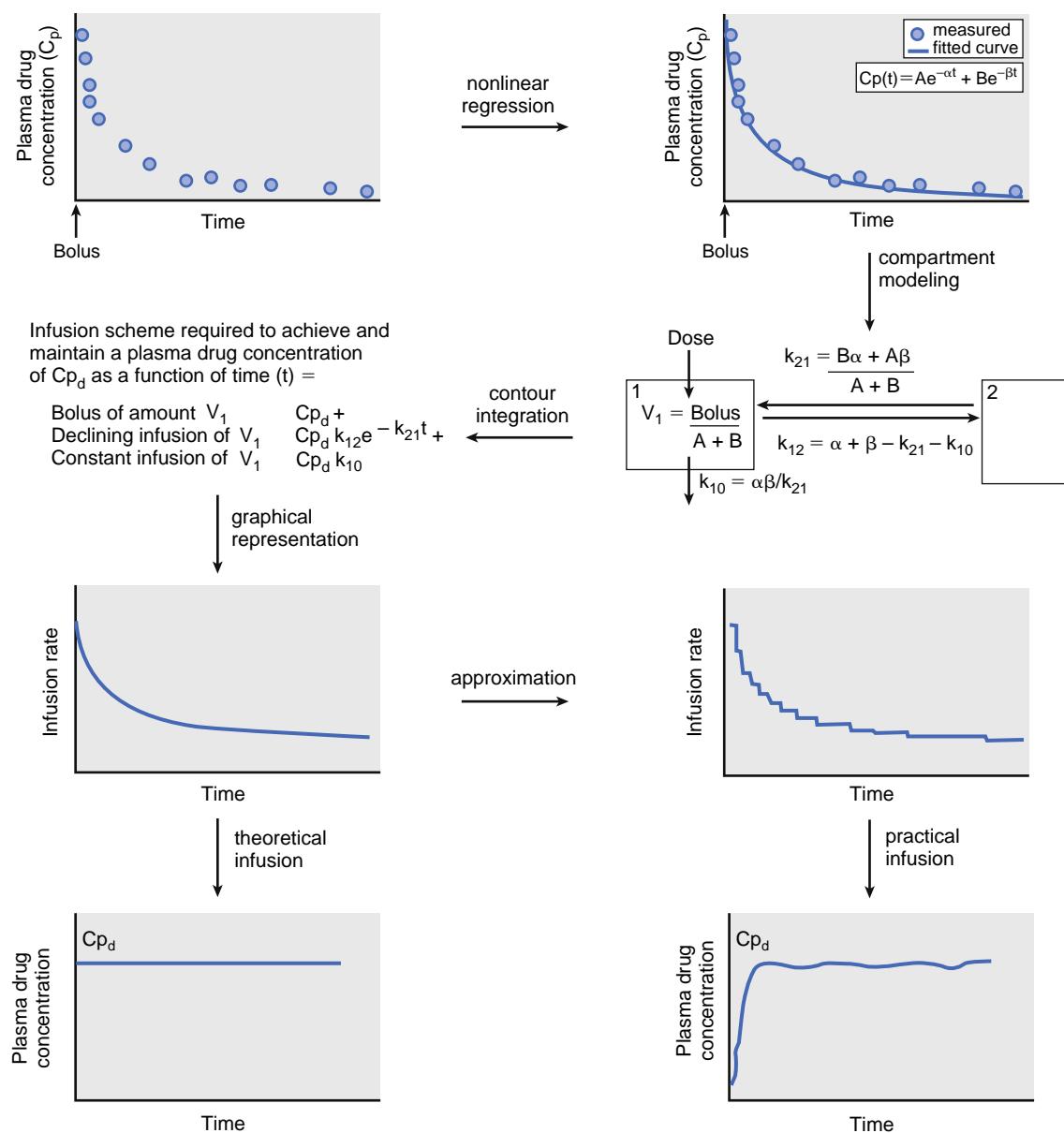
where  $C(t)$  is the plasma concentration at time  $t$  and  $I(t)$  is drug input (i.e., a bolus or infusion). The summation after the asterisk (described later in this chapter) is the function describing how each bit of drug is disposed (hence the name, *disposition function*). Note that this is again a sum of  $n$  exponentials, as described in the previous paragraph.

Pharmacokinetic modeling is the process of estimating the parameters within this function. The integer  $n$  is the number of exponentials (i.e., compartments) and is usually two or three. Each exponential term is associated with a coefficient  $A_i$  and an exponent  $\lambda_i$ . The  $\lambda$  values are inversely proportional to the half-lives (half-life =  $\ln 2/\lambda = 0.693/\lambda$ ), with the smallest  $\lambda$  representing the longest (terminal) half-life. The  $A$  values are the relative contribution of each half-life to overall drug disposition. If a drug has a very long terminal half-life but a coefficient that is significantly smaller than the other coefficients, then the long half-life is likely to be clinically meaningless. Conversely, if a drug has a very long half-life with a relatively large coefficient, then the drug will be long lasting even after brief administration. The asterisk (\*) operator is the mathematic process called *convolution*, which is simply the process of breaking the infusion into *bits* of drug and then adding up the results to observe the overall concentrations resulting from the disposition of the different bits up to a time point  $t$ .

The pharmacokinetic model shown has some useful characteristics that account for its enduring popularity in pharmacokinetic analysis. Most important, the model describes observations from studies reasonably well, the *sine qua non* for models. Second, these models have the useful characteristic of *linearity*. Simply stated, if the dose,  $I$ , is doubled (e.g., administering a bolus twice as large or an infusion twice as fast), then the resulting concentrations should be doubled.

More generally, linearity implies that the system (i.e., the body acting to produce a plasma drug concentration output from a drug dosage input) behaves in accordance with the principle of superposition. The superposition principle states that the response of a linear system with multiple inputs can be computed by determining the response to each individual input and then summing the individual responses. In other words, when the body treats each bit of drug by polyexponential decay over time, the *disposing* of each bit of drug does not influence the disposing of other bits of drug.

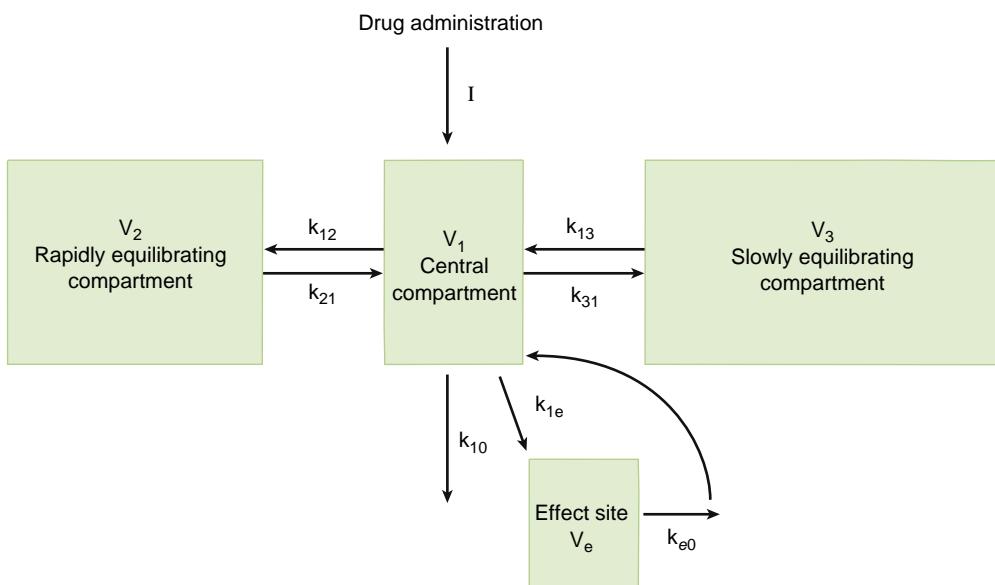
The third reason for the continuing popularity of these models is that they can be mathematically transformed from the admittedly nonintuitive exponential form shown



**Fig. 26.4** Steps involved in pharmacokinetic model–driven infusion. Typically, pharmacokinetic models are derived from experiments in which plasma drug concentrations are measured at intervals after bolus administration of the drug. Nonlinear regression is used to fit a monoexponential, biexponential, or triexponential curve to the resulting concentration-versus-time data. An algebraic relationship exists between the exponential decay curves and a one-, two-, or three-compartment pharmacokinetic model. The bolus-elimination-transfer (BET) infusion scheme is developed and consists of a bolus, a continuous infusion to replace drug eliminated from the body, and an exponentially declining infusion to replace drug transferred out of plasma to other body compartments. BET infusion results in the maintenance of a constant specified plasma drug concentration. Practical implementation of the BET scheme with real infusion pumps and infusion rates that change only at discrete intervals of time results in a plasma drug concentration profile that approximates that resulting from a BET infusion.

earlier to a more intuitive compartment form (Fig. 26.5). The fundamental parameters of the compartment model are the volumes of distribution (central, rapidly equilibrating, and slowly equilibrating peripheral volumes) and clearances (systemic, rapid, and slow intercompartment). The central compartment ( $V_1$ ) represents a distribution volume and includes the rapidly mixing portion of the blood and first-pass pulmonary uptake. The peripheral compartments are made up of tissues and organs that show a time course and extent of drug accumulation (or dissipation) different from that of the central compartment. In the three-compartment model, the two peripheral compartments

may roughly correspond to splanchnic and muscle tissues (rapidly equilibrating) and fat stores (slowly equilibrating). The sum of the compartment volumes is the apparent volume of distribution at steady state ( $V_{dss}$ ) and is the proportionality constant relating the plasma drug concentration at steady state to the total amount of drug in the body. The intercompartment rate constants ( $k_{12}$ ,  $k_{21}$ , and so on) describe the movement of drug between the central and peripheral compartments. The elimination rate constant ( $k_{10}$ ) encompasses processes acting through biotransformation or elimination that irreversibly removes drug from the central compartment.



**Fig. 26.5** Three-compartment model (including the biophase) illustrating the basic pharmacokinetic processes that occur after intravenous drug administration.  $I$ , Dosing scheme as a function of time;  $k_{10}$ , rate constant reflecting all processes acting to remove drug irreversibly from the central compartment;  $k$ , intercompartment rate constants;  $V_i$ , central compartment volume, usually expressed in liters or liters per kilogram.

Despite their physiologic flavor, compartment models are simply mathematic transformations of the polyexponential disposition functions computed from observed plasma concentrations. Thus physiologic interpretation of volumes and clearances (with the possible exception of systemic clearance and  $V_{dss}$  [the algebraic sum of the volumes]) is entirely speculative.

The last reason behind the popularity of these models is that they can be used to design infusion regimens. If the disposition function (Eq. 26.2)

$$\sum_{i=1}^n A_i e^{-\lambda_i t} \quad (26.2)$$

is abbreviated as simply  $D(t)$ , then the relationship among concentration, dose, and the pharmacokinetic model  $D(t)$  can be rewritten as (Eq. 26.3)

$$C(t) = I(t) * D(t) \quad (26.3)$$

where  $*$  is the convolution operator, as noted earlier. In the usual pharmacokinetic study,  $I(t)$  is known, the dose that is given to the patient, and  $C(t)$  is measured, the concentrations over time. The goal is to find  $D(t)$ , the pharmacokinetic disposition function. Pharmacokinetic analysis can be thought of as a simple rearrangement of Eq. 26.3 to solve for  $D(t)$  (Eq. 26.4)

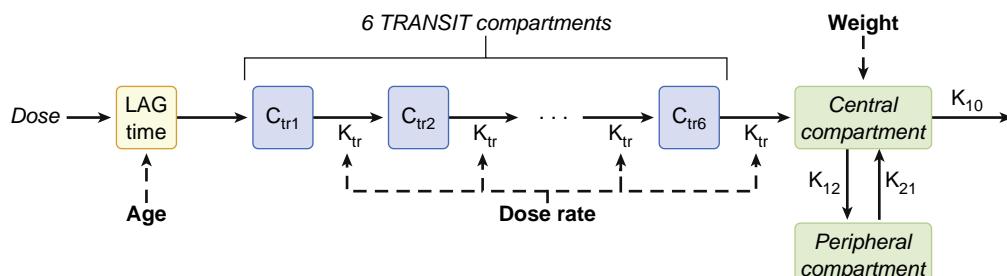
$$D(t) = \frac{C(t)}{I(t)} \quad (26.4)$$

where the symbol  $\rightarrow\leftarrow$  means *deconvolution*, the inverse operation of convolution. Deconvolution is similar to division, but of functions rather than simple numbers. When dosing regimens are designed from known pharmacokinetic models and a desired course for the plasma concentration over time, the known values are  $D(t)$  (the pharmacokinetics) and  $C_T(t)$  (the desired target concentrations), and the drug dosing scheme is (Eq. 26.5)

$$I(t) = \frac{C_T(t)}{D(t)} \quad (26.5)$$

Thus the necessary infusion rates,  $I(t)$ , can be calculated, given the desired target concentrations,  $C_T(t)$ , and the pharmacokinetics,  $D(t)$ , by applying the same tools used to calculate the original pharmacokinetics. Unfortunately, such a solution might require some negative infusion rates, which are obviously impossible. Because a drug cannot be retracted from the body (i.e., give inverse infusions), clinicians must restrict themselves to plasma concentrations over time that can be achieved with noninverse infusion rates.

The standard pharmacokinetic model has one glaring shortcoming. It assumes that after a bolus injection there is complete mixing within the central compartment such that the peak concentration occurs precisely at time 0. It actually takes approximately 30 to 45 seconds for the drug to make its transit from the venous injection site to the arterial circulation. This model misspecification over the first minute or so may not seem significant, but it can cause problems in attempts to relate the drug effect after a bolus to drug concentrations in the body,<sup>11</sup> which becomes even more important when using effect-site TCI.<sup>12</sup> The standard polyexponential pharmacokinetic models are being modified to provide more accurate models of plasma drug concentration in the first minute after bolus injection, also taking into account infusion rate. Recently, Masui and associates<sup>13</sup> found that a pharmacokinetic model consisting of a two-compartment model with a LAG (the time shift of dosing as if the drug were, in fact, administered to the pharmacokinetic model at a later time) and presystemic compartments model accurately described the early pharmacologic phase of propofol during infusion rates between 10 and 160 mg/kg/h. The infusion rate has an influence on kinetics. Age was a covariate for LAG time (Fig. 26.6). Besides compartment models, various physiologically based



**Fig. 26.6** Scheme of the final two-compartment pharmacokinetic model with a LAG time and six TRANSIT compartments ( $C_{tr\,n}$ ). The equilibration rate constants between the central and peripheral compartments were calculated using the following equations:  $k_{12} = C_{12} \div V_1$ ,  $k_{21} = C_{21} \div V_2$ . The elimination rate constant was calculated using the following equation:  $k_{10} = C_{10} \div V_1$ .  $C_{11}$ , Clearance of central compartment;  $C_{22}$ , clearance of peripheral compartment;  $V_1$ , distribution volume of central compartment;  $V_2$ , distribution volume of peripheral compartment. LAG time represents the time shift of dosing as if the drug was, in fact, administered to the pharmacokinetic model at a later time. TRANSIT compartments depict a multiple-step process represented by a chain of presystemic compartments. (From Masui K, Kira M, Kazama T, et al. Early phase pharmacokinetics but not pharmacodynamics are influenced by propofol infusion rate. *Anesthesiology*. 2009;111:805–817. Used with permission.)

models have been developed to model the pharmacokinetic behavior of anesthetics.<sup>14</sup> So far, these models are not superior at predicting the time course of drug concentration.<sup>13</sup> None of these models have been used to control intravenous drug delivery devices.

## Pharmacodynamic Considerations

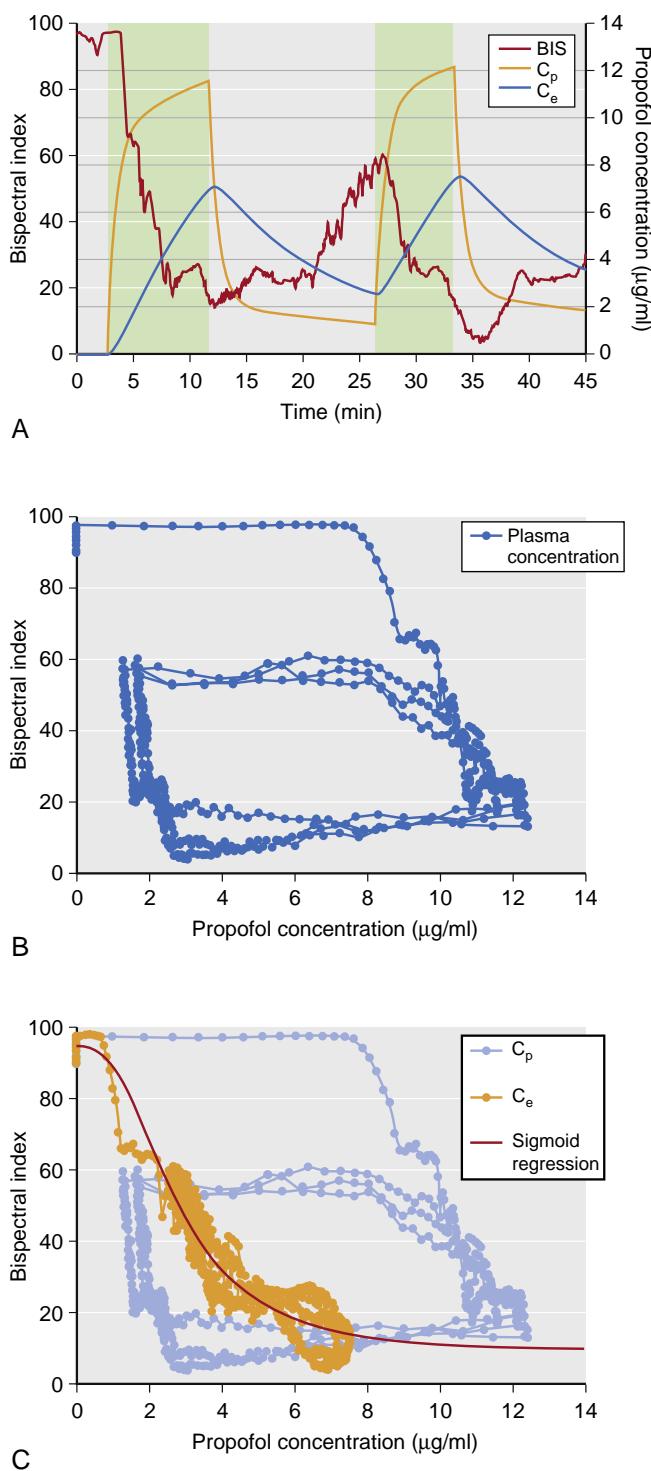
### THE BIOPHASE

The goal of drug titration during anesthesia is to reach and maintain a stable therapeutic drug concentration at the site of drug effect, also defined as the *effect site* or *biophase*. For most drugs used in anesthesia, the plasma is not the biophase and thus even after the drug has reached the arterial circulation, a further delay occurs before a therapeutic effect is observed. The reason is that additional time is required for the drug to be transported to the target organ, penetrate the tissue, bind to a receptor, and induce intercellular processes that ultimately lead to the onset of drug effect. This delay between peak plasma concentration and peak concentration at the effect site is called *hysteresis*. Fig. 26.7 illustrates an example of hysteresis revealed during an experiment published by Soehle and coworkers.<sup>15</sup> Two periods of continuous propofol infusions were given. The time course of the plasma concentration and effect-site concentration are simulated using pharmacokinetic and pharmacodynamic models. The cerebral drug effect was measured using the EEG-derived bispectral index (BIS). A clear delay between the time course of the plasma concentration and that of the BIS can be observed. The plasma concentration versus effect curve forms a counterclockwise hysteresis loop. This loop represents the plasma concentration, which is not the site of drug effect. Using nonlinear mixed-effect modeling, the hysteresis is minimized to reveal the effect-site concentration versus clinical effect relationship. The typical sigmoidal population model is also depicted in Fig. 26.7.

The concentration of drug in the biophase cannot be measured because it is usually inaccessible, at least in human subjects. The time course of drug effect can be calculated by using rapid measures of drug effect. Knowing the time course of drug effect, the rate of drug flow in and out of the biophase (or effect site) can be calculated with the use of

mathematic models. As such, the time course of the plasma concentration and the measured effect can be linked using the concept of the *effect compartment*, developed by Hull<sup>16</sup> and Sheiner.<sup>17</sup> The effect-site concentration is not a real measurable concentration but rather a virtual concentration in a theoretic compartment without a volume and, as such, also without any significant amount of drug present. For any concentration in this virtual compartment, a corresponding assumed effect is observed. This relationship between the effect-site concentration and effect is usually nonlinear and static (i.e., does not explicitly depend on time). If the plasma concentration is maintained at a constant level, then the model assumes that, at equilibrium, the effect-compartment concentration equals the plasma concentration. The delay between the plasma and the effect compartment is mathematically described by a single parameter, defined as  $k_{e0}$ , the effect-site equilibration rate constant (see Fig. 26.5).<sup>18</sup>

Measures of drug effect used to characterize the time course of drug transfer between plasma and the biophase vary with the drug being evaluated. For some drugs, a direct measure of drug effect can be applied. For neuromuscular blocking agents, the response from peripheral nerve stimulation (i.e., the twitch) is an ideal measure of effect. Various authors have used the T1% (percentage change of the T1 response compared with baseline T1 response during supramaximal stimulus) derived from electromyogram to measure the drug effect of newer drugs such as rocuronium<sup>19</sup> and cisatracurium.<sup>20</sup> For other categories of drugs such as opioids and hypnotics, the real clinical effects (e.g., unconsciousness, amnesia, memory loss, antinociception) are not measurable. For these reasons, surrogate measures are used to quantify the time course of clinical effects. These surrogate measures can be categorical or continuous. For example, the Observer's Assessment of Alertness/Sedation (OAA/S) scale was used to measure quantal changes in hypnotic drug effects during propofol administration.<sup>21</sup> Egan and colleagues<sup>22</sup> applied a noxious pain stimulus and used an algometer to measure the balance between nociception and antinociception during remifentanil infusion. Various spontaneous and evoked EEG-derived and processed measures were used to measure cerebral drug effects for opioids and hypnotics.<sup>15,23–27</sup> Ludbrook and associates measured propofol concentrations in the carotid artery and



**Fig. 26.7** (A) Time course of an experiment showing the hysteresis between plasma concentration ( $C_p$ ) and hypnotic effect as measured by the electroencephalographic (EEG)-derived bispectral index (BIS). Propofol was given at a constant rate during the shaded periods, resulting in  $C_p$  (orange line) and effect-site concentration ( $C_e$ ) (blue line). The corresponding BIS values are shown as a solid red line. (B) Relation between  $C_p$  and BIS using data from the experiment reveals a hysteresis loop. (C) After modeling, this hysteresis is minimized as shown in the relation between the effect-site concentration and BIS. ([A] Modified from Soehle M, Kuech M, Grube M, et al. Patient state index vs bispectral index as measures of the electroencephalographic effects of propofol. *Br J Anesth*. 2010;105:172–178. Used with permission; [B and C] Courtesy M. Soehle, Bonn, Germany.)

jugular bulb to establish movement of propofol into and equilibration with the brain. They simultaneously measured the BIS and found a close correlation between brain concentration (calculated by mass balance) and changes in the BIS.<sup>28</sup>

## DIRECT-EFFECT MODELS

As with plasma pharmacokinetics, the biophase concentration is the convolution of an input function (in this case, the plasma drug concentration over time) and the disposition function of the biophase. This relationship can be expressed as (Eq. 26.6)

$$C_{\text{biophase}}(t) = C_{\text{plasma}}(t) * D_{\text{biophase}}(t) \quad (26.6)$$

The disposition function of the biophase is typically modeled as a single exponential decay (Eq. 26.7)

$$D_{\text{biophase}}(t) = K_{e0} e^{-K_{e0} t} \quad (26.7)$$

The monoexponential disposition function implies that the effect site is simply an additional compartment in the standard compartment model that is connected to the plasma compartment (see Fig. 26.5). The effect site is the hypothetical compartment that relates the time course of plasma drug concentration to the time course of drug effect, and  $k_{e0}$  is the rate constant of elimination of drug from the effect site. By convention, the effect compartment is assumed to receive such small amounts of drug from the central compartment that it has no influence on plasma pharmacokinetics.

Neither  $C_{\text{biophase}}(t)$  nor  $D_{\text{biophase}}(t)$  can be directly measured, but the drug effect can be measured. Knowing that the observed drug effect is a function of the drug concentration in the biophase, the drug effect can be predicted as (Eq. 26.8)

$$\text{Effect} = f_{PD}[C_{\text{plasma}}(t) * D_{\text{biophase}}(t), P_{PD}, k_{e0}] \quad (26.8)$$

where  $f_{PD}$  is a pharmacodynamic model (typically sigmoidal in shape),  $P_{PD}$  represents the parameters of the pharmacodynamic model, and  $k_{e0}$  is the rate constant for equilibration between plasma and the biophase. Nonlinear regression programs are used to find values of  $P_{PD}$  and  $k_{e0}$  that best predict the time course of drug effect. This method is called *loop-collapsing* (see Fig. 26.7). Knowledge of these parameters can then be incorporated into dosing regimens that produce the desired time course of drug effect.<sup>29,30</sup>

If a constant plasma concentration is maintained, then the time required for the biophase concentration to reach 50% of the plasma concentration ( $t_{1/2}k_{e0}$ ) can be calculated as  $0.693/k_{e0}$ . After a bolus dose, the time to peak biophase concentration is a function of both plasma pharmacokinetics and  $k_{e0}$ . For drugs with a very rapid decline in plasma concentration after a bolus (e.g., adenosine with a half-life of several seconds), the effect-site concentration peaks within several seconds of the bolus, regardless of  $k_{e0}$ . For drugs with a rapid  $k_{e0}$  and a slow decrease in concentration after a bolus injection (e.g., pancuronium), the peak effect-site concentration is determined more by  $k_{e0}$  than by plasma pharmacokinetics.

An accurate estimation of  $k_{e0}$  demands an integrated pharmacokinetic-pharmacodynamic study combining rapid blood sampling with frequent measurements of drug

effect, yielding an overall model for the dose-response behavior of the drug. Historically, the time constants of pharmacokinetic models and the  $k_{e0}$  of pharmacodynamic studies were sometimes naively merged, possibly leading to inaccurate predictions of the clinical drug effect. Coppens and colleagues proved that pharmacodynamic models of BIS in children developed by using estimates of plasma propofol concentrations from published pharmacokinetic models and estimating the pharmacodynamic model do not ensure good pharmacokinetic accuracy or provide informative estimates for pharmacodynamic parameters.<sup>31</sup> If no integrated pharmacokinetic-pharmacodynamic model exists, then the time to peak effect ( $t_{peak}$ ) after a bolus injection can be used to recalculate  $k_{e0}$  using the pharmacokinetic model of interest to yield the correct time to peak effect. Under these circumstances, this alternative approach might lead to a more accurate prediction of the dose-response time course.<sup>32,33</sup> However, the correct covariates for  $t_{peak}$  should be estimated in a specific population.<sup>34</sup> A second caveat is that the time course of drug effect is specific for a given effect (e.g., cerebral drug effect as measured by a specific processed EEG). The time course of other side effects (e.g., hemodynamic effect for hypnotics) most frequently follows a different trajectory.<sup>35,36</sup> The time to peak effect and the  $t_{1/2} k_{e0}$  for several intravenous anesthetics are listed in Table 26.1.

All methods discussed so far incorporate  $k_{e0}$  values calculated on the assumption that hysteresis between plasma concentration and clinical effect is explained by a delay in drug transfer between plasma and biophase and thus that anesthesia is a smooth, path- and state-independent, symmetric process. Although still commonly used, this assumption might be suboptimal. Data from animal experiments suggest that neural processes and pathways involved in anesthesia induction and recovery are different.<sup>37,38</sup> In an animal study, measured brain drug concentrations at loss of consciousness and at return of consciousness were significantly different.<sup>39</sup> If these data are confirmed, then

a more complex model (e.g., one incorporating a second, serial effect-site model) might be required to depict the time course of drug effect. Several groups have investigated this hypothesis in humans, and so far the published findings are not consistent. One clinical study specifically designed to address this topic showed evidence supportive of the concept of neural inertia.<sup>40</sup> Two other studies involving secondary analyses of existing data, of which one indicated supportive evidence<sup>41</sup> and the other showed that neural inertia was not present in all subjects, and appeared to occur only with propofol (and not with sevoflurane), and to be present only with certain pharmacodynamic endpoints.<sup>42</sup>

## INDIRECT-EFFECT MODELS

Thus far, clinical effects that are an instantaneous function of drug concentration at the site of drug effect have been discussed, as implied by Eq. 26.8. For example, once a hypnotic drug reaches the brain or a neuromuscular-blocking drug reaches the muscles, drug action is almost immediately observed. On the other hand, some effects are significantly more complex. For example, consider the effect of opioids on ventilation. Initially, opioids depress ventilation, and arterial tension of carbon dioxide ( $CO_2$ ) gradually accumulates. Yet, the accumulation of  $CO_2$  at normal conditions is a strong stimulant for ventilation, thereby partly counteracting the ventilatory depressant effects of opioids. Ventilatory depression is an example in which direct and indirect drug effects are incorporated. The direct effect of the opioid is to depress ventilation, and the indirect effect is to increase arterial tension of  $CO_2$ . Modeling the time course of opioid-induced ventilatory depression requires consideration of both components. Bouillon and colleagues developed a model of ventilatory depression that incorporates both direct and indirect effects.<sup>43-45</sup> As is generally the case with indirect-effect models, characterizing drug-induced ventilatory depression requires a consideration of the entire time course of drug therapy, which is embodied by the following differential equation (Eq. 26.9):

$$\frac{d}{dt} PaCO_2 = k_{el} \cdot \left[ 1 - \frac{C_p(t)\gamma}{C_{50}\gamma + C_p(t)\gamma} \right] \cdot \left[ \frac{P_{biophase} CO_2(t)}{P_{biophase} CO_2(0)} \right]_F \cdot PaCO_2(t) \quad (26.9)$$

where partial pressure of arterial carbon dioxide ( $PaCO_2$ ) is arterial  $CO_2$ ,  $P_{biophase} CO_2$  is  $CO_2$  in the biophase (i.e., brain-stem respiratory control circuits),  $k_{el}$  is the rate constant for the elimination of  $CO_2$ ,  $C_{50}$  is the effect-site opioid concentration associated with a 50% reduction in ventilatory drive, and  $F$  is the steepness or *gain* of the effect of  $CO_2$  on ventilatory drive.

## DOSE IMPLICATIONS OF THE BIOPHASE

The delay in onset of clinical effects has important clinical implications. After a bolus, the plasma concentration peaks nearly instantly and then steadily declines. The effect-site concentration starts at zero and increases over time until it equals the descending plasma concentration. The plasma concentration continues to decline. After the moment of identical concentrations, the gradient between plasma and

**TABLE 26.1** Time to Peak Effect and  $t_{1/2} k_{e0}$  After a Bolus Dose

Drug	Time to Peak Drug Effect (min)*	$t_{1/2} k_{e0}$ (min)
Morphine	19	264
Fentanyl	3.6	4.7
Alfentanil	1.4	0.9
Sufentanil	5.6	3.0
Remifentanil	1.8	1.3
Ketamine	—	3.5
Propofol	1.6	1.7
Thiopental	1.6	1.5
Midazolam	2.8	4.0
Etomidate	2.0	1.5

\*Measured by electroencephalography.

$k_{e0}$  is the rate constant for transfer of drug from the site of drug effect to the environment.

$t_{1/2} k_{e0} = 0.693/k_{e0}$

the biophase favors removal of drug from the biophase, and the effect-site concentration decreases. The rate at which the effect-site concentration rises toward the peak after a bolus dictates how much drug must be injected into plasma to produce a given effect. For alfentanil, its rapid plasma effect-site equilibration (large  $k_{e0}$ ) causes the effect-site concentration to rise rapidly, with a peak produced in approximately 90 seconds. At the time of the peak, approximately 60% of the alfentanil bolus has been distributed into peripheral tissues or eliminated from the body. For fentanyl, the effect-site concentration rises significantly more slowly and peaks 3 to 4 minutes after the bolus.<sup>46</sup> At the time of the peak, more than 80% of the initial bolus of fentanyl has been distributed into tissues or eliminated. As a result of slower equilibration with the biophase, relatively more fentanyl than alfentanil must be injected into plasma, which makes the rate of offset of drug effect after a fentanyl bolus slower than after an alfentanil bolus.

This difference in pharmacokinetics indicates that  $k_{e0}$  must be incorporated into dosing strategies on which rational drug selection is dependent. For rapid onset of effect, a drug with a large  $k_{e0}$  (short  $t_{1/2}$   $k_{e0}$ ) should be chosen. For example, for rapid sequence induction of anesthesia, alfentanil or remifentanil may be the optimal opioid because its peak effect-site concentration coincides with the likely time of endotracheal intubation. However, for a slower induction of anesthesia in which a nondepolarizing neuromuscular blocking agent is used, an opioid with a slower onset of drug effect should be selected to coincide with the peak effect of the neuromuscular blocking agent. In this case, a bolus of fentanyl or sufentanil at the time of induction may be more appropriate. The time to peak effect for the commonly used opioids is shown in Fig. 26.8. Knowing  $k_{e0}$  (or time to peak effect) also improves titration of the drug by identifying the time at which the clinician should make an assessment of drug effect. For example, midazolam has a slow time to peak effect, and repeat bolus doses should be spaced at least 3 to 5 minutes apart to avoid inadvertent overdosing.

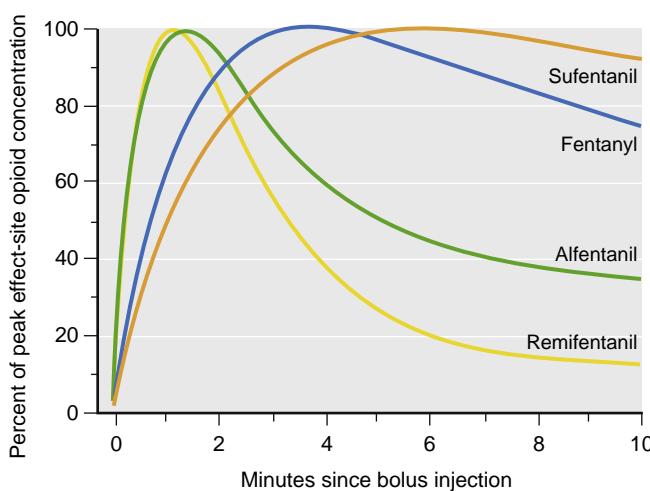
An accurate  $k_{e0}$  is also crucial during TCI titrating to a specific effect-site concentration because the initial bolus given to reach the targeted effect-site concentration depends on both the pharmacokinetics and the  $k_{e0}$ .<sup>47</sup>

## DRUG POTENCY

### Single Drugs

Knowledge about adequate therapeutic drug concentration is crucial to achieve the aim of providing optimal anesthetic conditions. Therefore information on drug potency is essential. Analogous to the concept of minimum alveolar concentration (MAC), the concentration associated with a 50% likelihood of movement in response to skin incision for inhaled anesthetics<sup>48</sup> is the  $C_{50}$  for intravenous drugs, which provides a measure of relative potency between intravenous anesthetics.

There are many ways to look upon  $C_{50}$ , taking into consideration whether the clinical effect is a binary or continuous effect. When considering binary effects, the  $C_{50}$  might be the drug concentration that prevents response (e.g., movement, hypertension, release of catecholamines) to a particular stimulus (e.g., surgical incision, endotracheal intubation, spreading of the sternum) in 50% of patients. In



**Fig. 26.8** Simulated onset and time to peak effect of commonly used opioids based on their  $k_{e0}$  and pharmacokinetic parameters.  $k_{e0}$ , Rate constant for the transfer of drug from the site of drug effect to the environment.

this case, each combination of stimulus and response may have a unique  $C_{50}$ . When  $C_{50}$  is defined as the drug concentration that produces a given response in 50% of patients, a 50% probability of response is also likely in a given patient. Defining  $C_{50}$  as the concentration that produces a given drug effect in 50% of individuals implicitly assumes that the effect can be achieved in all individuals. Some drugs exhibit a ceiling effect. For example, a ceiling effect may exist on the ability of opioids to suppress response to noxious stimulation. When a ceiling in drug effect exists, some patients may not exhibit the drug effect even at infinitely large doses. In this case,  $C_{50}$  is not the concentration that causes the drug effect in 50% of patients but is the concentration associated with the drug effect in one half of whatever fraction of patients is able to respond.

Several studies have been performed to establish appropriate concentrations of intravenous anesthetics and opioids for various clinical endpoints and the effect of drug interactions (Table 26.2).<sup>49-56</sup>

Another interpretation of  $C_{50}$  is the concentration that produces 50% of the maximum possible physiologic response. For example, the  $C_{50}$  for an EEG response is the drug concentration that provides 50% depression of the maximal EEG effect. The  $C_{50}$  for EEG response has been measured for the opioids alfentanil,<sup>57</sup> fentanyl,<sup>57</sup> sufentanil,<sup>58</sup> and remifentanil.<sup>59-61</sup> It has also been determined for thiopental,<sup>51,62,63</sup> etomidate,<sup>56</sup> propofol,<sup>24</sup> and benzodiazepines (see Table 26.2).<sup>57,64</sup> Other measures such as pupillary dilation in response to a noxious stimulus<sup>65</sup> and pressure algometry<sup>22</sup> were used to measure opioid potency and revealed slightly different values for  $C_{50}$ , which indicates that observation of drug potency also depends on the applied measure of drug effect.

As mentioned,  $C_{50}$  can be used to compare potency among drugs. For example, Glass and colleagues<sup>66</sup> determined the potency of remifentanil compared with alfentanil using ventilatory depression as the measure of opioid effect. In their study, the  $C_{50}$  for depression of minute ventilation was 1.17 ng/mL and 49.4 ng/mL for remifentanil and alfentanil, respectively. Using this difference in  $C_{50}$ ,

**TABLE 26.2** Steady-State Concentrations for Predefined Effects

Drug	$C_{50}$ for EEG Depression*	$C_{50}$ for Incision or Painful Stimulus†	$C_{50}$ for Loss of Consciousness‡	$C_{50}$ for Spontaneous Ventilation§	$C_{50}$ for Isoflurane MAC Reduction	MEAC
Alfentanil (ng/mL)	500-600	200-300	—	170-230	50	10-30
Fentanyl (ng/mL)	6-10	4-6	—	2-3	1.7	0.5-1
Sufentanil (ng/mL)	0.5-0.75	(0.3-0.4)	—	(0.15-0.2)	0.15	0.025-0.05
Remifentanil (ng/mL)	10-15	4-6	—	2-3	1.2	0.5-1
Propofol ( $\mu$ g/mL)	3-4	4-8	2-3	1.33	—	—
Thiopental ( $\mu$ g/mL)	15-20	35-40	8-16	—	—	—
Etomidate ( $\mu$ g/mL)	0.53	—	0.55	—	—	—
Midazolam (ng/mL)	250-350	—	125-250	—	—	—

\* $C_{50}$  for depression of the EEG is the steady-state serum concentration that causes a 50% slowing of the maximal EEG, except for midazolam, in which the  $C_{50}$  is associated with 50% activation of the EEG.

† $C_{50}$  for skin incision is the steady-state plasma concentration that prevents a somatic or autonomic response in 50% of patients.

‡ $C_{50}$  for loss of consciousness is the steady-state plasma concentration for absence of a response to a verbal command in 50% of patients.

§ $C_{50}$  for spontaneous ventilation is the steady-state plasma concentration associated with adequate spontaneous ventilation in 50% of patients.

Values in parentheses are estimated by scaling to the alfentanil  $C_{50}$  (see text for details).

EEG, Electroencephalography; MAC, minimum alveolar concentration; MEAC, minimum effective plasma concentration providing postoperative analgesia.

they concluded that remifentanil is approximately 40 times more potent than alfentanil.

To be entirely independent of dosing history,  $C_{50}$  must be determined at steady state, which is rarely possible because most anesthetic drugs do not reach steady state during a continuous infusion until many hours have passed. However, if the drug exhibits rapid equilibration between plasma and the effect site and the investigator waits long enough after starting the infusion, then this choice can be reasonably satisfactory. For example, Ausems and colleagues<sup>67,68</sup> used a continuous infusion of alfentanil in their experiments, which quickly equilibrated. They also recorded their measurements after the effect-site concentration had equilibrated with plasma.

A second alternative to performing a true steady-state experiment is to use mathematic modeling to calculate the effect-site concentrations of drug at the time of measurement, as proposed by Hull and colleagues<sup>16</sup> and Sheiner and colleagues.<sup>17</sup> The relationship between effect-site and plasma concentrations is graphically represented in Fig. 26.5 and mathematically in Eq. 26.6. Calculating effect-site concentrations is the same as attempting to determine the steady-state plasma concentrations that produce the observed drug effect. When the  $C_{50}$  reflects effect-site concentrations, it is represented as  $C_{e50}$  to distinguish it from values of  $C_{50}$  that are based on plasma concentrations, which are then termed  $C_{p50}$ . However, the distinction is artificial. In both cases,  $C_{50}$  is intended to represent the steady-state plasma drug concentration associated with a given drug effect.

A third alternative to performing a steady-state experiment is to establish a pseudo-steady state with the use of computer-controlled drug delivery. By this term we mean that a steady state is assumed to exist, because a varying rate drug infusion is being administered with the intent of achieving stable plasma concentrations. This method has become the state of the art for determining the  $C_{50}$  for anesthetic drugs, and many of the  $C_{50}$  values referenced earlier were determined at pseudo-steady state with the

use of computer-controlled drug delivery. Commonly, two or more measurements of the plasma concentration during pseudo-steady state conditions are performed to verify whether this is indeed the case.<sup>40-42</sup> Typically, maintaining a constant plasma steady-state concentration for four to five plasma effect-site equilibration half-lives (e.g., 10-15 minutes for fentanyl) is required. Such a long delay is not necessarily needed when computer-controlled drug delivery is used.

Effect-compartment TCIs can be used to target the concentration at the effect site rather than the plasma concentration and thereby rapidly establishing plasma–effect site equilibration.<sup>29,47</sup> For example, Kodaka and associates reported predicted values of propofol effect-site concentration  $C_{50}$  between 3.1  $\mu$ g/mL and 4.3  $\mu$ g/mL for insertion of various laryngeal airway masks, depending on the type of laryngeal mask.<sup>69</sup> Cortinez and associates used TCI to determine the  $C_{50}$  of remifentanil and fentanyl for accurate pain relief during extracorporeal shock wave lithotripsy in relation with possible side effects and found that remifentanil and fentanyl  $C_{50}$  were 2.8 ng/mL and 2.9 ng/mL, respectively.<sup>70</sup> At  $C_{50}$ , the probability of having a respiratory rate less than 10 breaths per minute was 4% for remifentanil and 56% for fentanyl.

Likewise, TCI has been used to estimate the following  $C_{50}$  values for dexmedetomidine: the  $C_{50}$  for half-maximal effect on the BIS (BIS ~48) was 2.6 ng/mL, for half-maximal effect on the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale was 0.438 ng/mL, for half-maximal hypotensive effect was 0.36 ng/mL, and the  $C_{50}$  for half-maximal hypertensive effects was 1.6 ng/mL.<sup>71,72</sup>

Thus there are several ways to establish  $C_{50}$  in terms of steady-state concentrations.  $C_{50}$  can be estimated through mathematic effect-site modeling or can be experimentally measured with the use of computer-controlled drug delivery to establish a pseudo-steady state quickly. Either way, when performing studies to define the concentration–effect relationship, equilibrium must exist or be modeled between

the biophase (the site of effect) and plasma or blood (where the concentration is actually measured).

When  $C_{50}$  is defined in terms of the concentration associated with a response in one half of a population, that same  $C_{50}$  is the concentration associated with a 50% probability of response in a typical individual. However, individual patients are not typical individuals but rather will have their own value for  $C_{50}$ . Expressed in clinical terms, different patients have different anesthetic requirements for the same stimulus. For example, the minimal effective analgesic concentration of fentanyl is 0.6 ng/mL, but it varies among patients from 0.2 to 2.0 ng/mL.<sup>73</sup> The minimal effective analgesic concentrations of alfentanil<sup>74</sup> and sufentanil<sup>75</sup> similarly vary among patients by a factor of 5 to 10. This range encompasses both variability in the intensity of the stimulus and variability of the individual patient.

One factor known to be responsible for this interindividual pharmacodynamic variability is the patient age. Thus with the pharmacodynamic for propofol developed by Eleveld and colleagues, and based on pharmacokinetic-pharmacodynamic data from a large number of patients and volunteers, the estimated effect-site propofol concentrations required for a BIS of 47 for patients whose ages are 20, 40, and 70 years, are 3.5, 3.1, and 2.6 ug/mL, respectively.<sup>76</sup>

Although age has a strong effect on the  $C_{50}$ , it does not explain all the variability. This wide range reflects the clinical reality that must be accounted for when dosing regimens are designed. Because of this variability, intravenous anesthetics should be titrated to each patient's unique anesthetic requirement for the given stimulus.

### Pharmacodynamic Drug Interactions

Drug interactions cause the potency of one drug (e.g., as measured by the  $C_{50}$ ) to shift in response to the administration of a second drug. This drug interaction can be additive, supra-additive (synergistic), or infra-additive (antagonistic). As observed in the isobologram (Fig. 26.9), for additive drugs with equal potency, the cumulative effect resulting from doses  $a$  and  $b$  for substances A and B, respectively, equals the effect obtained with the injection of either drug A or B solely in a dose  $a + b$ . If the drugs interact synergistically, then the combination of A and B will generate a more pronounced effect than additive. For antagonistic drug interaction, the combination of A and B will result in

a less pronounced effect than additive. In general, additive drug interactions occur when combining drugs acting by the same mechanism and synergistic or antagonistic interaction when combining drugs acting by a different mechanism.<sup>77</sup> Hendrickx and coworkers (Fig. 26.10) reviewed the available literature and summarized the available data on drug interactions in humans and animals for hypnosis and immobility.<sup>77</sup>

Investigating only one isobole of the interaction spectrum (e.g., the 50% probability level of a specific drug response) provides a rudimentary insight into the interaction characteristics but reveals only limited information about other levels of drug effect (e.g., at the clinically more important level of 95% probability of drug response). As drug interactions may vary among drug effect levels (e.g., additive at the 50% level but synergistic at the 95% level), the ultimate aim is to characterize the response surface describing all levels of effect. Pharmacodynamic response surface models generate figures that are three- (or even higher) dimensional structures that have been developed to describe the relationship quantitatively between two or more drug concentrations and their combined clinical effect (Fig. 26.11). Response surface models are powerful representations of drug interactions as they combine information about the full range of isoboles resulting from the concentration response curves of all combinations of the drugs involved.<sup>78,79</sup> Using the mathematically defined response surface, the corresponding drug effect for any two or more drug concentrations of the interacting drugs can be predicted.<sup>80,81</sup> Various methodological approaches to response surface models are found in the literature.<sup>82</sup>

Intravenous opioids are frequently combined with volatile anesthetics during anesthesia. The reduction of the MAC for a given volatile by a given opioid dose can be applied to investigate the potency and efficacy of opioids.<sup>83-85</sup> These MAC reduction studies reveal a general pattern, irrespective of which opioid or volatile anesthetic has been used. Low concentrations of an opioid result in a substantial reduction of MAC (Fig. 26.12). With increasing concentrations of the opioid, MAC continues to decrease until a plateau is reached and, consequently, a further increase of the opioid dose is futile.<sup>86</sup>

The previously mentioned MAC reduction studies show the effect of a single opioid dose on a single point of a dose-response curve but, nonetheless, form the basis for more detailed surface interaction studies.<sup>87</sup> To characterize the interaction between sevoflurane and remifentanil in blunting responses to verbal (OAA/S scale) and painful stimuli (pressure algometry, electrical tetanic stimulus, and thermal stimulation), Manyam and coworkers constructed a response surface for each pharmacodynamic response using a Logit model approach and found synergy between sevoflurane and remifentanil for all responses. More specifically, a remifentanil effect-site concentration of 1.25 ng/mL was able to more than halve the sevoflurane requirements for preventing movement to pain.<sup>88</sup> Because this study suffered from nonsteady-state conditions at the moment of measurements, the authors improved their data using calculated effect-site sevoflurane concentrations and a Greco model instead of a Logit approach.<sup>89</sup> Accounting for the time lag between sevoflurane effect-site concentration and end-tidal concentration improved the predictions of

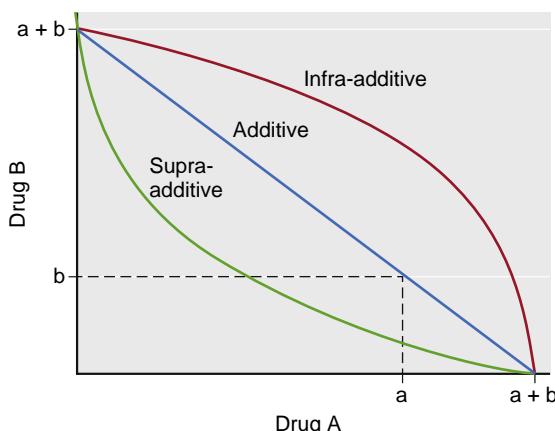
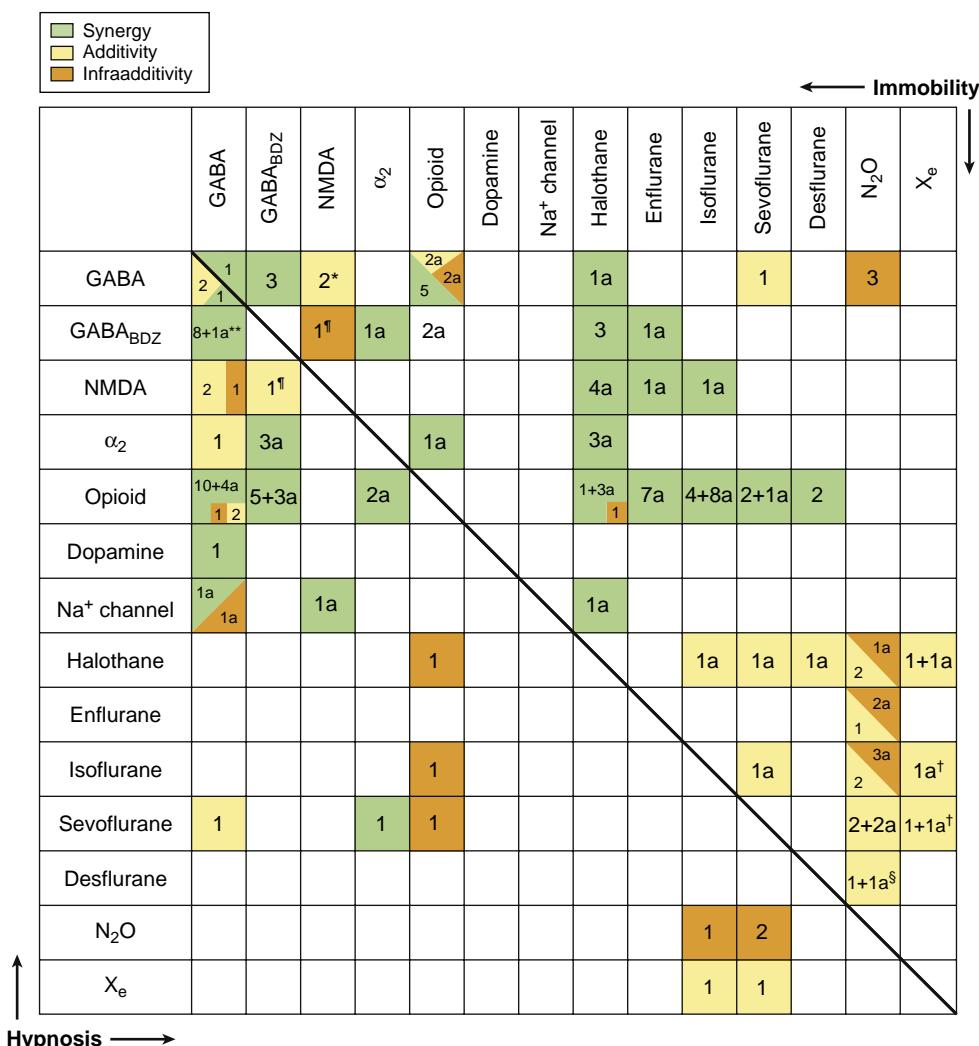


Fig. 26.9 Pharmacodynamic drug interactions.

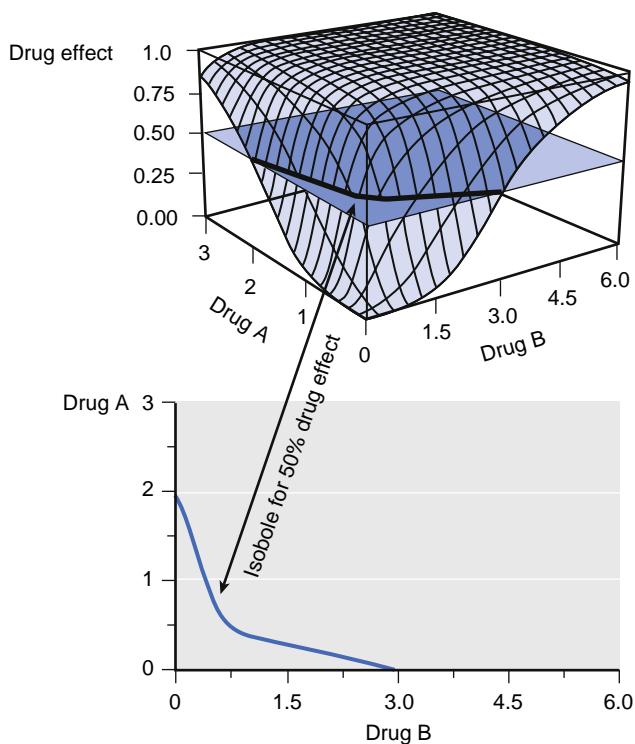
responsiveness during anesthesia but had no effect on the accuracy of prediction of a response to a noxious stimulus in recovery. They concluded that models may be useful in predicting events of clinical interest, but large-scale evaluations with numerous patients are needed to better characterize model performance. Heyse and colleagues (Fig. 26.13) found that the pharmacodynamic interaction between sevoflurane and remifentanil for tolerance to shaking and shouting (TOSS), tetanic stimulation (TTET), laryngeal mask airway insertion (TLMA), and laryngoscopy (TLAR) using the Fixed C50<sub>0</sub> Hierarchical model was strongly synergistic for both the hypnotic and the analgesic components of anesthesia and showed the importance of

exploring various surface model approaches when studying drug interactions.<sup>82,90</sup>

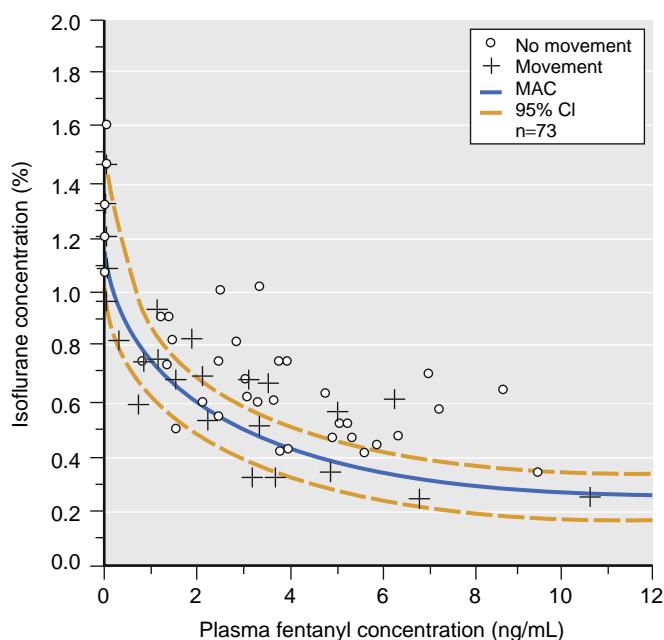
For total intravenous anesthesia, interactions associated with various drug combinations and concentrations have been described. The concept of *balanced* anesthesia is based on the assumption that drug combinations will be synergistic in anesthetic effect (however defined) but not in toxicity. Such synergism has been demonstrated for a variety of drug combinations but not for others (see Fig. 26.10).<sup>77,91</sup> Zanderigo and colleagues<sup>92</sup> developed the *well-being* model, a new interaction model to describe both positive and negative effects of drug combinations (Fig. 26.14).



**Fig. 26.10** Interaction grid summarizing the available data on drug interactions in humans and animals for hypnosis and immobility. Drugs are organized by pharmacologic class: gamma-aminobutyric acid (GABA)-acting drugs (propofol, thiopental, methohexitol, and etomidate); GABA agents acting at the benzodiazepine (GABA<sub>BDZ</sub>)-binding site (midazolam, diazepam); N-methyl-D-aspartate (NMDA)-receptor antagonist (ketamine); adrenergic agonists (α<sub>2</sub>) (dexmedetomidine, clonidine); opioid-acting drugs at opioid receptor (morphine, alfentanil, fentanyl, sufentanil, and remifentanil); dopamine at dopamine antagonists (droperidol, metoclopramide); sodium (Na<sup>+</sup>) channel blockers (lidocaine, bupivacaine); and anesthetic gases. The right upper half of the grid (*above the thick diagonal*) summarizes the interactions for the endpoint of immobility; the left lower half (*below the thick diagonal*) summarizes the interactions for the endpoint of hypnosis. Synergy is coded as green, additivity as yellow, and infra-additivity as dark orange. The number refers to the number of studies attesting to a particular interaction; if one study documents two interactions (e.g., isoflurane with both fentanyl and alfentanil), then they are counted separately. Animal data carry the suffix *a* after the number of studies; human data have no suffix. \*Reanalysis: propofol-ketamine interaction in humans is infra-additive for immobility. \*\*Reanalysis: thiopental-midazolam interaction in humans is additive for hypnosis. <sup>†</sup>Because the MAC of Xe in swine is uncertain, data in swine are not included. <sup>‡</sup>Reanalysis: ketamine-midazolam interaction in humans is infra-additive for hypnosis and additive for immobility. <sup>§</sup>Infra-additivity between desflurane and nitrous oxide (N<sub>2</sub>O) has been suggested in a small subgroup of 18- to 30-year-old patients. (From Hendrickx JF, Eger EI 2nd, Sonner JM, et al. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. *Anesth Analg*. 2008;107:494–506. Used with permission.)



**Fig. 26.11** Relationship between a response surface and a standard isobogram. Conventional isobolographic analysis, whether for doses or concentrations, describes only the concentration of both drugs that yields a 50% drug effect and thus fails to capture the entire response surface. (From Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. *Anesthesiology*. 2000;92:1603–1616. Used with permission.)



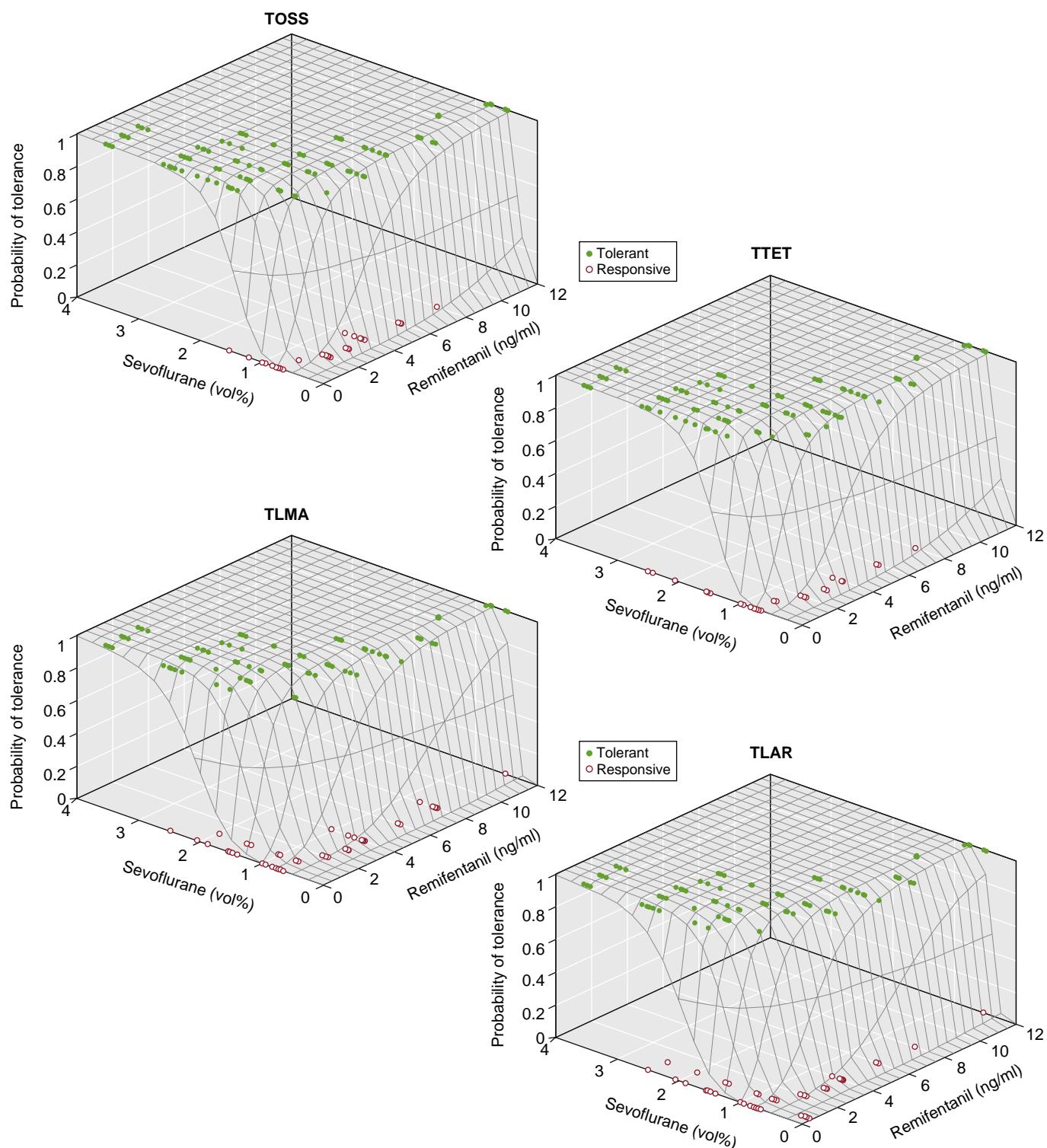
**Fig. 26.12** Interaction of isoflurane and fentanyl in preventing a somatic response at skin incision (i.e., minimum alveolar concentration [MAC] reduction of isoflurane). The blue line represents the concentrations of isoflurane and fentanyl when administered together that are required to prevent purposeful movement in 50% of patients at skin incision. The dotted gold lines represent the 95% confidence interval (CI) of the MAC at each combination of fentanyl and isoflurane. (From McEwan AI, Smith C, Dyar O, et al. Isoflurane MAC reduction by fentanyl. *Anesthesiology*. 1993;78:864–869. Used with permission.)

More profound synergy for specific endpoints related to analgesia and hypnosis has also been demonstrated for the interaction between propofol and opioids. Thus when anesthetic regimens are designed that rely on synergy to produce the anesthetic state, distinguishing the desired endpoint—loss of consciousness or ablation of response to noxious stimulation—is important. Different combinations of drugs may be used to achieve any endpoint. Vuyk and colleagues characterized the interaction between propofol and alfentanil for several endpoints: loss of response to endotracheal intubation, loss of response to incision and retraction of the peritoneum, and emergence from anesthesia (Fig. 26.15).<sup>93</sup> The most profound stimulation was tracheal intubation, and when no opioid was used, the abolition of responses to that stimulus required a propofol concentration equal to or more than 12  $\mu$ g/mL. More details for optimal drug combinations based on the findings from Vuyk and coworkers<sup>93</sup> are provided in Table 26.3.

Minto and colleagues published *response surfaces* for combinations of midazolam-alfentanil, propofol-alfentanil, and midazolam-propofol associated with the loss of response to verbal command (Fig. 26.16).<sup>78</sup> They also extended response surface methodology to describe the simultaneous interaction of three drugs. Rendering the full interaction surface for three drugs would require drawing the graph in four dimensions. If the graph is limited to the interaction at 50% drug effect, then it can be rendered in three dimensions (Fig. 26.17).

In addition to studies of quantal responses, various studies investigated the interaction between hypnotics and opioids as measured with continuous measures. The effect of combined drug administration on spontaneous and evoked EEG-derived indices was found to be important and existing but often in studies that did not provide sufficient data for full-response surface model development.<sup>24,94,95</sup> Fortunately, more accurately designed studies<sup>81</sup> using surface modeling techniques revealed the interaction between hypnotics and opioids. Bouillon and colleagues found synergy between propofol and remifentanil regarding hypnosis as measured by the BIS and EEG approximate entropy. They also found that both indices were more sensitive to propofol than remifentanil.<sup>96</sup> Others found conflicting results for the effect of opioids on the BIS.<sup>97</sup> More recently, Gambus and colleagues modeled the effect of propofol and remifentanil combinations for sedation-analgesia in endoscopic procedures using an adaptive neurofuzzy inference system.<sup>98</sup> Both spontaneous and evoked EEG-derived indices (e.g., BIS or autoregressive auditory-evoked potential index [AAI/2] and index of consciousness [IoC]) were used. They found, based on these models, that the propofol and remifentanil effect-site concentration pairs provide a Ramsay Sedation Score of 4 ranging from (1.8  $\mu$ g/mL, 1.5 ng/mL) to (2.7  $\mu$ g/mL, 0 ng/mL), associated with a BIS of 71 to 75, AAI/2 values of 25 to 30, and IoC of 72 to 76, respectively. The presence of noxious stimulation increases the requirements of propofol and remifentanil to achieve the same degree of sedative effects.<sup>98</sup>

Other effects of drug combinations were also studied. Bouillon and associates and Nieuwenhuijs and associates

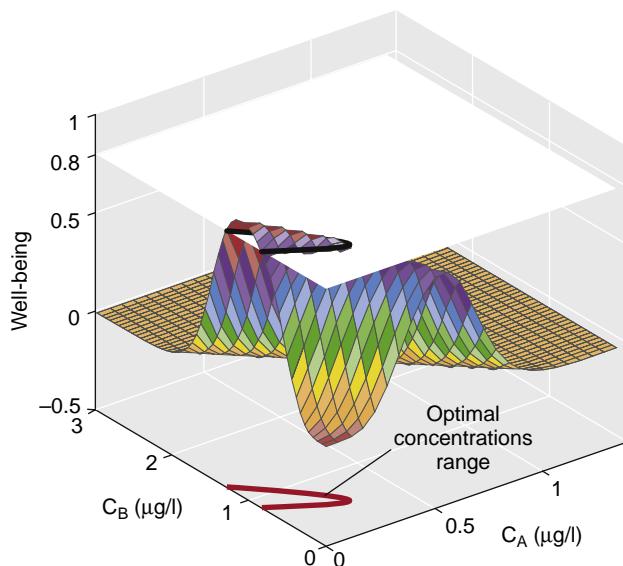


**Fig. 26.13** Response surface for probability of tolerance to shaking and shouting (TOSS), tetanic stimulation (TTET), laryngeal mask airway insertion (TLMA), and laryngoscopy (TLAR) for the Fixed C50(O) Hierarchical model. The solid lines at probability 0.5 represent the 50% isoboles. (From Heyse B, Proost JH, Schumacher PM, et al. Sevoflurane remifentanil interaction: comparison of different response surface models. *Anesthesiology*. 2012;116:311–323. Used with permission.)

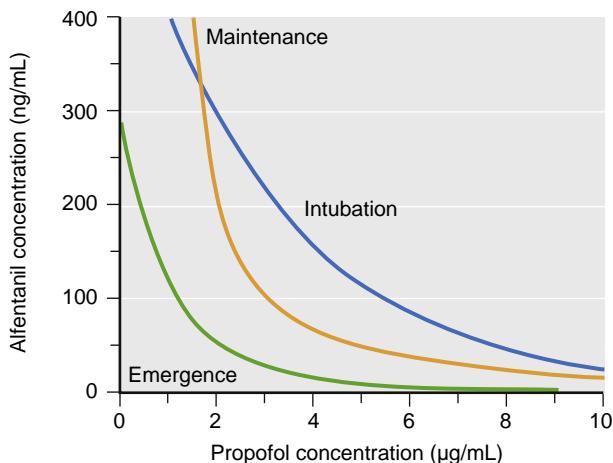
investigated the effects of hypnotic-opioid combinations on cardiorespiratory control.<sup>97,99</sup> These data show dose-dependent effects on respiration at relatively low concentrations of propofol and remifentanil. When combined,

their effect on respiration is strikingly synergistic, resulting in severe respiratory depression.

Surface models were also used to optimize drug administration in challenging situations such as short-duration



**Fig. 26.14** Definition of the optimal concentrations range for the combined administration of drugs A and B, in the case of zero interactions. The optimal concentrations range results from the intersection between the well-being surface and the plane representing a well-being value of 0.8. (From Zanderigo E, Sartori V, Sveticic G, et al. The well-being model. A new drug interaction model for positive and negative effects. *Anesthesiology*. 2006;104:742–753. Used with permission.)



**Fig. 26.15** Interaction between alfentanil and propofol on three different endpoints. Response to intubation (blue line), maintenance of anesthesia (gold line), and concentrations associated with emergence from anesthesia (green line). The curve shows the concentrations associated with a 50% probability of the respective endpoint. (Modified from Vuyk J, Lim T, Engbers FH, et al. The pharmacodynamic interaction of propofol and alfentanil during lower abdominal surgery in women. *Anesthesiology*. 1995;83:8–22.)

procedures in spontaneous breathing patients. LaPierre and coworkers<sup>100</sup> explored remifentanil-propofol combinations that led to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or an onset of ventilatory depression requiring intervention. They found that the combinations that allowed esophageal instrumentation and avoided intolerable ventilatory depression and/or loss of responsiveness primarily clustered around remifentanil-propofol effect-site concentrations ranging from 0.8 to 1.6

ng/mL and 1.5 to 2.7 µg/mL, respectively. However, blocking the response to esophageal instrumentation and avoiding both intolerable ventilatory depression and/or a loss of responsiveness is difficult. It may be necessary to accept some discomfort and blunt, rather than block, the response to esophageal instrumentation to consistently avoid intolerable ventilatory depression and/or loss of responsiveness.

In a previously mentioned study, using response surface modeling, Bouillon and colleagues also determined the interactions between propofol and remifentanil on the probability to tolerate laryngoscopy (PTOL).<sup>96</sup> Luginbuhl, working with a group that included Bouillon, normalized and calibrated PTOL, to produce an index called the noxious stimulus response index (NSRI).<sup>101</sup> The NSRI is a dimensionless integer number between 0 and 100, where 50 corresponds to a PTOL of 50% and 20 to a PTOL of 90%.

The interactions between hypnotics such as propofol and sevoflurane should also be understood, because these drugs are frequently used sequentially. Schumacher and colleagues<sup>102</sup> used response surface methodology to examine the influence of this interaction on the probability of TOSS and three noxious stimuli (TTET, TLMA, and TLAR). They found that for both EEG suppression and tolerance to stimulation, the interaction of propofol and sevoflurane were additive. Others found similar results on the C<sub>50</sub> level.<sup>103</sup> Hammer and colleagues<sup>104</sup> determined the pharmacodynamic interaction of propofol and dexmedetomidine during pediatric esophagogastroduodenoscopy and concluded that the concentration of propofol at which 50% of patients are adequately anesthetized (EC<sub>50</sub>) in children was unaffected by a concomitant intravenous infusion of dexmedetomidine 1 µg/kg body weight given over 10 minutes.

Hannivoort and colleagues took this work a step further by using response surface modeling to develop a model that predicts the effect of combinations of sevoflurane, propofol, and remifentanil in terms of PTOL and the NSRI.<sup>105</sup>

Although models of the pharmacokinetics and pharmacodynamics of drug, and models of drug interactions, are essentially just that—models that attempt to provide qualitative and quantitative representations of reality—they are based on many assumptions, and inherently involve many sources of error.<sup>106</sup> Nonetheless, the models provide information that is useful to clinicians to help guide rational practice. Information on drug interactions, including the NSRI, has been incorporated in commercially available anesthetic display monitors and are described by van den Berg and associates in a concise summary of current knowledge, and the ways that it has and can be incorporated into clinical practice.<sup>107</sup>

## Designing Dosing Regimens

### BOLUS DOSE CALCULATIONS

The definition of concentration is drug mass per unit of volume. The definition of concentration can be rearranged to find the amount of drug required to produce any desired concentration for a known volume (Eq. 26.10):

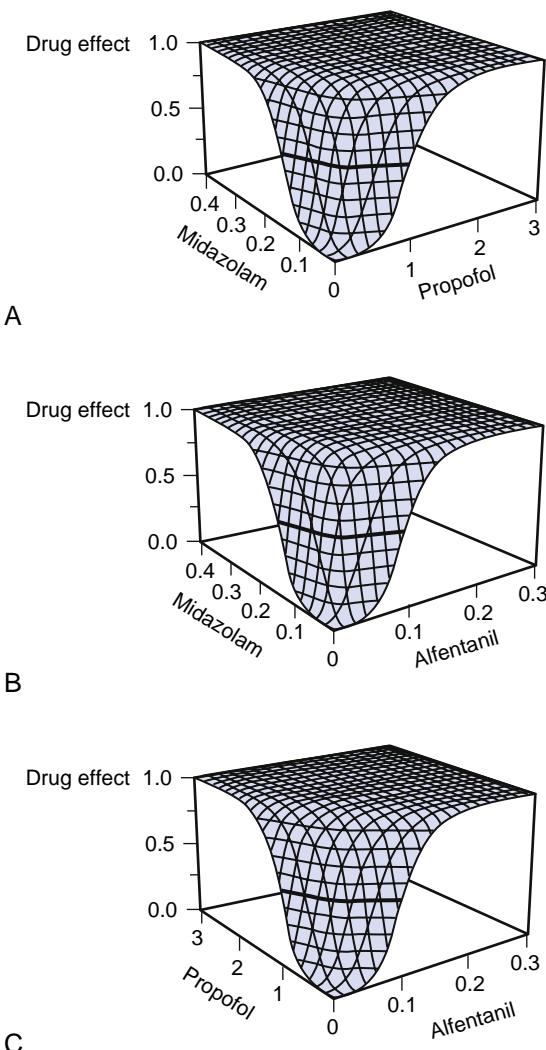
$$\text{Amount} = C_T \cdot \text{Volume} \quad (26.10)$$

**TABLE 26.3** Propofol/Opioid Combinations Associated with the Fastest Recovery from Anesthesia

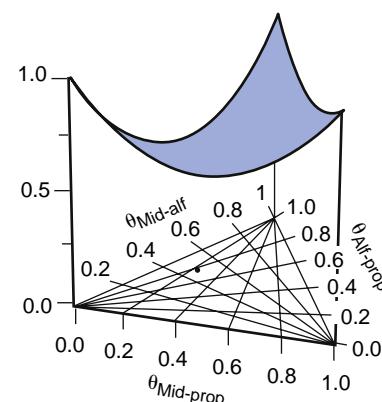
Infusion Duration (min)		Propofol/Alfentanil ( $\mu\text{g/mL}$ ; $\text{ng/mL}$ )	Propofol/Sufentanil ( $\mu\text{g/mL}$ ; $\text{ng/mL}$ )	Propofol/Remifentanil ( $\mu\text{g/mL}$ ; $\text{ng/mL}$ )
15	$C_{\text{optimal}}$	3.25/99.3	3.57/0.17	2.57/4.70
	$C_{\text{awakening}}$	1.69/65.0	1.70/0.10	1.83/1.93
	Time to awakening (min)	8.2	9.4	5.1
60	$C_{\text{optimal}}$	3.38/89.7	3.34/0.14	2.51/4.78
	$C_{\text{awakening}}$	1.70/64.9	1.70/0.10	1.83/1.93
	Time to awakening (min)	12.2	11.9	6.1
300	$C_{\text{optimal}}$	3.40/88.9	3.37/0.14	2.51/4.78
	$C_{\text{awakening}}$	1.70/64.9	1.70/0.10	1.86/1.88
	Time to awakening (min)	16.0	15.6	6.7

$C_{\text{optimal}}$  represents combinations associated with a 50% probability of a response to surgical stimuli;  $C_{\text{awakening}}$  concentrations represent the estimated concentrations at which consciousness will be regained; and Time to awakening represents the estimated time from termination of the infusion to return of consciousness in 50% of patients.

From Vuyk J, Mertens MJ, Olofson E, et al. Propofol anesthesia and rational opioid selection. Determination of optimal  $\text{EC}_{50}$ - $\text{EC}_{95}$  propofol-opioid concentrations that assure adequate anesthesia and a rapid return of consciousness. *Anesthesiology*. 1997;87:1549–1562; and modified from Absalom A, Struys MMRF. *An Overview of TCI and TIVA*. ed 2. Gent, Belgium: Academia Press; 2007. Used with permission.



**Fig. 26.16** Response surface for each of the paired interactions between propofol and midazolam (A), alfentanil and midazolam (B), and alfentanil and propofol (C) on the probability of opening eyes to a verbal command. The isoboles for a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% response are shown. (From Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. *Anesthesiology*. 2000;92:1603–1616.)



**Fig. 26.17** Interaction at 50% drug effect ( $C_{50}$ ) among propofol, midazolam, and alfentanil. Downward deflection of the surface represents synergy, in units of fractional reduction in  $C_{50}$ . The three edges represent relative amounts of propofol to midazolam ( $\theta_{\text{Mid-prop}}$ ), alfentanil to midazolam ( $\theta_{\text{Mid-alf}}$ ), and alfentanil to propofol ( $\theta_{\text{Alf-prop}}$ ). The surface between the edges represents the relative synergy of all three drugs taken together. (From Minto CF, Schnider TW, Short TG, et al. Response surface model for anesthetic drug interactions. *Anesthesiology*. 2000;92:1603–1616.)

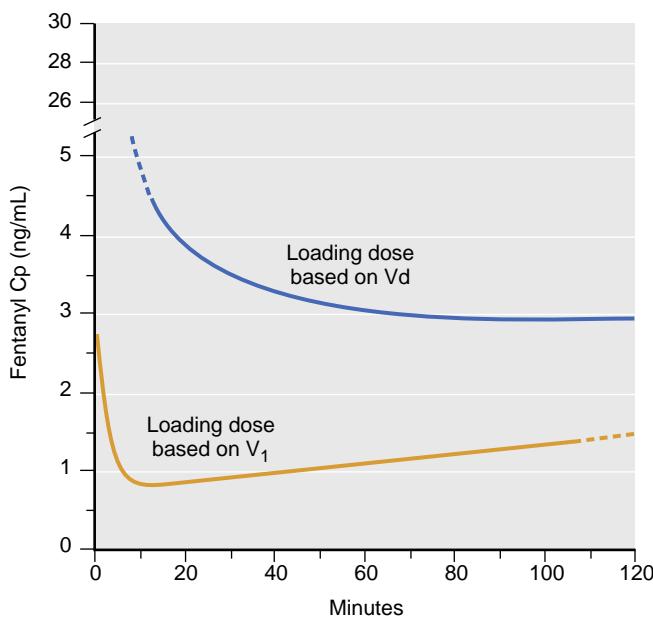
where  $C_T$  is the desired or *target* concentration. This formula is often used to calculate the initial (loading) bolus dose required to achieve a given concentration. The problem with applying this concept to anesthetic drugs is that there are several volumes of distribution:  $V_1$  (central compartment),  $V_2$  and  $V_3$  (the peripheral compartments), and  $Vd_{ss}$  (the sum of the individual volumes).  $V_1$  is usually significantly smaller than  $Vd_{ss}$ , and thus saying that the loading dose should be something between  $C_T \times V_1$  and  $C_T \times Vd_{ss}$  is tempting.

Consideration should be given to the dose of fentanyl required to attenuate the hemodynamic response to endotracheal intubation when combined with thiopental. The  $C_{50}$  for fentanyl, combined with thiopental for intubation, is approximately 3 ng/mL. The  $V_1$  and  $Vd_{ss}$  for fentanyl are 13 L and 360 L, respectively. The aforementioned equations can thus be interpreted as suggesting that an appropriate dose of fentanyl to attenuate the hemodynamic response is between 39  $\mu\text{g}$  (3 ng/mL  $\times$  13 L) and 1080  $\mu\text{g}$  (3 ng/mL

$\times 360$  L). A fentanyl bolus of 39  $\mu$ g achieves the desired concentration in plasma for an initial instant, but plasma levels almost instantly decrease below the desired target. Levels at the effect site will never be close to the desired target concentration of 3 ng/mL. A fentanyl bolus of 1080  $\mu$ g, not surprisingly, produces a significant overshoot in plasma levels that persists for hours (Fig. 26.18). Additionally, using equations to calculate the fentanyl dose if the resulting recommendation is to “use a fentanyl dose between 39 and 1080  $\mu$ g” is absurd.

The usual dosing guidelines for a bolus dose, presented earlier, are designed to produce a specific plasma concentration. Because plasma is not the site of drug effect, calculating the initial bolus on the basis of a desired plasma concentration is irrational. By knowing the  $k_{e0}$  of an intravenous anesthetic, a dosing regimen can be designed that yields the desired concentration at the site of drug effect. To avoid an overdose for the patient, a bolus should be selected that produces the desired peak concentration at the effect site.

The decline in plasma concentration between the initial concentration after the bolus (amount/ $V_1$ ) and the concentration at the time of peak effect can be thought of as dilution of the bolus into a larger anatomic volume than the volume of the central compartment. This introduces the concept of  $Vd_{pe}$ , the apparent volume of distribution at the time of peak effect,<sup>28,94</sup> or pseudoequilibration between plasma and the site of drug effect.<sup>95</sup> The size of this volume can be readily calculated from the observation that the



**Fig. 26.18** Pharmacokinetic simulation demonstrating the limitations of infusion regimens based on simple pharmacokinetic parameters with fentanyl used as an example. These infusion schemes were designed to achieve a fentanyl plasma concentration ( $C_p$ ) of 3 ng/mL. The upper blue curve shows that a regimen using a loading dose based on the volume of distribution followed by a constant infusion based on clearance results in a transient period of very high plasma concentrations. If the same maintenance infusion is given but the loading dose is based on the volume of the central compartment, then the distribution of drug to the peripheral compartments causes the plasma concentration to fall below the desired level until the compartments reach steady-state concentrations as shown in the lower gold curve.

plasma and effect-site concentrations are the same at the time of peak effect (Eq. 26.11):

$$Vd_{pe} = \frac{\text{Bolus amount}}{C_{pe}} \quad (26.11)$$

where  $C_{pe}$  is the plasma concentration at the time of peak effect.

If the clinical goal is to select the dose required to achieve a certain drug effect without producing an overdose, then Eq. 26.11 can be rearranged by substituting  $C_T$ , the target concentration (which is the same in plasma and the effect site at the moment of peak effect), for  $C_{pe}$  to calculate the size of the initial bolus (Eq. 26.12)

$$\text{Loading dose} = C_T \times Vd_{pe} \quad (26.12)$$

The  $Vd_{pe}$  for fentanyl is 75 L. To achieve a peak fentanyl effect-site concentration of 3.0 ng/mL requires 225  $\mu$ g, which produces a peak effect in 3.6 minutes. This dosing guideline is more reasonable compared with the previous recommendation of a dose between 39 and 1080  $\mu$ g. Table 26.4 lists  $V_1$  and  $Vd_{pe}$  for fentanyl, alfentanil, sufentanil, remifentanil, propofol, thiopental, and midazolam. Table 26.1 lists the time to peak effect and the  $t_{1/2} k_{e0}$  of the commonly used intravenous anesthetics.

## MAINTENANCE INFUSION RATES

By definition, the rate at which active drug exits the body is systemic clearance ( $Cl_S$ ) times the plasma concentration. To maintain a given target concentration ( $C_T$ ), drug must be delivered at the same rate that it is exiting the body. Thus (Eq. 26.13),

$$\text{Maintenance infusion rate} = C_T \times Cl_S \quad (26.13)$$

For drugs with multicompartment pharmacokinetics, which includes all of the intravenous drugs used in anesthetic practice, drug is distributed into the peripheral tissues, as well as cleared from the body. The rate of distribution into tissues changes over time as the tissues equilibrate with plasma. Eq. 26.13 is correct only after the peripheral tissues have fully equilibrated with plasma, which requires many hours. At all other times, this maintenance infusion rate underestimates the infusion rate necessary to maintain a target concentration.

Yet in some situations, this simple maintenance rate calculation may be acceptable. For example, if an infusion at this rate is used along with a bolus dose based on  $Vd_{pe}$  and the drug has a long delay between the bolus and peak effect, then most of the distribution of drug into tissues may have occurred by the time that the effect-site concentration reaches the target concentration. In this case, the maintenance infusion rate calculated as clearance times target concentration may be accurate because  $Vd_{pe}$  is sufficiently higher than  $V_1$  to account for the distribution of drug into peripheral tissues. Unfortunately, most drugs used in anesthesia achieve sufficiently rapid equilibration between plasma and the effect site that  $Vd_{pe}$  does not adequately encompass the distribution process, thus making this approach unsuitable.

As such, approaches need to be used that are mathematically and clinically sound. Because the net flow of drug into peripheral tissues decreases over time, the infusion rate required to maintain any desired concentration must also decrease over time. If the initial bolus has been based on

$Vd_{pe}$ , no infusion needs be administered until the effect-site concentration peaks. After the peak in effect-site concentration, the (nearly) correct equation to maintain the desired concentration is (Eq. 26.14)

Maintenance infusion rate

$$= C_T \times V_1 \times (k_{10} + k_{12}e^{-k_{21}t} + k_{13}e^{-k_{31}t}) \quad (26.14)$$

This equation indicates that a rapid infusion rate is initially required to maintain  $C_T$ . Over time, the infusion rate

gradually decreases (see Fig. 26.14). At equilibrium ( $t = \infty$ ), the infusion rate decreases to  $C_T \times V_1 \times k_{10}$ , which is the same as  $C_T \times Cl_S$ . Few clinicians would choose to solve such an equation during the administration of an anesthetic. Fortunately, simple techniques can be used in place of solving such a complex expression.

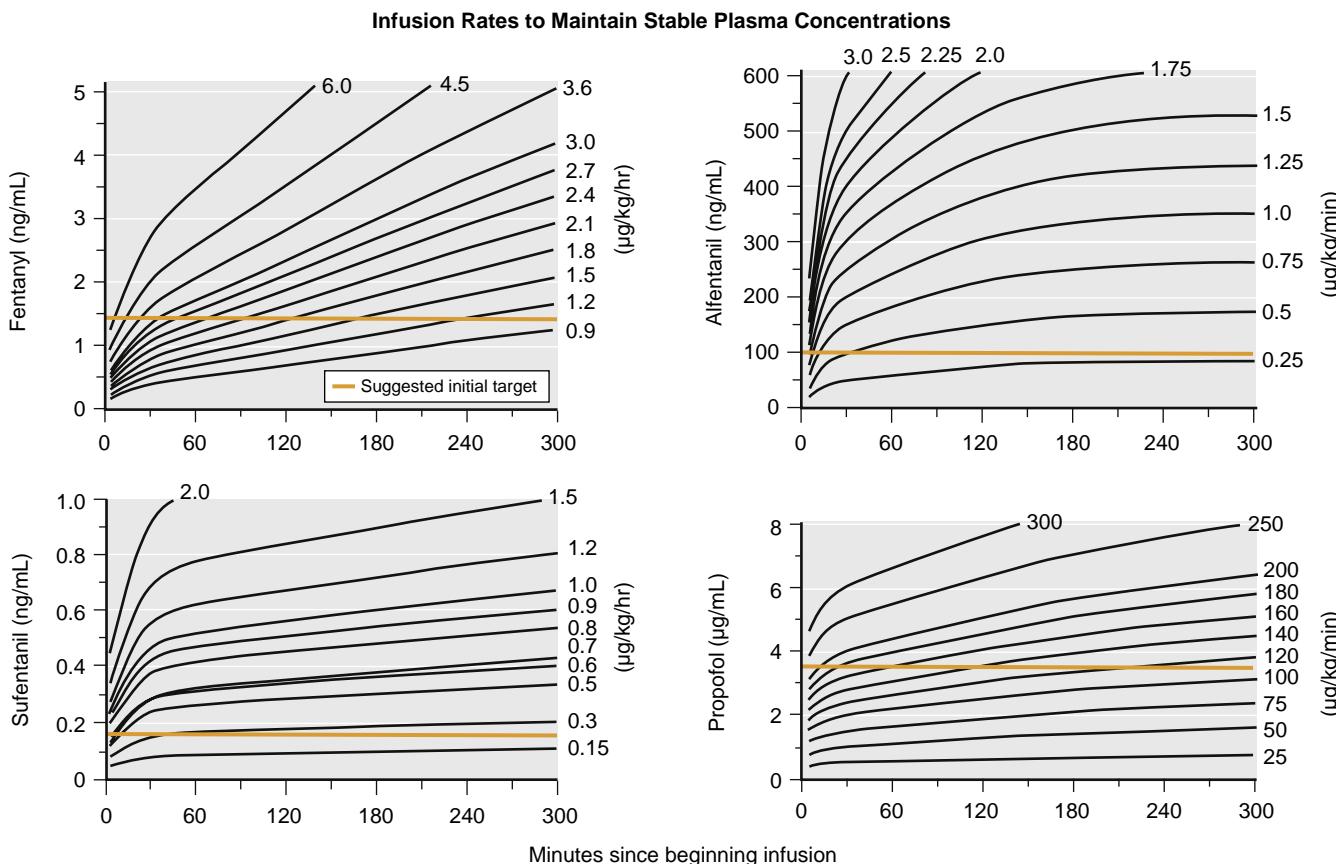
Fig. 26.19 is a nomogram in which Eq. 26.14 has been solved; the infusion rates at different times necessary to maintain any desired concentration of fentanyl, alfentanil, sufentanil, and propofol are shown. Because this nomogram is complex, the following review is provided:

The  $y$  axis represents the target concentration  $C_T$ . The  $x$  axis is the time since the beginning of the anesthetic (i.e., since the initial bolus). The suggested initial target concentrations (shown in gold) are based on the work of Vuyk and colleagues<sup>93</sup> with propofol and alfentanil (see Fig. 26.15) and are scaled to fentanyl and sufentanil according to their relative potencies.<sup>108</sup> The intersections of the target concentration line and the diagonal lines indicate the infusion rate appropriate at each point in time. For example, to maintain a sufentanil concentration of 0.16 ng/mL, the appropriate rates are approximately: 0.6  $\mu\text{g}/\text{kg}/\text{h}$  at 5 minutes, 0.5  $\mu\text{g}/\text{kg}/\text{h}$  at 10 minutes, 0.4  $\mu\text{g}/\text{kg}/\text{h}$  at 20 minutes, and 0.3  $\mu\text{g}/\text{kg}/\text{h}$  at 40 minutes. Of course, selecting target concentrations and different times of rate adjustment is possible, depending on the clinical circumstances and an assessment of how accurately the intravenous drug needs to be titrated.

**TABLE 26.4** Volume of Distribution at the Time of Peak Effect

Drug	$V_1$ (L)	$Vd_{pe}$ (L)
Fentanyl	12.7	75
Alfentanil	2.19	5.9
Sufentanil	17.8	89
Remifentanil	5.0	17
Propofol	6.7	37
Thiopental	5.6	14.6
Midazolam	3.4	31

$V_1$ , Volume of the central compartment;  $Vd_{pe}$ , apparent volume of distribution at the time of peak effect.



**Fig. 26.19** Nomogram for calculating maintenance infusion rates to maintain a stable concentration of fentanyl, alfentanil, sufentanil, or propofol. The  $y$  axis is the desired concentration. The  $x$  axis is the time relative to the initial bolus. The *diagonal lines* show the infusion rates at different times required to maintain the desired concentration selected on the  $y$  axis.

## RECOVERY FROM ANESTHESIA

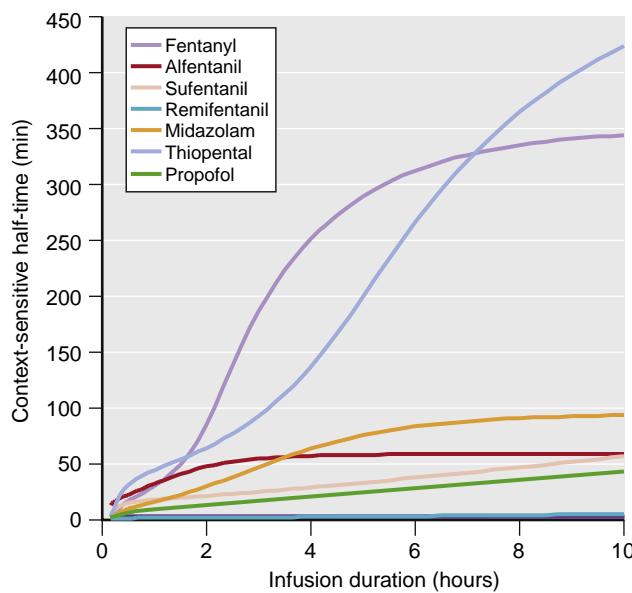
Recovery from anesthesia is determined by the pharmacokinetic principles that govern the rate of decrease in drug from the effect compartment once drug administration is terminated, as well as by the pharmacodynamics of the drug. Although the terminal elimination half-life is often interpreted as a measure of how short- or long-lasting a drug is, the rate at which drug plasma concentration decreases is dependent on both elimination and redistribution of the drug from the central compartment. The contribution of redistribution and elimination toward the rate of decrease in drug concentration varies according to the duration for which the drug has been administered<sup>108,109</sup> and also the time since the infusion has stopped, because these processes have different rate constants.

In 1985, Schwilden<sup>110</sup> developed a mathematic model to relate the time course of offset of action of inhaled anesthetics to the duration of anesthetic drug delivery. Similarly, Fisher and Rosen<sup>111</sup> demonstrated how the accumulation of neuromuscular blocking agents in peripheral volumes of distribution results in slowed recovery with increasing duration of administration. They introduced two measures of the time course of recovery, the time for twitch tension to recover from 5% to 25% and the time for twitch tension to recover from 25% to 75%.

Since then, the time for the plasma concentration to decrease by 50% from an infusion that maintains a constant concentration (e.g., infusion given by (Eq. 26.14) has been termed the *context-sensitive half-time* (Fig. 26.20),<sup>109</sup> with the context being the duration of the infusion. The 50% decrease was chosen both for tradition (e.g., half-lives are the time for a 50% decrease with a one-compartment model) and because, very roughly, a 50% reduction in drug concentration appears to be necessary for recovery after the administration of most intravenous hypnotics at the termination of surgery. Depending on circumstances, decreases other than 50% may be clinically relevant. Additionally, sometimes it is the plasma concentration that is of interest, and sometimes it is the effect-site concentration that is of interest. A more general term is the *context-sensitive decrement time*,<sup>112</sup> in which the decrement in concentration is specifically noted, as is the compartment where the decrease is modeled (plasma or effect site). For example, the relationship between infusion duration and the time required for a 70% decrease in fentanyl effect-site concentration is the *context-sensitive 70% effect-site decrement time*.

Context-sensitive effect-site decrement times for varying percent decreases in alfentanil, fentanyl, sufentanil, and remifentanil concentration are illustrated in Fig. 26.21. To determine when an infusion should be terminated (to enable awakening of the patient at the end of surgery), the clinician needs to bear in mind the decrease in concentration necessary for recovery, the duration of the infusion (the context), and the context-sensitive, effect-site decrement time required for the necessary decrease.

Context-sensitive decrement times are fundamentally different from the elimination half-life. With monoexponential decay, each 50% decrease in concentration requires the same amount of time, and this time is independent of how the drug is given. This is not true for the context-sensitive half-time. First, as the name is intended to imply, the time needed



**Fig. 26.20** Context-sensitive half-times as a function of infusion duration (context) derived from pharmacokinetic models of fentanyl, sufentanil, alfentanil, remifentanil, propofol, midazolam, and thiopental. (From Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology*. 1992;76:334–341.)

for a 50% decrease is absolutely dependent on how long the drug was given, with infusion duration being the context to which the name refers. In addition, small changes in percent decrement can result in surprisingly large increases in the time required. The time required for a 60% decrease in drug concentration can be more than twice the time required for a 50% decrease in some situations (see Fig. 26.21).

Context-sensitive decrement times are based on the assumption that plasma or the effect site is maintained at a constant concentration. Such is rarely the case clinically, but the maintenance of constant concentrations is a necessary assumption to provide a unique mathematic solution to the time required for a given percent decrement in plasma or effect-site concentration. Because plasma and effect-site concentrations are rarely kept constant, it is important that context-sensitive decrement times are used as *general* guidelines for interpreting the pharmacokinetics of intravenous drugs and not as *absolute* predictions for any given individual patient case or infusion regimen. Automated drug delivery systems can provide more precise predictions of the time required for the plasma or effect-site concentration to decrease to any desired concentration, based on the actual drug dosing in the individual patient, which provides the clinician with guidance for the most appropriate time to terminate the infusion.

Context-sensitive decrement times focus on the role of pharmacokinetics in recovery from anesthesia. Pharmacodynamics plays an important role in recovery as well. Bailey<sup>113</sup> used integrated pharmacokinetic-pharmacodynamic models to define the *mean effect time* as the average time to responsiveness after maintenance of anesthesia at the 90% probability of unresponsiveness. The mean effect time demonstrates that when drugs have a very shallow concentration-versus-response relationship, concentrations must decrease by a significant fraction to provide adequate emergence, which delays recovery from anesthesia. In contrast,