Pharmacology of Intravenous Sedative/Anesthetic Medications Used in Oral Surgery

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KEYWORDS

• Total intravenous anesthesia (TIVA) • Pharmacology of sedative/anesthetic drugs
• Emergence delirium • Dental sedation

KEY POINTS

- Total intravenous anesthesia (TIVA) is a technique whose time has come because of the advent of ultra–short-acting drugs and computerized infusion technology.
- Patients may be sedated to any desired level, maintained there for indefinite periods, and recovered to near baseline within minutes.
- Future trends in TIVA may include patient-controlled sedation, whereby patients sedate themselves with an infusion device similar to those used for postoperative analgesia.
- The future may also bring titration of sedatives to target blood levels, leading to more precise dosing and greater efficiency.

INTRODUCTION

Patients have historically been considered to be in a state of general anesthesia when the following parameters were met: unconsciousness, analgesia, amnesia, immobility, and attenuation of the autonomic response to noxious stimulation. This was, and is, accomplished easily by the inhalation of potent halogenated hydrocarbons such as isoflurane, sevoflurane, and desflurane. In the past, when inhalational anesthesia was not desired or was contraindicated, a balanced technique was advocated using various intravenous drugs to achieve the desired level of anesthesia. The evolution of total intravenous anesthesia (TIVA) began when Stanley Drummond-Jackson, using methohexital in the UK, and Adrian Hubbell, using sodium pentothal in the United States, first used incremental boluses of these drugs to produce unconsciousness for dental surgery. These introductions were followed by the introduction of intravenous drug combinations to produce sedation by Niels Jorgensen, Leonard Monheim, and C. Richard Bennett. With the advent of designer medications and sophisticated computer-aided technologies and monitoring, TIVA has come into its own. During TIVA, each individual agent is typically selected for its ability to achieve a particular parameter of general anesthesia. Drugs such as propofol are used to induce and maintain unconsciousness, opioids are used for analgesia, benzodiazepines are selected for their amnestic qualities, and muscle relaxants produce immobility. The classic induction agents, thiopental and methohexital, have been largely supplanted by propofol as the primary agent for the production and maintenance of unconsciousness. Adjunctive agents such as fentanyl,

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remifentanil, midazolam, ketamine, and dexmedetomidine are used for analgesia, amnesia, immobility, and attenuation of the autonomic stress response. This article highlights these drugs, explores the rationale for their use, and discusses their clinical usefulness in an office-based setting.

THIOPENTAL

Thiopental is an ultra–short-acting thiobarbiturate first introduced into clinical practice by Dr Ralph Waters in 1934 (**Fig. 1**). Its use ushered in the age of intravenous anesthesia. It is the prototypical intravenous induction agent against which all others are compared. Although currently no longer being manufactured, it is necessary to understand its pharmacology to understand the rationale for the use of induction agents and their evolution into drugs that are now used for induction and maintenance of anesthesia via continuous infusion techniques. Until it was supplanted by propofol in popularity and usefulness, thiopental was the standard intravenous induction agent for general anesthesia for years. Despite its widespread use, it had detractors. After the attack on Pearl Harbor, thiopental was maligned as "the ideal form of euthanasia in war surgery"[1] because of its propensity to produce cardiovascular collapse in extremely hypovolemic patients. More recently, thiopental was part of the regimen for lethal injection executions in the United States. Hospira (Lake Forest, IL), the sole manufacturer of thiopental, removed the drug from the market when the government of Italy (where thiopental was produced) demanded that Hospira guarantee that thiopental would not be used for lethal injection. This development prompted the company to halt manufacture of the drug.[2]

Mechanism of Action

Many of the pharmacologic effects of barbiturates closely resemble the effects of benzodiazepines. Barbiturates enhance gamma-aminobutyric acid (GABA)–activated chloride ion channel opening by acting at specific barbiturate binding sites on the $GABA_A$ receptor complex, leading to hyperpolarization and decreased neuronal firing.[3] Barbiturates also act directly on the chloride channel, not requiring the presence of GABA. These actions produce what is known as barbiturate anesthesia and may explain the lower margin of safety and steeper dose-response curve relative to benzodiazepines.

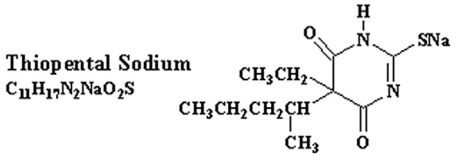

Fig. 1. Thiopental, the prototypical induction agent.

Pharmacologic Effects

Thiopental rapidly achieves therapeutic plasma concentrations and can induce unconsciousness within 15 to 30 seconds. After a single intravenous induction dose of 4 mg/kg, the clinical duration of effect is between 20 and 30 minutes. Because thiopental is highly lipid soluble, it has the ability to enter tissues at a rate proportional to blood flow. The vessel-rich group, which includes the brain, receives the highest proportion of the cardiac output relative to body mass (**Fig. 2**). Thus it achieves the highest concentration of thiopental following intravenous injection, and its effects are exerted almost immediately. Redistribution to the more poorly perfused tissues such as muscle, and later fat, results in a rapid decline in the concentration of the drug, which terminates the effect. Because the drug accumulates in fatty tissue, especially after repeated administration or continuous infusion, the clinical duration and recovery time may be prolonged in obese patients.

Cardiovascular Effects

Peripheral vasodilation is the primary effect of an induction dose of thiopental. This dose is usually accompanied by a reflex increase in heart rate. Mean arterial pressure may be unchanged or slightly diminished. Further myocardial depression occurs with higher doses, and blood pressure may decrease precipitously. Hypovolemic patients are especially susceptible to profound hypotension and cardiovascular collapse.

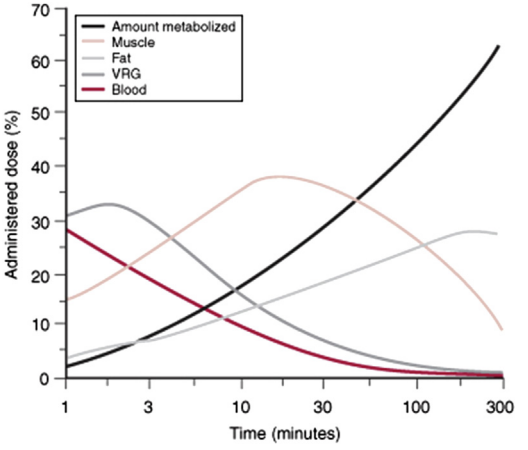

Fig. 2. Thiopental distribution in different tissues. VRG, vessel rich group.

Respiratory Effects

Thiopental produces dose-dependent respiratory depression via decreased minute ventilation. Both tidal volume and respiratory rate are decreased, and apnea ensues, especially in the presence of other respiratory-depressant drugs. Airway reflex activity may be increased with a predisposition to coughing and laryngospasm.

Other Effects

Thiopental is an anticonvulsant and can be used to treat patients with status epilepticus. It also reduces cerebral blood flow, intracranial pressure, and cerebral metabolic rate. It is hyperalgesic, and patients may exhibit heightened responses to pain stimulation. Analgesics must be given concurrently with barbiturates to ensure adequate increase of the pain threshold. Thiopental is highly alkaline and care must be taken to ensure that the drug is only given intravenously. Extravasation into the tissues may result in tissue necrosis, and intra-arterial injection results in severe vasospasm. Thiopental also releases histamine, which may produce hives, urticaria, edema, and bronchospasm. An interesting, but common, effect of thiopental is the perception of a garlic or onion taste after the drug has been administered.

Contraindications

Patients with chronic obstructive lung disease or difficult airway predictors are adversely affected after thiopental administration. Thiopental produces profound hypotension and circulatory collapse in patients with cardiac instability or hemorrhagic shock. Because thiopental releases histamine, it is contraindicated in patients with status asthmaticus and in patients with poorly controlled asthma. Barbiturates are absolutely contraindicated in cases of acute intermittent porphyria. They stimulate the formation of D-aminolevulinic acid synthetase, leading to the accumulation of porphyrins and porphyrin precursors, and an acute exacerbation of the disease.

METHOHEXITAL

Methohexital is an ultra–short-acting oxybarbiturate similar in effect to thiopental, but approximately 2.5 times as potent and much shorter acting. An induction dose of 1 to 2 mg/kg rapidly produces unconsciousness for 5 to 7 minutes. Rapid redistribution is responsible for its abrupt termination of action. Advantages compared with thiopental include a more rapid recovery and clearance, no histamine release, less accumulation and saturation of peripheral tissues, and a more favorable context-sensitive half-time, making it suitable for maintenance of anesthesia via continuous infusion. An infusion of 50 to 150 μg/kg/min for a short-duration procedure lasting 60 minutes or less produces a recovery comparable with a similar propofol infusion. Thus, methohexital is more suitable for outpatient procedures than thiopental. The major disadvantage of methohexital is the frequency of excitatory phenomena such as coughing, hiccoughing, tremors and twitching, heightened airway reflexes, and laryngospasm. Methohexital is also associated with pain on injection and phlebitis. Despite these adverse effects, methohexital was the mainstay of anesthesia for oral surgery for decades, given either as a full induction dose or as an incremental bolus to deepen the level of sedation as needed. Methohexital has been supplanted by propofol for dental sedation and anesthesia. However, with the frequent drug shortages, it benefits the practitioner to become familiar with this drug if and when a backup medication becomes necessary.

PROPOFOL

Propofol is a 2,6-diisopropylphenol anesthetic drug available in several generic forms and the brand name Diprivan (APP Pharmaceuticals, Schaumberg, IL). Propofol is the most commonly used intravenous anesthetic, producing unconsciousness within 40 seconds after a single induction dose of 2 to 2.5 mg/kg, followed by a rapid recovery with minimal postoperative confusion. It is formulated in an oil-in-water emulsion containing soybean oil, glycerol, and egg lecithin and has a characteristic milky white appearance. This preparation has the potential to become a culture medium for bacterial growth, so any unused portion must be discarded 6 hours after puncturing the vial to prevent sepsis.

Mechanism of Action

Propofol is an *N*-methyl-D-aspartate (NMDA) receptor inhibitor and an agonist at the β_1 subunit of the $GABA_A$ receptor. Its termination of activity is similar to thiopental in that it is rapidly redistributed (distribution half-life 2–4 minutes), resulting in rapid recovery following induction or maintenance doses. It is metabolized in the liver (elimination half-life 3–12 hours), but the clearance of propofol exceeds liver blood flow, suggesting some extrahepatic metabolism. Other effects of propofol include pain on injection, amnesia, and possibly some antiemetic effects. It has a favorable context-sensitive half-time, which makes it ideal for maintenance of deep sedation or general anesthesia via continuous infusion.

Cardiovascular Effects

Propofol has some cardiovascular effects, specifically a reduction in stroke volume and peripheral vasodilation that may produce a significant decrease in systemic blood pressure. There is no compensatory increase in heart rate, as seen with thiopental. It therefore should be used with caution in the elderly or hypovolemic patient, or those with limited cardiac reserve.

Respiratory Effects

Propofol is a potent respiratory depressant, producing a significant reduction in tidal volume and apnea in 30% of patients following an induction dose. Unlike thiopental, propofol does not release histamine and may be used safely in asthmatic patients. Propofol does not promote airway hyperactivity, making patients less susceptible to laryngospasm compared with thiopental and methohexital. Propofol is useful in deepening sedation levels to aid in the management of laryngospasm.

Other Effects

Propofol is known for its amnestic and antiemetic properties. Propofol acts as an antiemetic during administration and may be helpful in the intraoperative management of patients with a significant history of postoperative nausea and vomiting. It is also useful as a treatment modality for patients who are actively nauseated in the immediate recovery period.

Propofol causes pain during injection, which can vary from mild to severe. The drug irritates the venous intima and activates the kallikrein-kinin system to increase bradykinin production. Pain on injection may be attenuated by slowly injecting the drug into a large vein, rapidly flushing with intravenous fluid, and the prior administration of intravenous lidocaine. However, to be effective, lidocaine should be held for a time within the vein before being released into the systemic circulation. Injecting lidocaine while the tourniquet is still applied, waiting for a few minutes, and then releasing the tourniquet before the administration of propofol may accomplish this.

Propofol infusion syndrome has been reported in critically ill patients undergoing prolonged sedation with propofol. Its features include rhabdomyolysis, severe metabolic acidosis, and renal and cardiac failure.[4] It has most often appeared in pediatric patients, but has also more recently been reported in adults. Propofol infusion syndrome is a multifactorial process with critical neurologic or inflammatory illnesses and prolonged propofol infusions as initiating factors, and concomitant catecholamine and glucocorticoid administration as triggering factors. The syndrome may manifest with infusions of more than 5 mg/kg/h for a period of more than 48 hours.

There has been concern that propofol should not be used in patients with egg allergy because of its formulation containing egg lecithin. The package insert for Diprivan states that the drug "is contraindicated in patients with allergies to eggs, egg products, soybeans or soy products."[5] However, a review of allergic reactions during anesthesia by Hepner and Castells[6] reveals that the incidence of propofol allergy during anesthesia is 1:60,000, and the cause is likely to be the presence of isopropyl groups and/or phenols, not egg or soy allergies. In addition, most patients with egg allergy are allergic to the protein, ovalbumin, found in egg whites. Egg lecithin, found in egg yolks, has a low allergic potential and its formulation in propofol is highly purified. Lizaso and colleagues[7] reported that skin-prick and intradermal testing with propofol and its lipid vehicle were negative in 25 patients with documented egg allergy. Current evidence suggests that patients with an egg allergy are no more likely to develop anaphylaxis than the nonallergic population when exposed to propofol.

ETOMIDATE

Etomidate is a short-acting intravenous anesthetic, chemically unrelated to other intravenous induction agents. It is similar pharmacokinetically to thiopental, but with less respiratory depression and minimal cardiovascular effect. Therefore, it is used primarily for induction of anesthesia (0.2–0.6 mg/kg) in patients in whom hypotension cannot be tolerated. It maintains hemodynamic stability and does not release histamine, making it the drug of choice for induction of anesthesia in hypovolemic patients or those with cardiopulmonary compromise. A severe side effect is the inhibition of steroidogenesis, making it unsuitable for prolonged maintenance administration. This effect may even occur following induction doses, which could potentially impair the patient's ability to respond appropriately to stress. The potential for this side effect severely limits the routine use of etomidate. Other disruptive effects of etomidate include a high incidence of nausea and vomiting, pain and phlebitis on injection, hiccough, and disruptive myoclonic movements.

OPIOIDS

Thomas Sydenham, a physician deemed the English Hippocrates, once profoundly asserted

that, "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium." Opioids have the ability to relieve pain, produce sedation and euphoria, alter the mood, attenuate the cardiovascular stress response, and coincidentally produce profound respiratory depression. The primary site of opioid activity occurs in the central nervous system (CNS) and the gut. Since 1973, it has been known that the activation of opioid-specific receptors in these areas is responsible for the pharmacologic actions of opioids (**Box 1**). The CNS effects include analgesia and sedation, changes in mood, and mental clouding. Opioids attenuate all types of pain regardless of origin or intensity, increase the pain threshold, and alter the affective response to pain. Gastrointestinal (GI) effects include decreased GI motility, which may produce constipation and delayed gastric emptying. This effect could potentially alter the patient's nil-by-mouth status. Opioids stimulate the chemoreceptor trigger zone and may produce nausea and vomiting. Esophageal sphincter tone is reduced, which may lead to vomiting and aspiration during anesthesia. Opioids may also increase biliary duct pressure and sphincter of Oddi tone and produce severe epigastric or abdominal pain in susceptible individuals.

Box 1
Opioid receptors and their actions

- μ1
  - Analgesia (supraspinal, spinal)
  - Miosis
  - Urinary retention
  - Nausea and vomiting
  - Pruritus
- μ2
  - Sedation
  - Respiratory depression
  - GI motility decrease
- σ
  - Dysphoria
  - Psychotomimesis
- δ
  - Analgesia (supraspinal, spinal)
  - Alterations of affective behavior
- κ
  - Analgesia (supraspinal, spinal)
  - Sedation
  - GI motility decrease
  - Psychotomimesis

The primary site of opioid activity is in the CNS and bowel.

Cardiovascular Effects

Opioids are generally accepted to promote cardiovascular and hemodynamic stability and are important in attenuating the cardiovascular response to surgical stress. A μ-receptor–mediated modulation of the hypothalamic-pituitary-adrenal axis reduces may prevent adrenocorticotropic hormone release, resulting in decreased sympathetic tone.[8] Opioids may also act directly on the vagal nuclei and inhibit the SA-node to produce bradycardia in most cases. These effects may produce hypotension in some individuals. Histamine-releasing opioids such as morphine and meperidine may also produce postural hypotensive changes secondary to peripheral vasodilation.

Respiratory Effects

Opioids are primary and continuous depressants of respiration through a direct and dose-dependent depression of the medullary respiratory center. Respiratory rate is slowed more in proportion to decreases in tidal volume. The net effect is a significant reduction in minute ventilation. Opioids obtund the respiratory center's hypercapnic response, diminishing the patient's drive to breathe as carbon dioxide levels increase. Thus, opioid-sensitive patients, or those receiving high doses, may become apneic even while conscious, but may breathe on command. Respiratory depression with opioids may be further enhanced by the administration of high doses, the concomitant administration of other CNS-depressant drugs, and in sensitive patients such as the elderly or those with severe renal disease.

Opioids depress upper airway reflexes and may be valuable in reducing the coughing spasms sometimes seen during the sedation of patients with reactive airway disease. They also may be helpful in attenuating laryngeal and bronchoconstrictive reflexes.

Other Effects

In addition to the effects of GI immobility and nausea and vomiting mentioned earlier, opioids exert a variety of ancillary effects. For example, opioids alone have minimal effect on intracranial pressure, but, in instances of closed head injury or with severe opioid-induced respiratory

depression, intracranial pressure increases with hypercapnia.

All opioids are capable of increasing skeletal muscle tone; however, this phenomenon is most often associated with the rapid administration of high doses of fentanyl, sufentanil, and remifentanil. Chest wall rigidity results in decreased lung compliance, decreased functional residual capacity, and vocal cord closure, which makes ventilation difficult and increases the risk of hypoxemia. Chest wall rigidity should be immediately recognized, and, if ventilation is difficult, muscle relaxation or reversal should be considered. The concomitant administration of benzodiazepines may help prevent rigidity.

A clinical sign of opioid use is pupillary constriction. This effect is mediated through the Edinger-Westphal nucleus of the occulomotor nerve, and is pathognomonic of their use. However, opioids do not increase intraocular pressure, and can prevent increases in intraocular pressure during intubation.[9]

Allergic reactions to opioids are rare. Most allergiclike reactions to opioids are related to the histamine-releasing drugs such as morphine and meperidine. Typical wheal and flare reactions may be noticed, especially along the vein as the drug travels centrally. Dilation of cutaneous blood vessels in the face, neck, and thorax is common, producing flushing and redness that may mimic an allergic response. Histamine release is also associated with pruritus; however, non–histamine-releasing opioids can produce itching as well. Facial itching is common and can be severe enough to be disruptive to dental surgery. The mechanism of facial itching is not known, but mediation through μ-receptors has been proposed.[10]

MORPHINE

Morphine is the prototypical opioid with which all other opioids are compared (**Table 1**). Once an integral part of a sedation regimen for prolonged procedures, morphine has no application in modern TIVA procedures. Its main usefulness is in acute pain management. Although a dose of 10 mg (0.1 mg/kg) provides optimal pain relief, the dose should be titrated intravenously to effect following anesthesia in the immediate postoperative period. The onset of morphine is slow: 5 to 10 minutes following intravenous administration and up to 20 minutes following intramuscular injection. It produces analgesia, euphoria, and sedation lasting from 2 to 4 hours. Its use may be limited by side effects such as histamine release, postural hypotension, and nausea and vomiting.

MEPERIDINE

Meperidine is the prototype of the phenylpiperidine series of opioids, which includes fentanyl, sufentanil, alfentanil, and remifentanil (**Fig. 3**). For years meperidine was the mainstay of intravenous sedation regimens for procedures of all durations. It has a more rapid onset than morphine, within 3 minutes following intravenous administration, making it more easily titratable than morphine. It is 10 times less potent than morphine, producing sedation and analgesia lasting 45 to 90 minutes. Meperidine was first investigated as an atropine-like agent and is unique among opioids in that it may produce tachycardia and drying of secretions. It also releases histamine, and may produce orthostatic hypotension with rapid position change. Severe asthma is a relative contraindication. Other side effects include dysphoria, especially in the absence of pain, and nausea and vomiting. Meperidine is associated with increased neuronal activity that may result in CNS excitation. Its metabolite, normeperidine, is twice as potent as meperidine in producing CNS excitation and convulsions. Meperidine is contraindicated in patients taking monoamine oxidase inhibitors because concentrations of normeperidine are increased with these drugs.

Although meperidine is still used on a limited basis for dental sedation, its main use is currently in the management of postanesthetic shivering. Opioids in general reduce thermoregulation thresholds similarly to potent inhalational agents.

Table 1
Comparative effects of commonly used opioids in oral surgery

	Meperidine	Morphine	Fentanyl	Sufentanil	Alfentanil	Remifentanil
Comparative potency	0.1	1	75–125	500–1000	10–25	250
Peak Effect (min)	5–7	20–30	3–5	3–5	1.5–2	1.5–2
Duration (h)	2–3	3–4	0.5–1	0.5–1	0.2–0.3	0.1–0.2
Half-life (h)	3–4	2–4	1.5–6	2.5–3	1–2	0.15–0.3

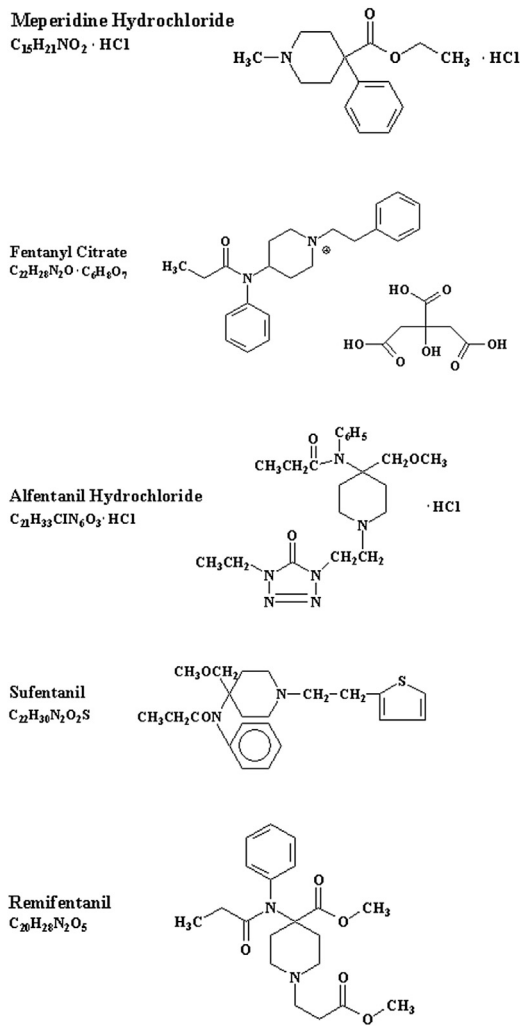

Fig. 3. Phenylpiperidine series of opioids.

However, meperidine is unique in that it can terminate shivering in 70% to 80% of cases. The exact mechanism is unknown, but may be related to a κ-receptor–mediated reduction in the shivering threshold and to α_2b-receptor agonism.[11]

FENTANYL

Fentanyl is the most popular and useful opioid in anesthesia today. It is used in every situation from moderate dental sedation to cardiothoracic surgery. It is approximately 100 times more potent than morphine, and has a rapid onset and short duration. It produces excellent analgesia and is useful during induction of anesthesia to provide background sedation and to attenuate the systemic effects of intubation. Fentanyl provides cardiovascular stability, but may produce bradycardia. It produces profound dose-dependent respiratory depression. Fentanyl may be difficult to titrate to effect because it produces little or no euphoria. There is a tendency to overshoot the goal if the clinician waits to see a clinical effect from fentanyl. Thus, dosing should be done on an empiric basis.

SUFENTANIL

Sufentanil is an ultrapotent opioid with a similar profile to fentanyl, but 10 times as potent. It may be used readily as a substitute for fentanyl, with 10 μg of sufentanil being equivalent to 100 μg of fentanyl. Its context-sensitive half-time is favorable enough to permit its use as a continuous infusion agent during TIVA.

ALFENTANIL

Alfentanil is 10 times less potent than fentanyl, with 1000 μg of alfentanil being equivalent to 100 μg of fentanyl. It also has a similar clinical profile to fentanyl and may be used in lieu of fentanyl in a sedation regimen. Alfentanil also has a context-sensitive half-time compatible with a continuous infusion technique.

REMIFENTANIL

Remifentanil is an ultra–short-acting opioid that is 2.5 times as potent as fentanyl and is ideally suited for continuous infusion techniques. It is unique in that it contains ester linkages, which are hydrolyzed in the plasma by nonspecific esterases that profoundly limit its duration of action. Its short context-sensitive half-time results in recovery within minutes, even after hours of infusion. It is primarily used for maintenance of deep sedation in doses of 0.05 to 0.1 μg/kg/min, or general anesthesia in doses of 0.05 to 2.0 μg/kg/min. It may also be used for the induction of general anesthesia in bolus doses of 1 μg/kg. Combined with propofol, this dosing regimen can produce excellent intubating conditions without the need for muscle relaxants.

BENZODIAZEPINES

Benzodiazepines form the basis of sedative drugs and techniques because of their selectivity of effect and high margin of safety (**Fig. 4**). Benzodiazepines exert their effect at the GABA-receptor complex to produce the clinical effects of anxiolysis, sedation, amnesia, anticonvulsant activity, and skeletal muscle relaxation. Benzodiazepine receptors are linked to a specific GABA-receptor subtype, the $GABA_A$ receptor. Binding at the $GABA_A$ receptor facilitates GABA-activated membrane hyperpolarization by enhancing chloride ion

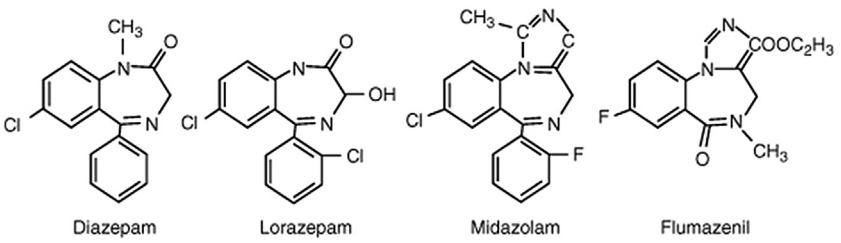

Fig. 4. Typical benzodiazepines and their reversal agent have similar chemical structures.

influx through the chloride channel associated with the macromolecular receptor complex.

Cardiovascular Effects

Benzodiazepines exert little effect on cardiovascular parameters in therapeutic doses. Excessive doses and concomitant use with other sedatives may result in cardiovascular system depression. Benzodiazepines are useful in attenuating the cardiovascular stress response.

Respiratory Effects

Benzodiazepines have little effect on the respiratory system, but can cause respiratory depression in a dose-dependent manner, or when administered in conjunction with other CNS-depressant drugs. Midazolam has been associated with respiratory depression and apnea, and clinically significant respiratory depression can occur when combined with opioids.[12]

Other Effects

Paradoxic reactions to benzodiazepines have been seen in all patients, but most notably in the elderly and pediatric populations. These reactions, also described as idiosyncratic, are manifested as excitement, agitation and confusion, irritability, rage, and hostility. The cause for these unusual reactions is not well known, but may be likened to the disinhibitory effects sometimes seen with alcohol. Caution should be exercised when administering benzodiazepines to these groups.

Diazepam has been associated with pain on injection and an increased incidence of phlebitis following intravenous administration. This effect is caused by its formulation in a propylene glycol solvent that is irritating to veins. Phlebitis is more likely to occur when using hand veins and with repeated injections. Patients who are smokers, the elderly, and those taking oral contraceptives are most likely to develop phlebitis. At the height of its popularity, diazepam-induced phlebitis was a leading cause of anesthetic-related lawsuits.

Benzodiazepines are contraindicated in pregnancy and are classified as pregnancy category D, except for triazolam, which is pregnancy category X.[13] If sedation or anesthesia is to be considered during pregnancy, benzodiazepines should be avoided. Except for lorazepam and oxazepam, benzodiazepines are also found in the breast milk of lactating mothers, which could result in the unwanted sedation of the infant. If benzodiazepines are to be used as part of a sedative or anesthetic regimen in these patients, the risk may be decreased by administering the medication immediately after the mother feeds the infant, or during periods in which the infant is asleep for long periods. A safer alternative would be to have the mother self-express and store the milk for later use before procedure, and self-express and discard the milk for 3 to 4 half-lives of the drug following the procedure.

Aside from the drug interactions involving other CNS depressants, interactions involving the cytochrome P450 (CYP) enzyme system are the most significant. Benzodiazepines are biotransformed in the liver by the CYP3A4 isoenzymes. Drugs such as rifampin and carbamazepine induce these enzymes in the liver and gut, reducing the bioavailability of various benzodiazepines by up to 96%.[14] Triazolam is so effectively metabolized in the gut by these induced enzymes that its bioavailability is reduced to only 12% of normal.[15] The clinical implications of this include loss of seizure control, and reduced or lack of effectiveness of benzodiazepines.

Drugs including calcium channel blockers, azole antifungals, macrolide antibiotics, protease inhibitors, and selective serotonin reuptake inhibitors inhibit the CYP3A4 isoenzymes. Thus, coadministration of benzodiazepines in patients taking these agents could result in increased bioavailability with significant augmentation and prolongation of their effects. Patients taking any of these drugs may exhibit extreme oversedation and respiratory depression.

DIAZEPAM

Diazepam is the prototypical benzodiazepine that is noted for excellent anxiolysis and sedation of

moderate duration. It was the mainstay of most enteral and parenteral sedation regimens for years, and is still used occasionally for this purpose. However, its many drawbacks have caused it to be supplanted by newer agents, such as midazolam and triazolam. Diazepam is a water-insoluble drug that is formulated with propylene glycol for injection. This formulation makes it unsuitable for effective intramuscular injection because of poor absorption. Propylene glycol is also known to contribute to pain on injection, venous irritation, and thrombophlebitis. Diazepam has 3 active metabolites: oxazepam, nordiazepam, and desmethyldiazepam. Their half-lives range from 22 to 100 hours, which may account for residual hangover effects sometimes seen after diazepam administration.

MIDAZOLAM

Midazolam is the benzodiazepine of choice for TIVA because of its water solubility and excellent sedative, anxiolytic, and amnestic effects. It has a short elimination half-life (2.5 hours) and lacks significant active metabolites. Midazolam can be counted on to produce reliable antegrade amnesia, attenuate the cardiovascular response to stress, and suppress the psychotomimetic effects of ketamine. Unlike diazepam, it is well absorbed intramuscularly and does not cause pain on injection or venous irritation. Its effects may be intensified in the presence of CYP3A4 inhibitors. Midazolam is also available as an oral elixir, which is an effective premedicant in doses of 0.5 to 1.0 mg/kg (maximum 20 mg) for pediatric and special-needs populations.

ADJUNCTIVE AGENTS

Ketamine

Ketamine is a water-soluble phencyclidine derivative first synthesized in 1963. It produces a characteristic dissociative state characterized by profound analgesia, amnesia, and catalepsy. Its racemic form, containing equal amounts of its dextro and levo isomers, is used clinically. Its high degree of lipid solubility enables it to enter the CNS rapidly. Ketamine is thought to produce its unique clinical state by inducing dissociation between the thalamnoneocortical and limbic systems, thus preventing the higher centers from perceiving visual, auditory, and painful stimuli.[16] The result is a cataleptic state manifested by a vacant stare, glassy eyes, and horizontal nystagmus. Patients may appear to be removed or detached from their physical beings, but may still respond to command when ketamine has been administered in a low dose. These effects are caused by the binding of ketamine to NMDA receptors in the CNS.

Peak plasma concentrations of ketamine are achieved in about 1 minute after intravenous administration and in about 5 minutes following intramuscular administration. The pharmacokinetic profile of ketamine is similar in both adults and children, conforming to a classic 2-compartment model. Termination of activity occurs through slow redistribution to the peripheral compartment. Thus, the clinical effects of ketamine begin to wane in about 15 minutes after intravenous administration and in about 30 to 120 minutes following intramuscular injection. The elimination half-life of ketamine is 2 to 3 hours in adults, but children metabolize the drug more rapidly.

Cardiovascular effects

Ketamine exerts sympathomimetic effects on the cardiovascular system, resulting in mild to moderate increases in blood pressure, heart rate, and cardiac output. Coronary perfusion increases along with myocardial oxygen consumption. Ketamine is therefore relatively contraindicated in patients with uncontrolled hypertension, arteriosclerotic heart disease, and severe congestive heart failure. Hypertensive responses to ketamine may be exaggerated by rapid intravenous bolus injection and may be minimized by slow administration of low-dose ketamine.

Respiratory effects

Ketamine preserves spontaneous respiration and enhances the muscular tone of the upper airway. Protective airway reflexes are preserved. Respiratory depression is rarely associated with ketamine administration, although it may occur after rapid intravenous bolus injection or with the concomitant use of opioids. Ketamine is a bronchodilator, decreasing airway resistance by direct smooth muscle dilation, increased circulating catecholamines, and inhibition of vagal outflow. The effect of ketamine on ventilation is clinically insignificant, although the carbon dioxide response curve is shifted to the right. The slope of the curve remains unchanged, indicating that hypercarbic respiratory stimulation remains intact but may require a slightly higher $Paco_2$ for a ventilatory response. Ketamine stimulates salivary and tracheobronchial secretions that may induce laryngospasm. These effects can be adequately controlled by the concomitant administration of an antisialogogue. Although laryngospasm is a possible side effect of ketamine administration and is potentially life threatening, a literature review conducted by Green and Johnson[17] revealed only 2 cases of

laryngospasm in 11,589 pediatric patients who required intubation. Because upper airway protective reflexes remain intact, there seems to be minimal risk of the aspiration of gastric contents. In the 20 years of ketamine use studied by Green and Johnson,[17] only 2 cases of aspiration were found.

Neuromuscular effects

Ketamine produces skeletal muscle hypertonicity and rigidity, which may interfere with dental procedures because of inability to open the mouth. This phenomenon seems to be dose related, and increasing the ketamine dose or the addition of other sedative agents alleviates this problem. Random movement unrelated to surgical or painful stimuli often occurs with ketamine administration. This random movement may be mistaken for an inadequate sedation level when it is unrelated to the dental procedure. Myoclonus, twitching and jerking movements, are common following ketamine administration. When these movements have been extensive, they have been mistaken for seizure activity. However, ketamine has been shown to have anticonvulsive properties and has been used without complication in patients with seizure problems. Ketamine also causes an increase in intracranial pressure by producing cerebral vasodilation and increased perfusion pressure. It is therefore relatively contraindicated in patients with serious head trauma, hydrocephalus, and intracranial lesions. In addition, ataxia and dizziness may persist for up to 4 hours following ketamine administration. Therefore, rapid independent ambulation is not recommended following the use of ketamine.

Emergence phenomenon

Psychic reactions associated with ketamine may result from the disconnection of external stimuli from higher cerebral function. The incidence of psychic phenomena with ketamine has been reported to be between 0% and 50% in adults and 0% and 10% in children.[17] These experiences have been described as detachment, floating or bodily suspension, out-of-body experiences, and strange thoughts or dreams. Factors that may place patients at increased risk for these reactions may include age greater than 10 years, female gender, rapid intravenous administration of high doses, and personality disorders. Not all psychic responses to ketamine are unpleasant. Blankstein and Anderson,[18] in a comparison of low-dose ketamine with methohexital in adults undergoing oral surgery, found that ketamine was not associated with unpleasant dreaming, whereas some subjects given methohexital experienced horrifying dreams. The psychotomimetic effects of ketamine seem to be readily attenuated with the adjunctive administration of benzodiazepines or propofol. As discussed later, dexmedetomidine may be useful in preventing or attenuating emergence delirium associated with ketamine.

A possible cause for concern with ketamine use is nausea and vomiting. Although reports indicate that the incidence of nausea and vomiting may be from 0% to 43%, the incidence in pediatric patients is less than 10%. When vomiting does occur, it usually occurs late in the recovery phase or when the patient becomes ambulatory. At this juncture, the patient is alert and the airway may be cleared without assistance.

Clinical use

Sedation with ketamine may be induced either intravenously or intramuscularly. An intramuscular induction dose of 2 to 4 mg/kg of ketamine is useful in gaining behavioral control of unruly pediatric patients or patients with special needs. Intraoperative maintenance may be achieved with either a continuous infusion at a rate of 50 μg/kg/min, or by intermittent boluses of 5 to 20 mg as needed. Midazolam may be administered in 1-mg increments to provide background sedation and to control possible psychotomimetic effects. An antisialogogue may be needed to control the excessive secretions sometimes seen with ketamine.

Ketamine may be combined with propofol in a single syringe (ketofol) and administered by continuous infusion for procedural sedation. Kramer and colleagues[19] compared the combination of propofol-remifentanil with propofol-ketamine for third molar surgery. The concentration of 10 mg/mL of propofol and 2.5 μg/mL of ketamine produced sedation hemodynamic stability, and respiratory stability that was comparable with the concentration of 10 mg/mL of propofol and 5 μg/mL of remifentanil. However, the combination of propofol and ketamine was associated with longer emergence and recovery times, which could limit its usefulness in third molar surgery.

Dexmedetomidine

Dexmedetomidine is a highly selective α_2-agonist similar to clonidine but with a greater affinity for the α_2-receptor. Alpha$_2$-receptors are located in the peripheral vasculature and produce vasoconstriction when activated. However, their primary site of action in the sympathetic nervous system is at the adrenergic neural endplate where they initiate a negative feedback loop that modulates the release of norepinephrine. This feedback results in an attenuation of the sympathetic stress response. Alpha$_2$-receptors are also found in the CNS in the locus ceruleus and the spinal column.

Activation of these areas results in anxiolysis, sedation, and analgesia.

Stimulation of α_2-receptors in the dorsal horn of the spinal column inhibits nociceptive neurons and reduces the release of substance P. Although there is some evidence for supraspinal and peripheral sites of action for dexmedetomidine, it is thought that the spinal mechanism produces most of the drug's analgesic action.[20,21] Dexmedetomidine is rapidly redistributed, with an elimination half-life of 6 minutes and an elimination half-life of 2 hours.

Cardiovascular effects

Dexmedetomidine produces a significant reduction in heart rate, systemic vascular resistance, and systolic blood pressure.[22] These effects aid in modulating the stress response, which may be particularly useful in patients with systemic hypertension and/or myocardial ischemia who could respond adversely to surgical stressors. Dexmedetomidine promotes stability and may protect against radical fluctuations in cardiovascular parameters intraoperatively.

Dexmedetomidine loses its α_2-receptor selectivity as the dose is increased by intravenous bolus injection or rapid infusion. This loss results in an initial increase in blood pressure and concomitant decrease in heart rate, which normalizes within 15 minutes, followed by a further reduction in blood pressure.[20,22]

Respiratory effects

A major advantage of dexmedetomidine compared with other anesthetic drugs is its minimal effect on the respiratory system. In patients with poor airways, obesity, and/or limited range of motion, dexmedetomidine produces excellent sedation without compromising the airway or depressing respiration.

Clinical use

Dexmedetomidine is a useful adjunct for procedural sedation, either via bolus injection or continuous infusion. A bolus injection of 0.25 μg/kg to 0.5 μg/kg given slowly in divided doses, to avoid a transient increase in blood pressure, produces a noticeable quieting or mellowing effect without respiratory depression. As an alternative, sedation may be induced by a continuous infusion of dexmedetomidine, 1 μg/kg over 10 minutes, followed by a maintenance infusion of 0.2 μg/kg/h to 0.7 μg/kg/h. Dexmedetomidine has been shown to decrease the requirement for the coadministration of propofol, opioids, and benzodiazepines.[23,24]

Emergence delirium can be a significant problem following outpatient anesthesia because of the potential for serious disruption of the office, damage to instruments and equipment, and injury to the patient or office personnel. Delirium is described as a disturbance of consciousness, characterized by the acute onset of impaired cognitive functioning, significantly impairing a patient's ability to process and store information. Pediatric patients, patients with special needs, and the elderly are particularly prone to emergence delirium following anesthesia, especially when benzodiazepines and potent inhalational agents are used. Patients who develop delirium are more likely to have poor outcomes when hospitalized, including increased length of stay, the need for subsequent institutionalization, and higher mortality. Cognitive impairment has been reported to negatively affect key outcome indicators such as removal from the ventilator, pneumonia, and total length of hospital stay.[25]

Dexmedetomidine has been studied to assess its efficacy in reducing the occurrence of emergence delirium. Riker and colleagues[26] compared the efficacy of dexmedetomidine with midazolam for the maintenance of mechanically ventilated patients, and also examined the incidence of delirium in those patients. Although the two drugs produced comparable levels of sedation, dexmedetomidine significantly reduced the incidence of delirium, 54% versus 75% for midazolam. In addition, the duration of delirium was reduced by 48% in the dexmedetomidine group. Patients treated with dexmedetomidine had a statistically significant greater ability to communicate and to cooperate than those treated with midazolam.

Pandharipande and colleagues[27] compared the efficacy and incidence of delirium of dexmedetomidine and lorazepam in mechanically ventilated intensive care patients. Lorazepam has been recommended by the Society of Critical Care Medicine for the sustained sedation of mechanically ventilated patients in the intensive care unit. However, it has been proposed that the GABA effects of lorazepam and other benzodiazepines may alter levels of potentially deliriogenic neurotransmitters, with negative consequences. Compared with the lorazepam group, the dexmedetomidine group had a lower prevalence of coma (63% vs 92%), fewer days with delirium (3 vs 7 days), and the 12-month time to death was 363 days versus 188 days.

Emergence delirium is also common in children recovering from deep sedation and general anesthesia. Shukry and colleagues[28] studied 2 groups of children between the ages of 1 and 10 years receiving general anesthesia with sevoflurane. One study group received an infusion of dexmedetomidine and the other received saline. The dexmedetomidine group had an emergence delirium

incidence of 26% versus 60% for the saline group. Another study investigated the incidence of emergence delirium in children receiving general anesthesia for a nonsurgical procedure.[29] One group received an infusion of dexmedetomidine after induction of anesthesia and the other group received a placebo infusion. The children who received dexmedetomidine had a 4.8% incidence of delirium compared with 47.6% for the placebo group.

Dexmedetomidine may be used either prophylactically or emergently for the prevention or control of emergence delirium. In patients who are deemed at risk for emergence delirium, 0.25 μg/kg of dexmedetomidine may be slowly injected intravenously during the maintenance phase of anesthesia. Should emergence delirium occur, another 0.25 μg/kg may be administered. In cases in which prophylaxis has not been administered, emergence delirium may be controlled with the intravenous administration of 0.5 μg/kg of dexmedetomidine.

SUMMARY

TIVA is a technique whose time has come because of the advent of ultra–short-acting drugs and computerized infusion technology. Patients may be sedated to any desired level, maintained there for indefinite periods, and recovered to near baseline within minutes, which gives the operator extreme, moment-to-moment control of the anesthetic and improves patient outcomes. Future trends in TIVA may include patient-controlled sedation, whereby patients sedate themselves with an infusion device similar to those used for postoperative analgesia. It seems that, of the drugs currently available, a remifentanil/propofol combination would be suitable. The future may also bring titration of sedatives to target blood levels, leading to more precise dosing and greater efficiency.

This article provides an overview of historical and current sedative agents available to the dentist anesthetist. The discussion is intended to provide the surgeon with rational choices for sedation and the individualization of drug selection for each patient.

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