Chapter 5: Analgesics

James A. Tolley

INTRODUCTION

FOCUS POINTS

1. Acetaminophen has no known pharmacologically active metabolites.
2. Oxidized acetaminophen leads to *N*-acetyl-*p*-benzoquinone imine (NAPQI), the compound responsible for hepatic toxicity in the event of an overdose.
3. The mechanism of action for nonsteroidal anti-inflammatory drugs (NSAIDs), which explains their anti-inflammatory and analgesic properties, is the ability to block the production of prostaglandin via inhibition of the COX-1 and COX-2 enzymes.
4. Short-term use of ketorolac has been extremely useful in the perioperative management of pediatric patients with minimal risks.
5. Codeine is metabolized in the liver to its active metabolite, morphine.
6. As a morphine metabolite, morphine-3-glucoronide is devoid of analgesic activity but morphine-6-glucuronide (M6G) is an opioid agonist more potent than the parent compound.
7. Remifentanil possesses unique characteristics among opioids with pharmacokinetics exhibiting independence of age and organ function. It is rapidly metabolized by non-specific blood and tissue esterases.
8. Meperidine is metabolized to normeperidine, an active metabolite with a long half-life and central excitatory and neurotoxic effects that can lead to seizures.
9. Methadone is extensively used in children and serves as first-line treatment for neonatal abstinence syndrome.
10. Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor noncompetitive antagonist with bronchodilator properties.

One of the primary roles of the anesthesiologist as perioperative physician is to provide adequate analgesia both during and after a painful procedure. It is therefore imperative to have a good working knowledge of the various analgesics that can be used to accomplish this goal. The purpose of this chapter is to provide that working knowledge.

Pharmacology can be divided into two broad areas, pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK) can be thought of as “what a body does to a drug” and includes such topics as drug absorption, distribution, metabolism, and elimination. Pharmacodynamics (PD) can be thought of as “what the drug does to the body” in terms of interacting with a target and eliciting a clinical response, and its potential side effects and toxicities.[1,2] Much more is known about pharmacokinetics in pediatric patients than is known about pharmacodynamics.[3]

The chapter begins with the basic pharmacokinetic differences of the pediatric patient compared to the adult before discussing the pharmacology of acetaminophen and other NSAIDs, multiple opioids used both intraoperatively and postoperatively, and an assortment of other drugs that are used in the perioperative setting for pain modulation and treatment. The pharmacology of local anesthetics is covered in a separate chapter.

MATURATIONAL PHARMACOKINETICS

Pediatric patients, especially neonates and infants, are not simply small adults. There are many rapidly maturing biological systems which can have an influence on the absorption, distribution, metabolism, and elimination of drugs. As a result, drug dosing and dosing schedules, accumulation of active, inactive, and toxic metabolites, and pathways of biotransformation and elimination can differ significantly from older patients. In this rapidly changing environment, it is essential for the pediatric anesthesiologist to understand the basic pharmacokinetic differences that occur during the first weeks and months of life.

Absorption

Since most analgesics utilized by the pediatric anesthesiologist are given via the intravenous route, absorption plays a little role in the pharmacokinetics of those drugs. However, some developmental changes occur which the anesthesiologist should be aware of.

Generally, gastric pH is elevated in the neonate, which can affect drug stability and absorption, and does not reach adult levels until 2 years of age. In addition, neonates have prolonged gastric emptying time which may lead to a slower overall rate of absorption,[4–6] not reaching adult levels until 6 to 8 months of age.[7,8] Intestinal motility is also reduced in the neonate.[7,9] These differences may or may not ultimately impact the bioavailability, maximum concentration (C_{max}), or time to maximum concentration (T_{max}) of a particular drug.

Ontogenetic changes in intestinal enzymes can also affect the overall absorption of various drugs. Drug metabolizing enzymes (DMEs), such as CYP3A4, are located in the small intestine. Its activity is very low at birth but increases to about 50% of adult levels by 6 to 12 months of age, meaning that less intestinal metabolism occurs at younger ages.[7,10] An active drug transporter, P-glycoprotein (P-gp), can be detected in the intestine at 1 month of age, but does possess large interindividual variability.[7,11] Rectal absorption can also be highly variable depending upon the characteristics of the drug and its residence time in the rectum.[7]

Percutaneous absorption of drugs in the neonate and infant is often elevated due to a greater surface area to body mass ratio, greater hydration of the skin, and increased blood flow.[7,12] Furthermore, preterm neonates have enhanced absorption for the first 3 weeks postnatally as the epidermis rapidly matures.[13] Intramuscular absorption of drugs can also be enhanced in younger patients due to the increased capillary density surrounding muscle that occurs at this young age.[14]

Distribution

Once absorbed, a drug is distributed to the various tissues of the body based upon its physicochemical properties and can be described by its volume of distribution (V_d). Body composition and protein binding can have a large impact upon the V_d of a drug. Because a newborn's body weight is composed of a greater percentage of water than an adult, hydrophilic drugs will have a greater apparent V_d requiring a larger initial dose to achieve therapeutic plasma concentrations.[6,7] The total body water content approaches adult levels by 4 months of age.

Neonates and infants also have decreased levels of circulating proteins, such as albumin and alpha-1-acid glycoprotein, that bind drugs in the plasma. The result is a larger apparent V_d as the resulting free fraction of drug distributes throughout the body tissues.[7,15] Circulating levels of plasma proteins reach adult levels by 3 years of age, but the impact upon the free fraction can vary depending on the drug.[16]

Metabolism

The liver serves as the primary organ for biotransformation of drugs into more water-soluble compounds for elimination. Phase I reactions create a more polar compound through reduction, oxidation, or hydrolysis. The cytochrome P450 (CYP) enzymes are primarily responsible for phase I reactions and with the exception of CYP3A7 are not very active at birth. Some, such as CYP2D6, will develop fairly rapidly while others will take several months to reach adult levels.[2,7,17,18]

Phase II reactions involve conjugation of small chemical groups to a drug or to its phase I metabolite. These enzymes will also demonstrate variable expression during different stages of development. Sulfation is fully present at birth, whereas glucuronidation will develop more slowly with some

isoenzymes reaching adult levels in the first few years of life and others not reaching adult levels until sometime after age 10.[2,7,19]

The variable expression of metabolizing enzymes at different stages of development can lead to interesting clinical implications when a drug is forced down a particular metabolic pathway. Furthermore, the presence of genetic polymorphisms can have profound effects on the efficacy or toxicity of several analgesics, which will be discussed when reviewing the pharmacology of the individual drugs later in the chapter.

Excretion

The kidney is the primary organ of excretion for the body. The glomerular filtration rate (GFR) is low at birth but rapidly increases, doubling in the first week of life. Adult GFR is reached by the first birthday and will exceed adult values by 20% to 30% until the age of 5, perhaps requiring larger weight-based dosing in this age group.[7,20] In addition to passive filtration of a drug and its metabolites, the kidney may actively secrete these compounds, although little is known about the development of the processes involved. This is an area where additional research is needed.[20]

Acetaminophen (Paracetamol)

Acetaminophen is one of the most widely used analgesics in the world. It is available in oral, rectal, and intravenous forms. When administered via the gastrointestinal tract, it is absorbed by passive nonionic diffusion primarily in the proximal portion of the small intestine.[21] It has an oral bioavailability of approximately 80%,[22] and while some experts suggest a bioavailability of close to 70% when given rectally,[23] there have been reports of great variability including significant differences in male vs female neonatal absorption.[24]

Protein binding of acetaminophen is relatively low (10–25%), leading to a V_d of approximately 1 L/kg.[22] Acetaminophen has no known pharmacologically active metabolites.[22] Its primary means of metabolism is glucuronidation via UGT1A6, with sulfation playing a greater role in the neonate due to the ontogeny of the hepatic enzymes.[22,25] A small amount of acetaminophen is oxidized via CYP2E1 to form *N*-acetyl-*p*-benzoquinone imine (NAPQI), the compound responsible for the hepatic toxicity of acetaminophen in the event of an overdose.[1,22,26] Since CYP2E1 activity is reduced in neonates, this group of patients seems to be somewhat resistant to the hepatotoxic effects of acetaminophen as demonstrated by several reports of neonatal overdose without long-term sequelae.[22,27–30]

Acetaminophen and its metabolites are primarily excreted in the urine with acetaminophen sulfate representing approximately 50% of renal clearance in infants.[22,31] Acetaminophen sulfate is highly protein bound (>50%), and in the presence of unconjugated hyperbilirubinemia, clearance is reduced by 40%. It has been recommended to reduce the dose of acetaminophen if this condition exists.[32,33]

The true mechanism of action of acetaminophen is unknown but is postulated to involve centrally mediated cyclooxygenase (COX) inhibition. It seems to have little clinical effect on peripheral inflammation, edema, and platelet aggregation.[34] Acetaminophen crosses the blood-brain barrier via passive diffusion, requiring a sufficient gradient between serum and CSF concentrations.[23] The existence of a central mechanism of action is suggested by a delay of approximately 1 hour between maximal effectiveness and peak plasma concentrations.[35]

The actual serum concentration associated with analgesia is unknown but is presumed to be 10 to 20 mcg/mL[23,35] with some suggestion that an analgesic ceiling effect exists.[36] When equal doses of acetaminophen are utilized, intravenous administration results in greater plasma and CSF concentrations with an earlier peak than either oral or rectal administration.[35]

Acetaminophen has been shown to have an opioid-sparing effect following major noncardiac thoracic or abdominal surgery in neonates and infants less than 1 year of age.[37] It also has been shown to benefit patients following tonsillectomy with or without adenoidectomy[38] and cleft palate repair.[38] The reduction in rescue opiate requirements was approximately 40% to 50%[37,39] when the IV form was used. Conversely, rectal acetaminophen was *not* effective in reducing postoperative narcotic requirements in young infants up to 2 months of age following major noncardiac thoracic or abdominal surgery,[40] nor was it effective in patients up to 24 months of age in cleft palate repair despite a maximum plasma concentration of 21 mcg/mL in the 40 mg/kg group.[41]

When oral elixir was compared to rectal paracetamol in children undergoing tonsillectomy, the oral form yielded significantly higher plasma

concentrations and superior pain relief.[42] In pediatric outpatient surgery, rectal acetaminophen doses of 40 mg/kg were required to produce a morphine-sparing effect.[43] In contrast, for pediatric ophthalmic surgery, even 20 mg/kg was more effective than placebo.[44] Thus, analgesic efficacy may be determined by the proper combination of drug delivery method and case selection.

The current IV acetaminophen product in the United States is approved for mild to moderate pain in patients 2 years of age and older.[45] Dosing recommendations are as noted in Tables 5-1 and 5-2.

Table 5-1

Acetaminophen IV Dosing Based on PMS *

Age	Weight	Dosage	Max
Any	<50 kg	15mg/kg q6h	75 mg/kg/day
PMA 32–34 wks		20 mg/kg load, 10 mg/kg q6h maintenance	
PMA 28–31 wks		20 mg/kg load, 10 mg/kg q12h maintenance	

*Postmenstrual age is defined as gestational age plus chronological age in weeks.[46]

Table 5-2

Acetaminophen Dosing[47]

Administration	Dosage	Max
IV	15mg/kg q6h	75 mg/kg/day
Oral	15mg/kg q4–6h	60 mg/kg/day
Rectal	40 mg/kg load, 20 mg/kg q6h	?

Recommended rectal doses in children aged 2 to 12 years showed large interindividual variability in pharmacokinetics with only 48% of observed plasma concentrations within the target range of 10 to 20 mcg/mL.[48]

Source: Data from de Martino M, Chiarugi A. Recent advances in pediatric use of oral paracetamol in fever and pain management. *Pain Ther.* 2015;4:149-168. https://www.springer.com/journal/40122.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

NSAIDs as a group contain such drugs as acetylsalicylic acid (aspirin), ibuprofen, ketoprofen, naproxen, indomethacin, ketorolac, celecoxib, parecoxib, and others. Many of these drugs are available in oral, rectal, and IV formulations. Rarely will the anesthesiologist be using rectal NSAIDs, so the discussion will be limited to oral and IV preparations. Furthermore, given the association of aspirin with Reye syndrome and the decreased usage in pediatric patients,[49] this drug will not be addressed.

Ibuprofen, **ketoprofen**, and **naproxen** are propionic acid derivatives and possess several similar pharmacokinetic characteristics but also some unique differences. These drugs are all weak acids with pK_a values of 5.38, 5.94, and 4.15, respectively.[50–52] They all have oral bioavailability approaching 100%, and a rate of absorption that depends upon the precise formulation.[51,53–55] In premature neonates, oral ibuprofen also has

excellent bioavailability with drug being detectable in plasma within 1 hour of administration.[56,57] Usage of ketoprofen and naproxen in neonates has not been reported. Cystic fibrosis can significantly impact the oral absorption of ibuprofen resulting in a decrease in peak serum concentration that is almost 30% lower than healthy individuals.[58]

Because these drugs are highly protein bound at 98% to 99%, the V_d approximates plasma volume.[51,53,59] Ibuprofen and ketoprofen are commonly administered as racemic drugs that undergo unidirectional inversion by hepatic enzymes from the inactive (*R*)-enantiomer to the biologically active (*S*)-enantiomer, whereas (*R*)-naproxen is known to be hepatotoxic necessitating the clinical use of the pure (*S*)-naproxen enantiomer.[60,61]

Ibuprofen is oxidized primarily by CYP2C9, and to a lesser extent CYP2C8, to inactive metabolites.[53,62,63] Genetic polymorphisms for CYP2C9 have been identified, but the clinical impact is unknown.[63] In neonates, the half-life of ibuprofen decreases rapidly from a mean of 43 hours on the third day of life to a mean of 27 hours on the fifth day of life. This is due to the rapidly increasing activity of CYP2C9 and CYP2C8 in the first week of life.[64] Ketoprofen undergoes glucuronidation, although the precise enzymes involved have not been completely elucidated.[63,65] About 60% of a dose of naproxen is metabolized by glucuronidation; oxidation via CYP2C8 and CYP1A2 also occurs.[63] These drugs and their metabolites are primarily excreted in the urine.[51,53,66]

The mechanism of action for NSAIDs, which explains their anti-inflammatory and analgesic properties, is the ability to block the production of prostaglandin via inhibition of the COX-1 and COX-2 enzymes. COX-1 is present in nearly all human tissues, while COX-2 is primarily found in the renal and central nervous systems (CNS).[67] COX-2 is also expressed in injured tissues[67] but may also play a significant role in the organogenesis of the small intestine, lungs, and kidneys.[68]

The serum level of ibuprofen that is required for analgesia is 5 to 10 mcg/mL.[69] Intravenous ibuprofen (10 mg/kg) given preoperatively to children undergoing tonsillectomy had a significant opioid sparing effect compared to placebo with no increase in serious adverse events, including surgical and postoperative blood loss.[70] A meta-analysis that looked at 18 studies of pediatric pain comparing ibuprofen and acetaminophen found that ibuprofen was at least as effective as, if not superior to, acetaminophen with no significant difference in adverse events.[71]

In neonates, ibuprofen is most often utilized as an alternative to indomethacin for closure of a patent ductus arteriosus (PDA). An intravenous dose of 10 mg/kg followed by two additional doses of 5 mg/kg every 24 hours is just one of the many dosing regimens. Alternatively, 10 mg/kg orally every 24 hours for 3 days can also be used.[67] Adverse side effects associated with ibuprofen in neonates include the rare possibility of severe nephrotoxicity and acute renal failure, pulmonary hypertension,[72] and intestinal perforation.[73]

Ketoprofen has also been studied in the perioperative setting. Intravenous doses of 1 to 2 mg/kg have been used effectively in tonsillectomy and adenoidectomy, ocular surgery, and orthopedic or soft tissue surgery. For major noncardiac surgeries, a loading dose of 1 mg/kg followed by a 4 mg/kg infusion over a 24-hour period for 1 to 3 days postoperatively provided superior analgesia compared to placebo as an adjunct to epidural sufentanil.[74]

Intravenous naproxen is not commercially available, so perioperative usage is limited in its scope.

Indomethacin and **ketorolac** are both acetic acid derivatives and like the other NSAIDs are weak acids that have an oral bioavailability of nearly 100% with peak plasma concentrations occurring approximately 1 to 1.5 hours after an oral dose.[75,76] Even in premature neonates as young as 27 weeks' gestation and 1 kg, the bioavailability of oral indomethacin is over 98%.[77] Oral ketorolac usage in neonates has not been reported. Both drugs are highly protein bound with indomethacin being at least 90% bound,[75,78] and ketorolac even more so at greater than 99%[76] resulting in a small V_d.

Indomethacin is metabolized in the liver by CYP2C9 and UGT2B7.[78] The metabolites of indomethacin are inactive and excreted in the urine. About one-third are also excreted in feces.[75] Not surprisingly, in premature neonates there is a greater interindividual variability in both V_d and clearance due to the immaturity of the hepatic and renal systems.[78] These values reach adult levels by 1 year of age.[79]

The majority of ketorolac is excreted unchanged in the urine with the remainder undergoing various degrees of glucuronidation and hydroxylation in the liver.[80] There are enantiomeric differences that exist with ketorolac. The (*S*)-enantiomer is active, but there is no chiral inversion from (*R*)-ketorolac

to (*S*)-ketorolac in the body. Furthermore, the clearance of (*S*)-ketorolac is four to five times higher leading to a half-life that is about 30% to 40% that of (*R*)-ketorolac. The half-life of (*S*)-ketorolac is about 1 hour in infants and 1.5 hours in children, as infants demonstrated a greater plasma clearance.[80,81]

Indomethacin is a nonselective inhibitor of COX-1 and COX-2. It is currently the drug of choice for prophylactic treatment of PDA in premature neonates due to lower incidence of pulmonary hemorrhage and severe intraventricular hemorrhage versus ibuprofen, which is the drug of choice for symptomatic treatment because of a decreased association with necrotizing enterocolitis and renal effects.[82] Indomethacin is unique among NSAIDs in that it is a known vasoconstrictor and decreases cerebral blood flow.[75] It has not, however, been extensively used in the perioperative period as ketorolac.

Ketorolac is also a nonselective inhibitor of COX-1 and COX-2. Because of its effectiveness in mitigating postoperative pain, it has been investigated following a wide range of surgical procedures and is available for use in oral, IV, IM, rectal, and intranasal formulations. In pediatric patients, ketorolac has been shown to be as effective as morphine for procedures causing moderate to severe pain, such as tonsillectomy, orthopedic surgery, or plastic surgery. In addition, patients had less postoperative nausea and vomiting.[83] Ketorolac infusion compared favorably to fentanyl infusion in patients undergoing ureteroneocystostomy, resulting in less rescue analgesia and frequency of bladder spasms.[84] Ketorolac has been used safely in neonates and infants following cardiac surgery without adverse hematologic or renal sequelae.[85]

The main concerns regarding side effects of ketorolac relate to the role that prostaglandins play in body homeostasis. Prostaglandins play a vital role in renal vascular tone and inhibition of COX-2 by NSAIDs leading to decreased renal blood flow and glomerular filtration rate.[86] The risk of acute renal failure was found to double in patients receiving more than 5 days of therapy.[87]

Prostaglandins are important in regulation of osteoclastic and osteoblastic activity, so concern has been raised regarding the use of NSAIDs during bone healing;[88] however, a retrospective review of 327 children undergoing 682 lower extremity osteotomies showed no difference in delayed union, wound complications, or bleeding in patients receiving ketorolac versus those that did not.[89] Nor was there any difference in pseudoarthrosis formation following posterior spinal fusion for idiopathic scoliosis in adolescents between those that received ketorolac postoperatively and those that did not.[90]

Ketorolac has been shown to increase bleeding time in healthy volunteers.[91] A meta-analysis revealed that its use in tonsillectomy patients led to a fivefold increased bleeding risk in adults, but not in children under 18.[92] The precise explanation for this difference is unclear. A retrospective review of 1451 pediatric neurosurgical patients did not show any association between clinically significant bleeding events and ketorolac use.[93] Thus, it would appear that short-term perioperative usage of ketorolac for pain management is acceptable in most pediatric patients for the majority of surgical procedures.

COX-2 selective inhibitors, such as **celecoxib** and **parecoxib**, were developed with the hope of minimizing the gastrointestinal and renal side effects associated with nonselective inhibition since COX-2 is preferentially induced during inflammation. Unfortunately, these drugs have shown an increased risk of thrombotic events such as myocardial infarction, stroke, and unexplained death, leading to withdrawal of some of them from the market.[94] Celecoxib is only available in oral form and parecoxib is not currently approved in the United States.

Opioids

As experts in analgesia, anesthesiologists are expected to be especially knowledgeable about opioids since this class of drugs is typically on the top of the list when it comes to pain medications due to their long history of use and effectiveness at managing pain. Anesthesiologists should also be keenly aware of the adverse effects, including the potential for addiction. Opioids can be classified into those that occur naturally, those that are semi-synthetic, and the synthetic opioids.[95] Morphine and codeine are the naturally occurring opioids that have therapeutic uses. Codeine is a prodrug that is converted to morphine for its analgesic effects,[96] so these drugs will be discussed together.

Both **codeine** and **morphine** are commonly used in oral and injectable formulations. Oral absorption is extensive with both drugs, but due to first-pass hepatic metabolism, the bioavailability is 60% to 70% for codeine and only about 24% to 40% for morphine, and somewhat variable.[97–99] The drug transporter, P-glycoprotein, may also help limit the bioavailability of morphine by pumping drug back into the intestinal lumen.[100]

Codeine is about 30% bound to plasma proteins, although it has been found to be about twice that value in patients with sickle cell anemia. This can be partially explained by the increased levels of gamma-globulin in the plasma of sickle cell patients.[101] Morphine binding ranges from 20% to 40%, and it has a V_d of 2.1 to 4.0 L/kg.[98]

In order to manifest its analgesic effects, codeine is metabolized in the liver by CYP2D6 to the active metabolite, morphine.[102] Over 100 different alleles of CYP2D6 have been identified. This degree of polymorphism has led to a great deal of interindividual variation in the ability to metabolize codeine into morphine. Patients have been separated into several phenotypes as a result. Poor metabolizers (PM) possess 2 of 15 possible inactive genes. Intermediate metabolizers (IM) have two copies of reduced activity genes or one reduced and one inactive gene. Extensive metabolizers (EM) have one or both copies of genes encoding for normal enzymatic activity, while ultra-rapid metabolizers (UM) have more than two copies of the wild-type allele because of gene duplication.[103]

These differences can have profound clinical implications ranging from little analgesic effect of codeine in PM to morphine overdose in UM due to a 30-fold or greater plasma concentration difference in morphine between the two extremes.[104] Pharmacokinetic modeling suggests that 10% of a codeine dose is converted to morphine in PM, compared to 40% in EM, and 51% in UM[105] with the remainder metabolized to norcodeine via CYP3A4 or via conjugation to codeine-6-glucuronide, which itself has analgesic activity.[106,107] These compounds are then excreted in the urine.[104]

Numerous deaths in children following adenotonsillectomy have prompted the reevaluation of using codeine in the pediatric population.[108,109] A review from 1984 to 2010 found 17 post-tonsillectomy deaths related to opioid toxicity.[110] These complications of codeine usage led the United States Food and Drug Administration (US FDA) to issue a warning contraindicating codeine use for pain or cough in children younger than 12 years in April 2017.[111] Furthermore, the report of a death in a breastfed infant whose mother was taking codeine for postpartum pain[112] has led to an additional warning.[111]

Morphine is likewise metabolized in the liver with the primary pathway being glucuronidation into morphine-3-glucuronide (45–55%) and morphine-6-glucuronide (10–15%), which are then excreted in the urine.[98] The primary enzyme responsible for these reactions is UGT2B7, although other isoforms may contribute to the formation of morphine-3-glucuronide (M3G).[113] Genetic polymorphisms of UGT2B7 are also being discovered, although the clinical significance is unclear at this time with one study showing no ability to predict postoperative morphine requirements[114] and another showing a significant difference in postoperative morphine requirements.[115] A small pilot study in preterm neonates showed that one of the UGT2B7 polymorphisms significantly influenced the pharmacokinetics of morphine metabolism in addition to postnatal age.[116]

As a metabolite, M3G is devoid of analgesic activity and is a mild opioid antagonist. On the other hand, morphine-6-glucuronide (M6G) is an opioid agonist more potent than the parent compound.[98,117] Thus, the ratio of M3G to M6G may be an important factor in a particular patient's response to morphine analgesia.

In general, opioids produce their therapeutic and adverse effects through binding with three main types of opioid receptors (mu, delta, and kappa) which are located in the central and peripheral nervous systems and in the neuroendocrine, gastrointestinal, and immune systems. Opioid receptors are G protein–coupled receptors that, when activated, ultimately influence the transmembrane gradients of calcium, sodium, and potassium ions or influence the release of neuropeptide transmitters such that the transmission of painful impulses is reduced.[118] The complete intracellular mechanism is beyond the scope of this chapter, but two excellent reviews on opioid receptors[118] and the molecular mechanism[119] of the pain pathway have been published.

All three opioid receptors play a role in analgesia both centrally and in the periphery but differ as to their adverse effects. The most serious adverse effect, respiratory depression, is mediated by centrally acting mu-receptors. These receptors are also responsible for the euphoria that is associated with opioid use, while central kappa-receptors are associated with dysphoria. Both mu- and delta-receptors contribute to constipation.[118] Neonates are especially sensitive to the central depressant effects of opioids partially due to the decreased levels of P-gp, which functions as an active drug transporter, present in the blood-brain barrier. Adult levels of P-gp are not reached until 3 to 6 months of age.[120]

The presence of polymorphisms at the mu-receptor may play a role not only in the analgesic efficacy of morphine but also in the development of

adverse effects. The OPRM1 gene codes for the mu-receptor and a single nucleotide polymorphism exist at base pair 118 in which adenine is substituted with guanine such that patients homozygous for 118GG have been found to have increased postoperative morphine requirements by several multiples.[117,121,122] A more recent study in adolescents undergoing spinal fusion demonstrated higher pain scores in patients with the presence of the G allele suggesting decreased sensitivity to morphine with less respiratory depression.[123] The G allele may also offer protection from other opioid-related side effects including pruritus from epidural morphine.[124]

Despite the potential for adverse effects in neonates, opioids have become an integral part of pain management in this population both in the perioperative period as well as in the neonatal intensive care unit based on a landmark study which showed a decreased sympathetic response and decreased mortality in neonates undergoing cardiac surgery.[125] Subsequently, morphine was shown to reduce circulating norepinephrine[126] and adrenaline[127] levels in ventilated preterm neonates leading to the inclusion of opioids, especially morphine and fentanyl, as part of the latest recommendations for managing procedural pain in the neonate.[128] However, information concerning the long-term effects is conflicting: one study has shown a negative impact on a short-term memory task and more social problems compared to placebo,[129] while another study has shown that morphine may even have beneficial effect on executive functions at 8 to 9 year follow-up.[130]

Morphine is available in oral, rectal, and injectable preparations and serves as the gold standard in perioperative pain management against which other analgesic compounds and techniques are measured. When given intravenously, morphine has been shown to be superior to placebo at reducing postoperative pain in children as well as reducing the need for rescue analgesia, albeit with a significantly higher incidence of nausea, vomiting, and sedation.[131] Epidural and intrathecal morphine has also been shown to be more effective at relieving pain than no intervention but with significantly more nausea, vomiting, pruritus, and respiratory depression when used epidurally.[131] Intraarticular morphine has also been shown to be more effective than placebo following arthroscopic knee surgery,[132] although little pediatric data exists.

Hydrocodone, **oxycodone,** and **hydromorphone** are semisynthetic opioids derived from naturally occurring opiates.[95] The first two drugs are mainly used for acute, postoperative, or chronic pain as there is no currently available injectable product in the United States, unlike hydromorphone. The oral bioavailability of hydrocodone has not been well studied in humans but is estimated to be between 38% and 60% but with interindividual variability.[133,134] Oxycodone has a bioavailability ranging from 60% to 87% due to less first-pass metabolism compared to some of the other opioids.[135]

Volume of distribution estimates for hydrocodone would suggest lower levels of plasma protein binding[133] when compared to oxycodone, which is 45% bound to albumin and has a V_d of approximately 2.5 L/kg.[135] Hydromorphone shows a similar V_d to that of oxycodone at roughly 2 to 3 L/kg, suggesting a similar degree of serum protein binding.[136,137]

Hydrocodone is metabolized in the liver primarily by *N*-demethylation via the enzyme CYP3A4 to norhydrocodone which is a less potent, active metabolite when compared to the parent drug,[138,139] but which may also accumulate during chronic administration due to its longer half-life.[139] Norhydrocodone has been shown to have central neuroexcitatory effects.[139] Hydrocodone is also metabolized via CYP2D6 to hydromorphone, which has a much stronger affinity for the opioid receptor than the parent compound. Due to the polymorphisms of CYP2D6, it has been suggested that the probability of hydrocodone acting as a pro-drug is 44% in the UM phenotype, 22% in EM, and 5% in PM.[140] The relative contribution of each metabolic pathway depends upon an individual's phenotype.[141,142]

Oxycodone is also metabolized in the liver via the two major pathways mentioned above with the major metabolite being the weakly active noroxycodone formed by CYP3A4. Oxymorphone is an active metabolite produced by *O*-demethylation via CYP2D6[135,143] which again raises the issue of the clinical impact of genetic polymorphisms.[141,144,145]

Hydromorphone is structurally like morphine and undergoes conjugation in the liver to hydromorphone-3-glucuronide via UGT2B7.[135,146] It also undergoes reduction reactions which serve as minor pathways yielding small amounts of active metabolites that may only become clinically important in renal failure.[136] The metabolites of all three of these drugs are excreted in the urine.[135,136,138]

In the United States, hydrocodone and oxycodone are only available in oral formulations so usage is limited to acute medical or postsurgical pain or chronic pain with hydrocodone being the most commonly prescribed opioid for pediatric emergency department patients in the decade ending in

2010.[147] Hydrocodone in combination with acetaminophen was prescribed to over 2% of pediatric hospitalized patients in 2008.[148] In a recent review of over 34,000 outpatient opioid prescriptions, the majority (73%) were for oxycodone.[149] Concerns have been raised about the risk of opioid-related deaths in pediatric patients given the role of CYP2D6 in the metabolism of both hydrocodone and oxycodone and whether patients would benefit from preoperative genotyping.[150]

Given hydromorphone's structural similarity to morphine, it should not be surprising that it would also be available in rectal, oral, and injectable formulations and used in a similar manner clinically to morphine. In pediatric patients, hydromorphone has been used as a continuous infusion in mechanically ventilated infants and children.[151] It has been used as an epidural infusion alone[152] or in combination with bupivacaine for posterior spinal fusion.[153] When compared to epidural morphine and fentanyl, epidural hydromorphone showed fewer side effects and similar analgesia for pediatric patients undergoing orthopedic procedures.[154]

Fentanyl is a synthetic opioid available in many types of formulations. It is highly lipid soluble, and, although not commonly ingested, has an oral bioavailability of about 30% due to a high degree of first-pass metabolism in the liver.[155] Oral transmucosal fentanyl has a bioavailability of approximately 50% and buccal tablets are higher at 65%.[156] Intranasal fentanyl, with a bioavailability of 89%, may even be able to enter the cerebrospinal fluid directly through the olfactory mucosa without having to cross the blood-brain barrier.[157] Finally, transdermal fentanyl has the highest bioavailability at 92%,[158] although there is some individual variation in all of these values.

Fentanyl is about 80% to 85% protein bound, primarily to albumin,[159] and has a V_d of approximately 1 to 4 L/kg.[155] It is metabolized in the liver by *N*-dealkylation to the inactive metabolite, norfentanyl, via the phase I enzyme CYP3A4 with additional contributions from CYP3A5 and CYP3A7.[155] This means that fentanyl seems less likely to be impacted by polymorphisms of the cytochrome P450 system; however, polymorphisms in CYP3A5 have led to increased serum concentrations of fentanyl[160] and alterations in the *ABCB1* gene encoding for P-gp can result in more CNS adverse effects in individuals with decreased function of P-gp.[155,161] Ultimately, the metabolic products of fentanyl are excreted in the urine.[155]

As a mu-receptor agonist, fentanyl is about 100 times more potent than morphine despite similar binding affinity in vitro. This is felt to be due to the lipophilicity of fentanyl and its ability to easily cross the blood-brain barrier.[162] Fentanyl's lipophilicity and ability to cross biologic membranes have permitted numerous formulations and applications for sedation and acute and chronic pain.

Fentanyl is one of the 10 most commonly used drugs in the NICU worldwide.[163] When used in combination with propofol for lumbar puncture in children with acute leukemia, it is associated with fewer adverse events and more rapid recovery than when propofol is used alone.[164] Fentanyl has been nebulized along with lidocaine as premedication for bronchoscopy in pediatric patients and was found to result in more stable hemodynamics and fewer intraprocedural respiratory difficulties, albeit with prolonged time to emerge compared to lidocaine alone or placebo.[165] Oral fentanyl has been suggested as a safe alternative to preoperative oral midazolam in children,[166] whereas oral *transmucosal* fentanyl caused mild pruritus, sedation, and preoperative emesis with no benefit in terms of separation,[167] although the episodes of emesis may have been a result of the amount of time between premedication and induction of anesthesia.[168]

In terms of pediatric pain management, fentanyl has found extensive applications from minor procedures to cardiac surgery and acute to chronic pain. Intranasal fentanyl has been shown to be more effective than placebo following bilateral myringotomy tube placement without an increase in adverse effects.[169] In the emergency department, it is effective in reducing pain from traumatic fracture within 10 minutes of administration allowing for more rapid analgesia despite lack of intravenous access.[170] At 25 mcg/kg intravenously, fentanyl is effective at reducing the stress response of open-heart surgery in infants and children.[171]

Transdermal fentanyl has been used to manage the pain of acute sickle cell crisis[172] and oral mucositis in pediatric patients undergoing stem cell transplant.[173] It has also been used as a convenient and well-tolerated alternative to oral morphine in patients with severe chronic pain from both malignant and nonmalignant diseases.[174,175]

One of the most concerning adverse effects of opioids is muscle rigidity, especially of the chest and respiratory muscles. There have been several reports of this phenomenon occurring in infants and children,[176] including an unusual report that occurred intraoperatively during maintenance of

general anesthesia.[177] It has also been reported in neonates at delivery following administration to the mother during cesarean section[178] and in a parturient requiring mechanical ventilation.[179] These varied episodes may resolve in a self-limited fashion or require supportive treatment with muscle relaxation and intubation or antagonism with naloxone.[176–179] Rarely, epinephrine has been required to treat severe bradycardia or asystole.[176]

Both **alfentanil** and **sufentanil** are synthetic derivatives of fentanyl[180] and are not commonly ingested, although alfentanil has been used orally in research as a probe for CYP3A activity[181] with a suggested oral bioavailability of 20% to 30% due to a combination of hepatic first-pass metabolism and intestinal activity of CYP3A4.[182] Nasal alfentanil has a reported average bioavailability of 65%.[183] These values compare to an oral bioavailability for sufentanil of 9%[184] and nasal bioavailability of 78%.[185] Sublingual and buccal bioavailability rates of sufentanil have also been investigated and found to be 59% and 78%, respectively.[184]

Alfentanil is bound to alpha-1-acid glycoprotein at a rate of approximately 92% leading to a smaller V_d than fentanyl.[186] Sufentanil is also highly protein bound with ranges of 88% to 92% in adults.[187,188] This value was more strongly correlated with alpha-1-acid glycoprotein levels across age groups likely explaining the observed protein binding in neonates of only 80%.[188] The V_d for sufentanil in pediatric patients has been reported to range from 1.3 to 4.1 L/kg.[189]

Alfentanil is metabolized in the liver via *N*-dealkylation at two different locations in its structure to form the inactive metabolites, noralfentanil and *N*-phenylpropionamide. These reactions are mediated by CYP3A4; however, there is considerable structural similarity between CYP3A4 and CYP3A5 such that CYP3A5 has been shown to be as active in alfentanil metabolism[190] leading to suggestions that the polymorphisms seen in CYP3A5 may help explain the interindividual variability in alfentanil clearance. However, when this question was examined, no difference in pharmacokinetic parameters based upon genotype was found[181] to the surprise of investigators.

Sufentanil is also metabolized into inactive metabolites primarily by CYP3A4, although the involvement of other cytochrome enzymes may be a possibility.[191] The metabolic byproducts of both drugs are excreted in the urine.[192,193]

Alfentanil is four times less potent than fentanyl but has a more rapid onset and shorter duration of action which is likely due to the fact that it is less ionized than fentanyl at physiologic pH.[180] These characteristics would suggest that it might have a role in procedures where rapid awakening would be beneficial. In cardiac bypass surgery, alfentanil allowed earlier tracheal extubation than fentanyl or sufentanil.[194] Alfentanil has been shown to be an effective sedative alone or in combination with midazolam for bone marrow aspiration in children.[195] When combined with propofol, alfentanil led to a greater incidence of respiratory depression compared to propofol and ketamine combined.[196]

Alfentanil has also been found to be effective in decreasing the pain upon injection of propofol,[197] reducing the movement associated with injection of rocuronium,[198,199] and decreasing the incidence of emergence agitation following sevoflurane anesthesia in children.[200] Its use in neonates without concomitant use of muscle relaxants is not recommended due to the high incidence of muscle rigidity impacting ventilation in this population.[201,202]

Sufentanil is 5 to 10 times more potent than fentanyl.[189] It has been used in pediatric cardiac surgery and is comparable to fentanyl in terms of hemodynamic effects[203] but should not be used as the sole anesthetic agent as a one-time bolus.[204] Sufentanil has been used intranasally alone[189] and in combination with ketamine[205] for premedication and for painful procedures in children. When added to caudal levobupivacaine, it is more effective in reducing the hemodynamic response to spermatic cord traction in orchidopexy than levobupivacaine alone,[206] and epidural sufentanil provides better postoperative analgesia after 24 hours than epidural fentanyl in pediatric urologic surgery.[207] When epidural ropivacaine and sufentanil infusion are used in infants, the plasma concentration of sufentanil increases throughout the duration of the infusion and continues to increase after the infusion is stopped, necessitating continued monitoring of vital signs for several hours following its cessation.[208]

Remifentanil is another synthetic opioid that has some unique properties. It is only available in injectable form and so does not possess a defined bioavailability, and although there has been one study utilizing nasal remifentanil to facilitate intubation in pediatric patients, the nasal bioavailability was not reported.[209] In that study, peak plasma concentrations were found to occur at 3 minutes and 47 seconds. Remifentanil is 92% protein bound, primarily to alpha-1-acid glycoprotein[210,211] and has a V_d that ranges from approximately 450 mL/kg in neonates to approximately 250 mL/kg in older

children and adolescents.[212]

The main factor that contributes to remifentanil's uniqueness among opioids is its chemical structure which contains an ester linkage allowing it to be metabolized by non-specific blood and tissue esterases.[213] Its metabolism is not impacted by pseudocholinesterase deficiency.[214] Over 80% of remifentanil undergoes ester hydrolysis to remifentanil acid (RA) which is excreted in the urine.[213,215] RA has been determined to be 4600 times less potent in dogs than the parent compound[216] and does not appear to alter the clinical effect of remifentanil infusion of up to 72 hours duration in patients with severe renal impairment.[215] Likewise, the pharmacokinetics of remifentanil and RA are not impacted in patients with severe hepatic impairment awaiting liver transplantation.[211]

Clinically, remifentanil has found broad application in pediatric anesthesia both in neonates and older children and adolescents. It has been used as an infusion for sedation in preterm neonates intubated for respiratory distress syndrome allowing for more rapid awakening and extubation compared to morphine infusion[217] or for laser surgery in neonates with retinopathy of prematurity.[218] It has also been used effectively for neurosurgical, thoracic, cardiovascular, and intraabdominal surgeries in neonates as well as to mitigate the stress response of endotracheal intubation in this population.[218] The simple fact that remifentanil possesses similar pharmacokinetics with rapid, non-organ dependent metabolism and a non-active metabolite across the age spectrum has allowed for its diversity of clinical uses.

Complicating the use of remifentanil in the perioperative period is the concern for the development of acute tolerance or opioid-induced hyperalgesia. While the exact mechanisms are unknown, these phenomena appear to be dose-related and may contribute to the development of persistent postsurgical pain.[219,220] Furthermore, concerns regarding tolerance and hyperalgesia may not be limited solely to remifentanil as demonstrated by a retrospective review comparing remifentanil and fentanyl for pediatric scoliosis surgery in which the fentanyl group had significantly higher pain scores and opioid usage in the immediate postoperative period.[221]

Meperidine, also known as pethidine, was the first synthetic opioid developed in 1939 as an anticholinergic[222,223] but was soon found to possess analgesic properties becoming widely used for pain for many years. It is available in oral and injectable forms, possessing an oral bioavailability of approximately 50% to 60%[224,225] which increases to 70% to 80% when given rectally[224] or in the presence of cirrhosis[225] due to the high first-pass metabolism. Meperidine is about 65% to 75% protein bound and has a volume of distribution of about 3.5 L/kg.[226]

Meperidine undergoes two main routes of metabolism in the liver. The primary route is via hydrolysis to meperidinic acid, an inactive metabolite.[223,226] It also undergoes *N*-demethylation to normeperidine, a reaction catalyzed by CYP2B6, CYP3A4, and CYP2C19.[222] Normeperidine is an active metabolite that possesses about half the analgesic effect of the parent drug but also has central excitatory and neurotoxic effects that can lead to anxiety, hyperreflexia, myoclonus, and seizures[223] as it accumulates due to its half-life being about seven times that of meperidine.[222] These metabolites are then excreted in the urine.[226]

Historically, meperidine was felt to cause fewer effects on smooth muscle, specifically the sphincter of Oddi, leading to its widespread use for pain associated with biliary colic and pancreatitis. Compared to other opioids at equianalgesic doses, this supposition has not proven to be true.[223] Meperidine has also been used extensively in sickle cell patients, for the treatment of migraines, and for rigors and shivering associated with certain drugs or following anesthesia; however, suitable and safer alternatives exist for all of these indications.[227]

Because of the ready availability of safer, more effective alternatives and the presence of serious neurotoxic effects of meperidine use, pediatric hospitals have begun to restrict its use,[228] and meperidine can no longer be recommended for use in the treatment of acute or chronic pain in pediatric patients.[229]

Methadone is a synthetic opioid with complex pharmacokinetics that shows a high degree of variability between individuals and within an individual over time. It is a chiral molecule administered as a racemic mixture with (*R*)-methadone being the active enantiomer.[230] It is available in oral and injectable formulations and has also been administered rectally, nasally, intramuscularly, subcutaneously, and epidurally.[230–232] An excellent review lists an oral bioavailability of 70% to 80% with a range in the literature of 36% to 100%,[230] while two studies comparing methods of administration found oral bioavailability of 85% to 86% with a rectal bioavailability of 76%[231] and a nasal bioavailability of 86%.[232] Methadone is highly bound to

plasma proteins, primarily alpha-1-acid glycoprotein (AAG), at 87% with a V_d of 4.0 L/kg.[230]

Methadone is metabolized in the liver into two main inactive metabolites which are excreted in the urine. It undergoes *N*-demethylation to 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and is also metabolized to 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP) by enzymes of the cytochrome P450 system.[230] There is some debate in the literature as to the role that each isoenzyme plays in the metabolism of methadone, but there are suggestions that CYP3A4, CYP3A7, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2D8 may be involved[230,233–235] leading to enantiomeric differences in metabolism. Furthermore, polymorphisms of the various cytochromes can add to the pharmacokinetic complexity of methadone.[236]

(*R*)-methadone is the enantiomer responsible for the typical opioid effects by acting on the mu-opioid receptor[236] with (*S*)-methadone being implicated in prolongation of the QT interval and the risk of sudden death from torsade de pointes.[237] Methadone also acts as a non-competitive antagonist of the *N*-methyl-d-aspartate (NMDA) receptor, much like ketamine, and may have a role in the management of chronic neuropathic pain and opioid-induced hyperalgesia.[238–241]

In pediatric patients, methadone serves as first-line treatment for neonatal abstinence syndrome which results from in utero exposure to opioids.[242] When compared to morphine, methadone has been found to result in lower pain scores and reduced supplemental opioid requirements for 36 hours following major surgery in 3- to 7-year-old children without adverse events.[243] It has been studied in adolescents undergoing posterior spinal fusion for scoliosis, but a single intraoperative dose was rapidly redistributed and did not maintain a therapeutic serum concentration into the postoperative period,[244] nor did it result in lower postoperative pain scores or lower opioid consumption.[245] However, when a single dose of methadone was added to a multimodal analgesia regimen for the Nuss procedure, it was found to be superior with lower postoperative opioid consumption and shorter length of stay compared to all other regimens including general anesthesia with epidural analgesia.[246] Methadone is also used in pediatric patients with malignant pain.[247]

Tramadol is a synthetic analogue of codeine that has two chiral centers and is available as a racemic mixture for oral, injectable, and rectal use.[248,249] Oral bioavailability has been reported at 65% to 70% due to first-pass metabolism.[249] Rectal bioavailability is reported at 77%.[250] Tramadol shows little protein binding at 20%[251] and has a V_d of 3.4 to 3.8 L/kg in pediatric patients.[252]

Tramadol can be considered a prodrug since one of its primary metabolites, (+)-*O*-desmethyltramadol (M1), is the major contributor to tramadol's pharmacologic mu-agonist effect. This reaction is catalyzed by CYP2D6[253] which, like codeine, is affected by the abundance of polymorphisms that exist impacting side-effect profile.

M1 is ultimately inactivated by glucuronidation via UGT2B7.[253] CYP2B6 and CYP3A4 form inactive metabolites through *N*-demethylation,[251] all of which are excreted in the urine. Tramadol has also been shown to inhibit serotonin and norepinephrine reuptake, possibly contributing to its analgesic effect.[249]

In pediatric patients, tramadol has been evaluated in multiple perioperative settings including neurosurgery, major abdominal surgery, and adenotonsillectomy.[254] It has been used as an adjunct in epidural blocks[255,256] for postoperative analgesia. Other applications have been peritonsillar infiltration for adenotonsillectomy,[257] prevention of pain from propofol injection,[258] sublingual usage for orthopedic trauma,[259] as well as an infusion for the treatment of sickle cell crisis.[260] It had been suggested that tramadol might fill the void in treating moderate pain that was created when codeine usage became restricted, but the experts rightly pointed out the similar pharmacokinetics between the two drugs and urged caution.[261] This caution was well founded in April 2017, the US FDA added a contraindication to the drug labels of codeine and tramadol stating that these two drugs should not be used for treating pain in children younger than 12 years of age and that tramadol should not be used to treat pain following adenotonsillectomy in any patient younger than 18.[111]

Butorphanol is a synthetic analogue of morphine that has mixed agonist-antagonist activity at the mu-receptor and agonist activity at the kappa-opioid receptor.[262] It undergoes extensive first-pass hepatic metabolism resulting in an oral bioavailability of 5% to 17%,[263] which increases to 70% when given transnasally. The serum protein binding is about 80%.[264] The V_d ranges from 466 to 637 L in adult humans.[265] Butorphanol is metabolized into the inactive hydroxybutorphanol and norbutorphanol, which are then conjugated with glucuronide along with the parent drug prior to excretion

in the urine.[266]

One of the potential benefits of butorphanol for use in moderate pain is the lack of dose-related respiratory depression.[266] Due to its effects on the kappa-receptor, sedation is also a prominent pharmacodynamic response.[262] In pediatric patients, butorphanol has compared favorably with midazolam for preoperative sedative effect with more sedation at the time of induction with less need for intraoperative and postoperative rescue analgesia.[267] It has been used intranasally for postoperative pain associated with myringotomy tube placement.[268,269] Butorphanol has been used as an adjunct in caudal analgesia and was found to prolong the duration of caudal bupivacaine[270] by almost 6 hours without an increase in side effects.[271] It has also been added to epidural morphine infusion to relieve pruritus.[272]

Ketamine

Ketamine is a derivative of phencyclidine, commonly known as PCP. It is a chiral molecule and is often utilized as a racemic mixture[273] that can be given orally, rectally, intranasally, and injected intravenously, intramuscularly, and into the epidural space. S(+) ketamine has four times the analgesic potency, but a shorter duration of action than the R(–) isomer.[273]

Due to extensive first-pass hepatic metabolism, oral and rectal bioavailability are only 17–20% and 25%, respectively.[273,274] Bioavailability by the nasal route is 50%, whereas IM administration results in a high bioavailability of 93%.[274] There is a range of values (10–60%) reported for protein binding of ketamine depending upon the patient group studied. Since ketamine has a much greater affinity for AAG, which is increased under physiologically stressful conditions, this may explain the disparity of results.[275] The V_d of ketamine is 2.3 L/kg.[274]

In the liver, most ketamine undergoes *N*-demethylation to norketamine, which has about 20% to 30% of the analgesic activity of the parent compound.[274] There is some disagreement in the literature as to whether this occurs primarily via CYP2B6, CYP3A4, or one of the other isoenzymes;[273] however, a recent study found no changes in single-dose ketamine pharmacokinetics associated with CYP2B6 polymorphisms,[276] which would suggest the potential involvement of several enzymes for its metabolism. A small amount of ketamine is hydroxylated in other tissues, such as the intestine, kidney, and lungs. These metabolites are then conjugated with glucuronide and excreted in the urine.[274]

Ketamine exerts its pharmacodynamic effects primarily via noncompetitive antagonism at the NMDA receptor in the CNS. It likely exerts some influence on opioid receptors, either directly or indirectly via the release of endogenous substances.[273] Ketamine's unique qualities result in "dissociative anesthesia," during which the eyes remain open, often with nystagmus, and laryngeal and corneal reflexes remain intact.[274] Patients often maintain spontaneous respirations, although apnea can occur if ketamine is given rapidly intravenously.[277] Ketamine increases systemic vascular resistance and cardiac output.[278] It is a strong bronchodilator and has been efficacious in the treatment of status asthmaticus.[273] Adverse effects include emergence delirium and hallucinations, the incidence of which may be decreased by concomitant use of midazolam.[273] It is also a sialagogue and is emetogenic especially when given intramuscularly.[277]

In pediatric patients, ketamine has found a wide range of applications across all age groups because it can provide for amnesia as well as analgesia. It has been used for induction of anesthesia in congenital cardiac surgery and as the sole anesthetic agent in burns.[278] It is also used for procedural sedation in the emergency department and other intrahospital settings.[277] Ketamine has been used alone or as an adjunct with local anesthetics in caudal analgesia.[278]

Recently, concern has been raised regarding the use of ketamine in pediatric patients, especially in neonates, since ketamine has been shown to have a role in apoptosis in developing brains in various animal models.[279,280] However, ketamine has also been shown to reduce cell death in an experimental inflammatory pain model in the neonatal rat.[281] An excellent summary of this research has been published and is left for the reader to review.[280]

CONCLUSION

The pendulum has swung from a time when neonates were not believed to experience pain to an understanding that pain can have profound physiologic consequences and developmental sequelae. However, the many analgesics that are currently being used in pediatric patients can have

their own distinct pharmacokinetics in preterm neonates, infants, children, and adolescents as the various organ systems undergo the maturational process. Furthermore, genetic influences can produce profound differences in the pharmacology of the drugs that pediatric anesthesiologists use daily, making the pharmacology of analgesics a rapidly changing topic requiring further research and investigation.

REFERENCES

1. Allagaert K, van de Velde M, van den Anker J. Neonatal clinical pharmacology. *Pediatr Anesth.* 2014;24:30–38.

2. Anderson BJ, Allagaert K. The pharmacology of anaesthetics in the neonate. *Best Pract Res Clin Anaesthesiol.* 2010;24:419–431. [PubMed: 21033017]

3. Kearns GL, Artman M. Functional biomarkers: an approach to bridge pharmacokinetics and pharmacodynamics in pediatric clinical trials. *Curr Pharmaceut Des.* 2015;21:5636–5642.

4. Anderson GD. Developmental pharmacokinetics. *Sem Pediatr Neurol.* 2010;17:208–213.

5. van den Anker JN. Developmental pharmacology. *Develop Disab Res Rev.* 2010;16:233–238.

6. Anderson GD, Lynn AM. Optimizing pediatric dosing: a developmental pharmacologic approach. *Pharmacotherapy*. 2009;29:680–690. [PubMed: 19476420]

7. Funk RS, Brown JT, Abdel-Rahman SM. Pediatric pharmacokinetics: human development and drug disposition. *Pediatr Clin N Am.* 2012;59:1001–1016.

8. Heimann G. Enteral absorption and bioavailability in children in relation to age. *Eur J Clin Pharmacol.* 1980;18:43–50. [PubMed: 7398747]

9. Berseth CL. Gestational evolution of small intestine motility in preterm and term infants. *J Pediatr.* 1989;115:646–651. [PubMed: 2507768]

10. de Wildt SN, Kearns GL, Leeder JS et al. Cytochrome P450 3A: ontogeny and drug disposition. *Clin Pharmacokinet.* 1999;37:485–505. [PubMed: 10628899]

11. Fakhoury M, Litalien C, Medard Y et al. Localization and mRNA expression of CYP3A and P-glycoprotein in human duodenum as a function of age. *Drug Metab Dispos.* 2005;33:1603–1607. [PubMed: 16049125]

12. Wester RC, Maibach HI. Cutaneous pharmacokinetics: 10 steps to percutaneous absorption. *Drug Metab Rev.* 1983;14:169–205. [PubMed: 6341024]

13. West DP, Halket JM, Harvey DR et al. Percutaneous absorption in preterm infants. *Pediatr Dermatol.* 1987;4:234–237. [PubMed: 3422856]

14. Carry MR, Ringel SP, Starcevich JM. Distribution of capillaries in normal and diseased human skeletal muscle. *Muscle Nerve*. 1986;9:445–454. [PubMed: 2941685]

15. Wood M, Wood AJJ. Changes in plasma drug binding and alpha-1-acid glycoprotein in mother and newborn infant. *Clin Pharmacol Therapeut.* 1981;29:522–526.

16. Sethi PK, White CA, Cummings BS et al. Ontogeny of plasma proteins, albumin and binding of diazepam, cyclosporine, and deltamethrin. *Pediatr Res.* 2016;79:409–415. [PubMed: 26571224]

17. Starkey ES, Sammons HM. Practical pharmacokinetics: what do you really need to know? *Arch Dis Childhood-E.* 2015;100:37–43.

18. Hines RN, McCarver DG. The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J Pharmacol Exp Ther.* 2002;300:355–360. [PubMed: 11805191]

19. McCarver DG, Hines RN. The ontogeny of human drug-metabolizing enzymes: phase II conjugation enzymes and regulatory mechanisms. *J Pharmacol Exp Ther.* 2002;300:361–366. [PubMed: 11805192]

20. Chen N, Aleksa K, Woodland C et al. Ontogeny of drug elimination by the human kidney. *Pediatr Nephrol.* 2006;21:160–168. [PubMed: 16331517]

21. Raffa RB, Pergolizzi JV Jr, Taylor R Jr et al. Acetaminophen (paracetamol) oral absorption and clinical influences. *Pain Pract.* 2014;14:668–677. [PubMed: 26013309]

22. Ji P, Wang Y, Li Z et al. Regulatory review of acetaminophen clinical pharmacology in young pediatric patients. *J Pharmaceut Sci.* 2012;101:4383–4389.

23. Singla NK, Parulan C, Samson R et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. *Pain Pract.* 2012;12:523–532. [PubMed: 22524979]

24. van Lingen RA, Deinum HT, Quak CME et al. Multiple-dose pharmacokinetics of rectally administered acetaminophen in term infants. *Clin Pharmacol Therap.* 1999;66:509–515.

25. Allegaert K, Vanhaesebrouck S, Verbesselt R et al. In vivo glucuronidation activity of drugs in neonates: extensive interindividual variability despite their young age. *Therap Drug Monitor*. 2009;31:411–415.

26. Martin LD, Jimenez N, Lynn AM. A review of perioperative anesthesia and analgesia for infants: updates and trends to watch. *F1000Research*. 2017;6:120. [PubMed: 28232869]

27. Porta R, Sanchez L, Nicolas M et al. Lack of toxicity after paracetamol overdose in an extremely preterm neonate. *Eur J Clin Pharmacol.* 2012;68:901–902. [PubMed: 22227961]

28. Nevin DG, Shung J. Intravenous paracetamol overdose in a preterm infant during anesthesia. *Pediatr Anesth.* 2009;20:105–114.

29. Isbister GK, Bucens IK, Whyte IM. Paracetamol overdose in a preterm neonate. *Arch Dis Childhood-F.* 2001;85:70–72.

30. de la Pintiere A, Betremieux PE. Intravenous paracetamol overdose in a term newborn. *Arch Dis Childhood-F.* 2003;88:351–352.

31. van der Marel CD, Anderson BJ, van Lingen RA et al. Paracetamol and metabolite pharmacokinetics in infants. *Eur J Clin Pharmacol.* 2003;59:243–251. [PubMed: 12761605]

32. Morris ME, Levy G. Renal clearance and serum protein binding of acetaminophen and its major conjugates in humans. *J Pharmaceut Sci.* 1984;73:1038–1041.

33. Palmer GM, Atkins M, Anderson BJ et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth.* 2008;101:523–530. [PubMed: 18628265]

34. Toussaint K, Yang XC, Zielinski MA et al. What do we (not) know about how paracetamol (acetaminophen) works? *J Clin Pharm Therapeut.* 2010;35:617–638.

35. Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. *Arch Dis Childhood*. 2008;93:241–247.

36. Hahn TW, Mogensen T, Lund C et al. Analgesic effect of iv paracetamol: possible ceiling effect of paracetamol in postoperative pain. *Acta Anaesthesiol Scand.* 2003;47:138–145. [PubMed: 12631041]

37. Ceelie I, de Wildt SN, van Dijk M et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants

undergoing major noncardiac surgery. *J Am Med Assoc.* 2013;309:149–154.

38. Subramanyam R, Varughese A, Kurth CD et al. Cost-effectiveness of intravenous acetaminophen for pediatric tonsillectomy. *Pediatr Anesth.* 2014;24:467–475.

39. Nour C, Ratsiu J, Singh N et al. Analgesic effectiveness of acetaminophen for primary cleft palate repair in young children: a randomized placebo-controlled trial. *Pediatr Anesth.* 2014;24:574–581.

40. van der Marel CD, Peters JWB, Bouwmeester NJ et al. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *Br J Anaesth.* 2007;98:372–379. [PubMed: 17284514]

41. Bremerich DH, Neidhart G, Heimann K et al. Prophylactically-administered rectal acetaminophen does not reduce postoperative opioid requirements in infants and small children undergoing elective cleft palate repair. *Anesth Analg.* 2001;92:907–912. [PubMed: 11273923]

42. Anderson B, Kanagasundarum S, Woollard G. Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care*. 1996;24:669–673. [PubMed: 8971314]

43. Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. *Anesthesiology*. 1999;91:442–447. [PubMed: 10443608]

44. Gandhi R, Sunder R. Postoperative analgesic efficacy of single high dose and low dose rectal acetaminophen in pediatric ophthalmic surgery. *J Anaesthesiol Clin Pharmacol.* 2012;28:460–464. [PubMed: 23225924]

45. OFIRMEV [package insert]. Hazelwood, MO: Mallinckrodt Hospital Products; 2017.

46. Veyckemans F, Anderson BJ, Wolf AR et al. Intravenous paracetamol dosage in the neonate and small infant [Letter to the Editor]. *Br J Anaesth.* 2014;112:380–381. [PubMed: 24431352]

47. de Martino M, Chiarugi A. Recent advances in pediatric use of oral paracetamol in fever and pain management. *Pain Ther.* 2015;4:149–168. [PubMed: 26518691]

48. Birmingham PK, Tobin MJ, Fisher DM et al. Initial and subsequent dosing of rectal acetaminophen in children: a 24-hour pharmacokinetic study of new dose recommendations. *Anesthesiology*. 2001;94:385–389. [PubMed: 11374595]

49. Hall SM. Reye's syndrome and aspirin: a review. *J R Soc Med.* 1986;79:596–598. [PubMed: 3537289]

50. Domanska U, Pobudkowska A, Pelczarska A et al. pK_a and solubility of drugs in water, ethanol, and 1-octanol. *J Phys Chem B.* 2009;113:8941–8947. [PubMed: 19518053]

51. Rencber S, Karavana SY, Ozyazici M. Bioavailability file: ketoprofen. *FABAD J Pharmaceut Sci.* 2009;34:203–216.

52. Li X, Cooper MA. Measurement of drug lipophilicity and pK_a using acoustics. *Analyt Chem.* 2012;84:2609–2613.

53. Davies NM. Clinical pharmacokinetics of ibuprofen: the first 30 years. *Clin Pharmacokinet.* 1998;34:101–154. [PubMed: 9515184]

54. Leung GJ, Rainsford KD, Kean WF. Osteoarthritis of the hand II: chemistry, pharmacokinetics and pharmacodynamics of naproxen, and clinical outcome studies. *J Pharm Pharmacol.* 2013;66:347–357. [PubMed: 24175972]

55. Dewland PM, Reader S, Berry P. Bioavailability of ibuprofen following oral administration of standard ibuprofen, sodium ibuprofen or ibuprofen acid incorporating poloxamer in healthy volunteers. *BMC Clin Pharmacol.* 2009;9:19–28. [PubMed: 19961574]

56. Barzilay B, Youngster I, Batash D et al. Pharmacokinetics of oral ibuprofen for patent ductus arteriosus closure in preterm infants. *Arch Dis Childhood-F.* 2012;97:F116–F119.

57. Sharma PK, Garg SK, Narang A. Pharmacokinetics of oral ibuprofen in premature infants. *J Clin Pharmacol.* 2003;43:968–973. [PubMed: 12971028]

58. Han EE, Beringer PM, Louie SG et al. Pharmacokinetics of ibuprofen in children with cystic fibrosis. *Clin Pharmacokinet.* 2004;43:145–156. [PubMed: 14871154]

59. Valitalo P, Kumpulainen E, Manner M et al. Plasma and cerebrospinal fluid pharmacokinetics of naproxen in children. *J Clin Pharmacol.* 2012;52:1516–1526. [PubMed: 22067196]

60. Nguyen LA, He H, Pham-Huy C. Chiral drugs: an overview. *Int J Biomed Sci.* 2006;2:85–100. [PubMed: 23674971]

61. Khan SJ, Wang L, Hashim NH et al. Distinct enantiomeric signals of ibuprofen and naproxen in treated wastewater and sewer overflow. *Chirality*. 2014;26:739–746. [PubMed: 25513681]

62. Gregoire N, Gualano V, Geneteau A et al. Population pharmacokinetics of ibuprofen enantiomers in very premature neonates. *J Clin Pharmacol.* 2004;44:1114–1124. [PubMed: 15342612]

63. Rodrigues AD. Impact of *CYP2C9* genotype on pharmacokinetics: are all cyclooxygenase inhibitors the same? *Drug Metab Dispos.* 2005;33:1567–1575. [PubMed: 16118328]

64. Pacifici GM. Clinical pharmacology of ibuprofen in preterm infants: a meta-analysis of published data. *Med Exp.* 2014;1:55–61.

65. Kuehl GE, Lampe JW, Potter JD et al. Glucuronidation of nonsteroidal anti-inflammatory drugs: identifying the enzymes responsible in human liver microsomes. *Drug Metab Dispos.* 2005;33:1027–1035. [PubMed: 15843492]

66. Vree TB, van den Biggelaar-Martea M, Verwey-van Wissen CPWGM et al. The pharmacokinetics of naproxen, its metabolite *O*-desmethylnaproxen, and their acyl glucuronides in humans. Effect of cimetidine. *Br J Clin Pharmacol.* 1993;35:467–472. [PubMed: 8512758]

67. Morris JL, Rosen DA, Rosen KR. Nonsteroidal anti-inflammatory agents in neonates. *Pediatric Drugs*. 2003;5:385–405. [PubMed: 12765488]

68. Olson DM, Mijovic JE, Zaragoza DB et al. Prostaglandin endoperoxide H synthase type 1 and type 2 messenger ribonucleic acid in human fetal tissues throughout gestation and in the newborn infant. *Am J Obstetr Gynecol.* 2001;184:169–174.

69. Mehlisch DR, Sykes J. Ibuprofen blood plasma levels and onset of analgesia. *Int J Clin Pract.* 2013;67(suppl 178):3–8.

70. Moss JR, Watcha MF, Bendel LP et al. A multicenter, randomized, double-blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy. *Pediatr Anesth.* 2014;24:483–489.

71. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *Ann PharmacoTher.* 2010;44:489–506. [PubMed: 20150507]

72. Erdeve O, Sarici SU, Sari E et al. Oral-ibuprofen-induced acute renal failure in a preterm infant. *Pediatr Nephrol.* 2008;23:1565–1567. [PubMed: 18446376]

73. Tatli MM, Kumral A, Duman N et al. Spontaneous intestinal perforation after oral ibuprofen treatment of patent ductus arteriosus in two very-low-birthweight infants. *Acta Paediatr.* 2004;93:999–1001. [PubMed: 15303820]

74. Kokki H. Ketoprofen pharmacokinetics, efficacy, and tolerability in pediatric patients. *Pediatr Drugs*. 2010;12:313–329.

75. Lucas S. The pharmacology of indomethacin. *Headache*. 2016;56:436–446. [PubMed: 26865183]

76. Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. *Eur J Clin Pharmacol.* 1988;35:423–425. [PubMed: 3264245]

77. Al Za'abi M, Donovan T, Tudehope D et al. Orogastric and intravenous indomethacin administration to very premature neonates with patent ductus arteriosus: population pharmacokinetics, absolute bioavailability, and treatment outcome. *Therapeut Drug Monitor*. 2007;29:807–814.

78. Alqahtani S, Kaddoumi A. Development of physiologically based pharmacokinetic/pharmacodynamic model for indomethacin disposition in pregnancy. *PLOS One*. 2015;10:e0139762.

79. Olkkola KT, Maunuksela EL, Korpela R. Pharmacokinetics of postoperative intravenous indomethacin in children. *Pharmacol Toxicol.* 1989;65:157–160. [PubMed: 2813287]

80. Kauffman RE, Lieh-Lai MW, Uy HG et al. Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children. *Clin Pharmacol Therapeut.* 1999;65:382–388.

81. Lynn AM, Bradford H, Kantor ED et al. Ketorolac tromethamine: stereo-specific pharmacokinetics and single-dose use in postoperative infants aged 2-6 months. *Pediatr Anesth.* 2011;21:325–334.

82. Sallmon H, Keohne P, Hansmann G. Recent advances in the treatment of preterm newborn infants with patent ductus arteriosus. *Clin Perinatol.* 2016;43:113–129. [PubMed: 26876125]

83. Watcha MF, Jones MB, Lagueruela RG et al. Comparison of ketorolac and morphine as adjuvants during pediatric surgery. *Anesthesiology*. 1992;76:368–372. [PubMed: 1539847]

84. Jo YY, Hong JY, Choi EK et al. Ketorolac or fentanyl continuous infusion for post-operative analgesia in children undergoing ureteroneocystostomy. *Acta Anaesthesiol Scand.* 2011;55:54–59. [PubMed: 21083540]

85. Moffett BS, Wann TI, Carberry KE et al. Safety of ketorolac in neonates and infants after cardiac surgery. *Pediatr Anesthes.* 2006;16:424–428.

86. Cheng HF, Harris RC. Renal effects of non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors. *Curr Pharmaceut Design*. 2005;11:1795–1804.

87. Feldman HI, Kinman JL, Berlin JA et al. Parenteral ketorolac: the risk for acute renal failure. *Ann Intern Med.* 1997;126:193–199. [PubMed: 9027269]

88. Vuolteenaho K, Moilanen T, Moilanen E. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. *Basic Clin Pharmacol.* 2007;102:10–14.

89. Kay RM, Leathers M, Directo MP et al. Perioperative ketorolac use in children undergoing lower extremity osteotomies. *J Pediatr Orthopaed.* 2011;31:783–786.

90. Sucato DJ, Lovejoy JF, Agrawal S et al. Postoperative ketorolac does not predispose to pseudoarthrosis following posterior spinal fusion and instrumentation for adolescent idiopathic scoliosis. *Spine*. 2008;33:1119–1124. [PubMed: 18449047]

91. Singer AJ, Mynster CJ, McMahon BJ. The effect of IM ketorolac tromethamine on bleeding time: a prospective, interventional, controlled study. *Am J Emerg Med.* 2003;21:441–443. [PubMed: 14523887]

92. Chan DK, Parikh SR. Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children. *Laryngoscope*. 2014;124:1789–1793. [PubMed: 24338331]

93. Richardson MD, Palmeri NO, Williams SA et al. Routine perioperative ketorolac administration is not associated with hemorrhage in pediatric neurosurgery patients. *J Neuros-Pediatr.* 2016;17:107–115.

94. Shi S, Klotz U. Clinical use and pharmacological properties of selective COX-2 inhibitors. *Eur J Clin Pharmacol.* 2008;64:233–252. [PubMed: 17999057]

95. Rudd RA, Seth P, David F et al. Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. *Morbid Mortal W.* 2016;65:1445–1452.

96. Wilcox RA, Owen H. Variable cytochrome P450 2D6 expression and metabolism of codeine and other opioid prodrugs: implications for the Australian anaesthetist. *Anaesth Intensive Care*. 2000;28:611–619. [PubMed: 11153286]

97. Tobias JD. Weak analgesics and nonsteroidal anti-inflammatory agents in the management of children with acute pain. *Pediatr Clin N Am.* 2000;47:527–543.

98. Lugo RA, Kern SE. Clinical pharmacokinetics of morphine. *J Pain Palliat Care PharmacoTher.* 2002;16:5–18. [PubMed: 14635822]

99. Masood AR, Thomas SHL. Systemic absorption of nebulized morphine compared with oral morphine in healthy subjects. *Br J Clin Pharmacol.* 1996;41:250–252. [PubMed: 8866928]

100. Kharasch ED, Hoffer C, Whittington D. Role of P-glycoprotein in the intestinal absorption and clinical effects of morphine. *Clin Pharmacol Therapeut.* 2003;74:543–554.

101. Mohammed SS, Christopher MM, Mehta P et al. Increased erythrocyte and protein binding of codeine in patients with sickle cell disease. *J Pharmaceut Sci.* 1993;82:1112–1117.

102. Poulsen L, Brosen K, Arendt-Nielsen L et al. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. *Eur J Clin Pharmacol.* 1996;51:289–295. [PubMed: 9010701]

103. Zahari Z, Ismail R. Influence of cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) polymorphisms on pain sensitivity and clinical response to weak opioid analgesics. *Drug Metab Pharmacokinet.* 2014;29:29–43. [PubMed: 23759977]

104. Kirchheiner J, Schmidt H, Tzvetkov M et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenom J.* 2007;7:257–265.

105. Linares OA, Fudin J, Schiesser WE et al. CYP2D6 phenotype-specific codeine population pharmacokinetics. *J Pain Palliat Care PharmacoTher.* 2015;29:4–15. [PubMed: 25562725]

106. Leppert W. CYP2D6 in the metabolism of opioids for mild to moderate pain. *Pharmacology*. 2011;87:274–285. [PubMed: 21494059]

107. Vree TB, van Dongen RTM, Koopman-Kimenai PM. Codeine analgesia is due to codeine-6-glucuronide, not morphine. *Int J Clin Pract.* 2000;54:395–398. [PubMed: 11092114]

108. Ciszkowski C, Madadi P. Codeine, ultrarapid-metabolism genotype, and postoperative death [Letter to the Editor]. *New Engl J Med.* 2009;361:827–828.

109. Kelly LE, Rieder M, van den Anker J et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics*. 2012;129:e1343–e1347. [PubMed: 22492761]

110. Subramanyam R, Varughese A, Willging JP et al. Future of pediatric tonsillectomy and perioperative outcomes. *Int J Pediatr Otorhinolaryngol.* 2013;77:194–199. [PubMed: 23159321]

111. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Available at https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed February 5, 2017.

112. Koren G, Cairns J, Chitayat D et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368:704. [PubMed: 16920476]

113. Stone AN, Mackenzie PI, Galetin A et al. Isoform selectivity and kinetics of morphine 3- and 6-glucuronidation by human UDP-glucuronosyltransferases: evidence for atypical glucuronidation kinetics by UGT2B7. *Drug Metab Dispos.* 2003;31:1086–1089. [PubMed: 12920162]

114. De Gregori M, Garbin G, De Gregori S et al. Genetic variability at *COMT* but not at *OPRM1* and *UGT2B7* loci modulates morphine analgesic response in acute postoperative pain. *Eur J Clin Pharmacol.* 2013;69:1651–1658. [PubMed: 23686330]

115. Bastami S, Gupta A, Zackrisson AL et al. Influence of *UGT2B7*, *OPRM1* and *ABCB1* gene polymorphisms on postoperative morphine consumption. *Basic Clin Pharmacol.* 2014;115:423–431.

116. Matic M, Norman E, Rane A et al. Effect of UGT2B7 -900G>A (-842G>A; rs7438135) on morphine glucuronidation in preterm newborns: results from a pilot cohort. *Pharmacogenomics*. 2014;15:1589–1597. [PubMed: 25340733]

117. Mazoit JX, Butscher K, Samii K. Morphine in postoperative patients: pharmacokinetics and pharmacodynamics of metabolites. *Anesth Analg.* 2007;105:70–78. [PubMed: 17578959]

118. Stein C. Opioid receptors. *Ann Rev Med.* 2016;67:433–451.

119. Basbaum AI, Bautista DM, Scherrer G et al. Cellular and molecular mechanisms of pain. *Cell*. 2009;139:267–284. [PubMed: 19837031]

120. Lam J, Baello S, Iqbal M et al. The ontogeny of P-glycoprotein in the developing human blood-brain barrier: implication for opioid toxicity in neonates. *Pediatr Res.* 2015;78:417–421. [PubMed: 26086643]

121. Sadhasivam S, Chidambaran V. Pharmacogenomics of opioids and perioperative pain management. *Pharmacogenomics*. 2012;13:1719–1740. [PubMed: 23171337]

122. Janicki PK, Schuler G, Francis D et al. A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. *Anesth Analg.* 2006;103:1011–1017. [PubMed: 17000822]

123. Chidambaran V, Mavi J, Esslinger H et al. Association of *OPRM1* A118G variant with risk of morphine-induced respiratory depression following spine fusion in adolescents. *Pharmacogenom J.* 2015;15:255–262.

124. Tsai FF, Fan SZ, Yang YM et al. Human opioid mu-receptor A118G polymorphism may protect against central pruritus by epidural morphine for post-cesarean analgesia. *Acta Anaesthesiol Scand.* 2010;54:1265–1269. [PubMed: 21039348]

125. Anand KJS, Phil D, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. *New Engl J Med.* 1992;326:1–9.

126. Quinn MW, Otoo F, Rushforth JA et al. Effect of morphine and pancuronium on the stress response in ventilated preterm infants. *Early Hum Dev.* 1992;30:241–248. [PubMed: 1468386]

127. Quinn MW, Wild J, Dean HG et al. Randomized double-blind controlled trial of effect of morphine on catecholamine concentrations in ventilated pre-term babies. *Lancet*. 1993;342:324–327. [PubMed: 8101584]

128. AAP Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine. Prevention and management of procedural pain in the

neonate: an update. *Pediatrics*. 2016;137:e20154271.

129. Ferguson SA, Ward WL, Paule MG et al. A pilot study of preemptive morphine analgesia in preterm neonates: effects on head circumference, social behavior, and response latencies in early childhood. *Neurotoxicol Teratol.* 2012;34:47–55. [PubMed: 22094261]

130. de Graf J, van Lingen RA, Valkenburg AJ et al. Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age? *Pain*. 2013;154:449–458. [PubMed: 23352760]

131. Duedahl TH, Hansen EH. A qualitative systematic review of morphine treatment in children with postoperative pain. *Pediatr Anesth.* 2007;17:756–774.

132. Joshi GP, McCarroll SM, O'Brien TM et al. Intraarticular analgesia following knee arthroscopy. *Anesthes Analg.* 1993;76:333–336.

133. Melhem MR, Rubino CM, Farr SJ et al. Population pharmacokinetic analysis for hydrocodone following the administration of hydrocodone bitartrate extended-release capsules. *Clin Pharmacokinet.* 2013;52:907–917. [PubMed: 23719682]

134. Liu W, Dutta S, Kearns G et al. Pharmacokinetics of hydrocodone/acetaminophen combination product in children ages 6-17 with moderate to moderately severe postoperative pain. *J Clin Pharmacol.* 2015;55:204–211. [PubMed: 25196888]

135. Lugo RA, Kern SE. The pharmacokinetics of oxycodone. *J Pain Palliat Care PharmacoTher.* 2004;18:17–30. [PubMed: 15760805]

136. Sarhill N, Walsh D, Nelson KA. Hydromorphone: pharmacology and clinical applications in cancer patients. *Supp Care Canc.* 2001;9:84–96.

137. Jeleazcov C, Saari TI, Ihmsen H et al. Population pharmacokinetic modeling of hydromorphone in cardiac surgery patients during postoperative pain therapy. *Anesthesiology*. 2014;120:378–391. [PubMed: 23958818]

138. Cone EJ, Heltsley R, Black DL et al. Prescription opioids. II. Metabolism and excretion patterns of hydrocodone in urine following controlled single-dose administration. *J Analyt Toxicol.* 2013;37:486–494.

139. Navani DM, Yoburn BC. In vivo activity of norhydrocodone: an active metabolite of hydrocodone. *J Pharmacol Exp Therapeut.* 2013;347:497–505.

140. Linares OA, Fudin J, Daly AL et al. Individualized hydrocodone therapy based on phenotype, pharmacogenetics, and pharmacokinetic dosing. *Clin J Pain*. 2015;31:1026–1035. [PubMed: 25621429]

141. de Leon J, Dinsmore L, Wedlund P. Adverse drug reactions to oxycodone and hydrocodone in CYP2D6 ultrarapid metabolizers [Letter to the Editor]. *J Clin PsychoPharmacol.* 2003;23:420–421. [PubMed: 12920424]

142. Madadi P, Hildebrandt D, Gong IY et al. Fatal hydrocodone overdose in a child: pharmacogenetics and drug interactions. *Pediatrics*. 2010;126:e986–e989. [PubMed: 20837591]

143. Poyhia R, Vainio A, Kalso E. A review of oxycodone's clinical pharmacokinetics and pharmacodynamics. *J Pain Sympt Manag.* 1993;8:63–67.

144. Zwisler ST, Enggaard TP, Mikkelsen S et al. Impact of the CYP2D6 genotype on post-operative intravenous oxycodone analgesia. *Acta Anaesthesiol Scand.* 2010;54:232–240. [PubMed: 19719813]

145. Andreassen TN, Eftedal I, Klepstad P et al. Do *CYP2D6* genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study. *Eur J Clin Pharmacol.* 2012;68:55–64. [PubMed: 21735164]

146. Toyama K, Uchida N, Ishizuka H et al. Single-dose evaluation of safety, tolerability and pharmacokinetics of newly formulated hydromorphone immediate-release and hydrophilic matrix extended-release tablets in healthy Japanese subjects without co-administration of an opioid antagonist. *J Clin Pharmacol.* 2015;55:975–984. [PubMed: 25807927]

147. Mazer-Amirshahi M, Mullins PM, Rasooly IR et al. Trends in prescription opioid use in pediatric emergency department patients. *Pediatr Emerg Care*. 2014;30:230–235. [PubMed: 24651218]

148. Lasky T, Ernst FR, Greenspan J. Use of analgesic, anesthetic, and sedative medications during pediatric hospitalizations in the United States 2008. *Anesth Analg.* 2012;115:1155–1161. [PubMed: 22575570]

149. George JA, Park PS, Hunsberger J et al. An analysis of 34,218 pediatric outpatient controlled substance prescriptions. *Anesth Analg.* 2016;122:807–813. [PubMed: 26579844]

150. Sadhasivam S, Myer CM III. Preventing opioid-related deaths in children undergoing surgery [Letter to the Editor]. *Pain Med.* 2012;13:982–983. [PubMed: 22694279]

151. Reiter PD, Ng J, Dobyns EL. Continuous hydromorphone for pain and sedation in mechanically ventilated infants and children. *J Op Manag.* 2012;8:99–104.

152. Hong R, Gauger V, Caird MS et al. Narcotic-only epidural infusion for posterior spinal fusion patients: a single-center, retrospective review. *J Pediatr Orthopaed.* 2016;36:526–529.

153. Gauger VT, Voepel-Lewis TD, Burke CN et al. Epidural analgesia compared with intravenous analgesia after pediatric posterior spinal fusion. *J Pediatr Orthopaed.* 2009;29:588–593.

154. Goodarzi M. Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. *Paediatr Anaesth.* 1999;9:419–422. [PubMed: 10447905]

155. Lotsch J, Walter C, Parnham MJ et al. Pharmacokinetics of non-intravenous formulations of fentanyl. *Clin Pharmacokinet.* 2013;52:23–36. [PubMed: 23100195]

156. Darwish M, Kirby M, Robertson P Jr et al. Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol.* 2007;47:343–350. [PubMed: 17322146]

157. Panagiotou I, Mystakidou K. Intranasal fentanyl: from pharmacokinetics and bioavailability to current treatment applications. *Exp Rev Anticanc Ther.* 2010;10:1009–1021.

158. Varvel JR, Shafer SL, Hwang SS et al. Absorption characteristics of transdermally administered fentanyl. *Anesthesiology*. 1989;70:928–934. [PubMed: 2729633]

159. Bista SR, Haywood A, Hardy J et al. Protein binding of fentanyl and its metabolite nor-fentanyl in human plasma, albumin and alpha-1 acid glycoprotein. *Xenobiotica.* 2015;45:207–212. [PubMed: 25314012]

160. Takashina Y, Naito T, Mino Y et al. Impact of CYP3A5 and ABCB1 gene polymorphisms on fentanyl pharmacokinetics and clinical responses in cancer patients undergoing conversion to a transdermal system. *Drug Metab Pharmacokinet.* 2012;27:414–421. [PubMed: 22277678]

161. Park H-J, Shinn HK, Ryu SH et al. Genetic polymorphisms in the *ABCB1* gene and the effects of fentanyl in Koreans. *Clin Pharmacol Therapeut.* 2007;81:539–546.

162. Volpe DA, McMahon Tobin GA, Mellon RD et al. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. *Regul Toxicol Pharmacol.* 2011;59:385–390. [PubMed: 21215785]

163. Krzyzaniak N, Pawlowska I, Bajorek B. Review of drug utilization patterns in NICUs worldwide. *J Clin Pharm Therapeut.* 2016;41:612–620.

164. Cechvala MM, Christenson D, Eickhoff JC et al. Sedative preference of families for lumbar punctures in children with acute leukemia: propofol

alone or propofol and fentanyl. *J Pediatr Hematol Oncol.* 2008;30:142–147. [PubMed: 18376267]

165. Moustafa MA. Nebulized lidocaine alone or combined with fentanyl as a premedication to general anesthesia in spontaneously breathing pediatric patients undergoing rigid bronchoscopy. *Pediatr Anesth.* 2013;23:429–434.

166. Tamura M, Nakamura K, Kitamura R et al. Oral premedication with fentanyl may be a safe and effective alternative to oral midazolam. *Eur J Anesth.* 2003;20:482–486.

167. Epstein RH, Mendel HG, Witkowski TA et al. The safety and efficacy of oral transmucosal fentanyl citrate for preoperative sedation in young children. *Anesth Analg.* 1996;83:1200–1205. [PubMed: 8942586]

168. Dsida RM, Wheeler M, Birmingham PK et al. Premedication of pediatric tonsillectomy patients with oral transmucosal fentanyl citrate. *Anesth Analg.* 1998;86:66–70. [PubMed: 9428853]

169. Galinkin JL, Fazi LM, Cuy RM et al. Use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia. *Anesthesiology*. 2000;93:1378–1383. [PubMed: 11149429]

170. Borland M, Milsom S, Esson A. Equivalency of two concentrations of fentanyl administered by the intranasal route for acute analgesia in children in a paediatric emergency department: a randomized controlled trial. *Emerg Med Australas.* 2011;23:202–208. [PubMed: 21489168]

171. Duncan HP, Cloote A, Weir PM 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. [PubMed: 10844829]

172. Christensen ML, Wang WC, Harris S et al. Transdermal fentanyl administration in children and adolescents with sickle cell pain crisis. *J Pediatr Hematol Oncol.* 1996;18:372–376. [PubMed: 8888744]

173. Kim JG, Sohn SK, Kim DH et al. Effectiveness of transdermal fentanyl patch for treatment of acute pain due to oral mucositis in patients receiving stem cell transplantation. *Transplant Proc.* 2005;37:4488–4491. [PubMed: 16387151]

174. Hunt A, Goldman A, Devine T et al. Transdermal fentanyl for pain relief in a paediatric palliative care population. *Palliat Med.* 2001;15:405–412. [PubMed: 11591092]

175. Finkel JC, Finley A, Greco C et al. Transdermal fentanyl in the management of children with chronic severe pain: results from an international study. *Cancer*. 2005;104:2847–2857. [PubMed: 16284992]

176. Dewhirst E, Naguib A, Tobias JD. Chest wall rigidity in two infants after low-dose fentanyl administration. *Pediatr Emerg Care*. 2012;28:465–468. [PubMed: 22561320]

177. Elakkumanan LB, Punj J, Talwar P et al. An atypical presentation of fentanyl rigidity following administration of low dose fentanyl in a child during intraoperative period [Letter to the Editor]. *Pediatr Anesth.* 18:1102–1143.

178. Lindemann R. Respiratory muscle rigidity in a preterm infant after use of fentanyl during Caesarean section. *Eur J Pediatr.* 1998;157:1012–1013. [PubMed: 9877042]

179. Eventov-Friedman S, Rozin I, Shinwell ES. Case of chest-wall rigidity in a preterm infant caused by prenatal fentanyl administration. *J Perinatol.* 2010;30:149–150. [PubMed: 20118943]

180. Bagley JR, Thomas SA, Rudo FG et al. New 1-(heterocyclylalkyl)-4-(proprionanilido)-4-piperidinyl methyl ester and methylene methyl ether analgesics. *J Med Chem.* 1991;34:827–841. [PubMed: 1847432]

181. Kharasch ED, Walker A, Isoherranen N et al. Influence of CYP3A5 genotype on the pharmacokinetics and pharmacodynamics of the cytochrome

*P*4503A probes alfentanil and midazolam. *Clin Pharmacol Therapeut.* 2007;82:410–426.

182. Kharasch ED, Hoffer C, Walker A et al. Disposition and miotic effects of oral alfentanil: a potential noninvasive probe for first-pass cytochrome P4503A activity. *Clin Pharmacol Therapeut.* 2003;73:199–208.

183. Schwagmeier R, Boerger N, Meissner W et al. Pharmacokinetics of intranasal alfentanil. *J Clin Anesth.* 1995;7:109–113. [PubMed: 7598917]

184. Willsie SK, Evashenk MA, Hamel LG et al. Pharmacokinetic properties of single- and repeated-dose sufentanil sublingual tablets in healthy volunteers. *Clin Therapeut.* 2015;37:145–155.

185. Helmers JH, Noorduin H, Van Peer A et al. Comparison of intravenous and intranasal sufentanil absorption and sedation. *Can J Anaesth.* 1989;36:494–497. [PubMed: 2529048]

186. Bosilkovska M, Walder B, Besson M et al. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. *Drugs*. 2012;72:1645–1669. [PubMed: 22867045]

187. Saari TI, Ihmsen H, Mell J et al. Influence of intensive care treatment on the protein binding of sufentanil and hydromorphone during pain therapy in postoperative cardiac surgery patients. *Br J Anaesth.* 2014;113:677–687. [PubMed: 25001621]

188. Meistelman C, Benhamou D, Barre J et al. Effects of age on plasma protein binding of sufentanil. *Anesthesiology*. 1990;72:470–473. [PubMed: 2137997]

189. Lundeberg S, Roelofse JA. Aspects of pharmacokinetics and pharmacodynamics of sufentanil in pediatric practice. *Pediatr Anesth.* 2011;21:274–279.

190. Klees TM, Sheffels P, Dale O et al. Metabolism of alfentanil by cytochrome P4503A (CYP3A) enzymes. *Drug Metab Dispos.* 2005;33:303–311. [PubMed: 15557344]

191. Guitton J, Buronfosse T, Desage M et al. Possible involvement of multiple cytochrome P450S in fentanyl and sufentanil metabolism as opposed to alfentanil. *Biochem Pharmacol.* 1997;53:1613–1619. [PubMed: 9264313]

192. Meuldermans W, Van Peer A, Hendrickx J et al. Alfentanil pharmacokinetics and metabolism in humans. *Anesthesiology*. 1988;69:527–534. [PubMed: 3140690]

193. Meuldermans W, Hendrickx J, Lauwers W et al. Excretion and biotransformation of alfentanil and sufentanil in rats and dogs. *Drug Metab Dispos.* 1987;15:905–913. [PubMed: 2893720]

194. Ahonen J, Olkkola KT, Hynynen M et al. Comparison of alfentanil, fentanyl and sufentanil for total intravenous anaesthesia with propofol in patients undergoing coronary artery bypass surgery. *Br J Anaesth.* 2000;85:533–540. [PubMed: 11064610]

195. Antmen B, Sasmaz I, Birbicer H et al. Safe and effective sedation and analgesia for bone marrow aspiration procedures in children with alfentanil, remifentanil and combinations with midazolam. *Pediatr Anesth.* 2005;15:214–219.

196. Chiaretti A, Ruggiero A, Barone G et al. Propofol/alfentanil and propofol/ketamine procedural sedation in children with acute lymphoblastic leukaemia: safety, efficacy and their correlation with pain neuromediator expression. *Eur J Canc Care*. 2010;19:212–220.

197. Kwak HJ, Min SK, Kim JS et al. Prevention of propofol-induced pain in children: combination of alfentanil and lidocaine vs alfentanil or lidocaine alone. *Br J Anaesth.* 2009;103:410–412. [PubMed: 19542104]

198. Oh AY, Seo KS, Goo EK et al. Prevention of withdrawal movement associated with injection of rocuronium in children: comparison of remifentanil, alfentanil and fentanyl. *Acta Anaesthesiol Scand.* 2007;51:1190–1193. [PubMed: 17711566]

199. Kim JY, Kwak HJ, Kim JY et al. Prevention of rocuronium-induced withdrawal movement in children: a comparison of remifentanil with alfentanil. *Pediatr Anesth.* 2008;18:245–250.

200. Tan Y, Shi Y, Ding H et al. Mu-opioid agonists for preventing emergence agitation under sevoflurane anesthesia in children: a meta-analysis of randomized controlled trials. *Pediatr Anesth.* 2016;26:139–150.

201. Pokela ML, Ryhanen PT, Koivisto ME et al. Alfentanil-induced rigidity in newborn infants. *Anesth Analg.* 1992;75:252–257. [PubMed: 1632539]

202. Saarenmaa E, Huttunen P, Leppaluoto J et al. Alfentanil as procedural pain relief in newborn infants. *Arch Dis Childhood*. 1996;75:F103–F107.

203. Glenski JA, Friesen RH, Berglund NL et al. Comparison of the hemodynamic and echocardiographic effects of sufentanil, fentanyl, isoflurane, and halothane for pediatric cardiovascular surgery. *J Cardiothorac Anesth.* 1988;2:147–155. [PubMed: 17171905]

204. Moore RA, Yang SS, McNicholas KW et al. Hemodynamic and anesthetic effects of sufentanil as the sole anesthetic for pediatric cardiovascular surgery. *Anesthesiology*. 1985;62:725–731. [PubMed: 3159311]

205. Nielsen BN, Friis SM, Romsing J et al. Intranasal sufentanil/ketamine analgesia in children. *Pediatr Anesth.* 2014;24:170–180.

206. Wang T, Xiang Q, Liu F et al. Effects of caudal sufentanil supplemented with levobupivacaine on blocking spermatic cord traction response in pediatric orchidopexy. *J Anesth.* 2013;27:650–656. [PubMed: 23608774]

207. Cho JE, Kim JY, Kim JE et al. Epidural sufentanil provides better analgesia from 24h after surgery compared with epidural fentanyl in children. *Acta Anaesthesiol Scand.* 2008;52:1360–1363. [PubMed: 19025528]

208. Woloszczuk-Gebicka B, Grabowski T, Borucka B et al. Pharmacokinetics of sufentanil administered with 0.2% ropivacaine as a continuous epidural infusion for postoperative pain relief in infants. *Pediatr Anesth.* 2014;24:962–967.

209. Verghese ST, Hannallah RS, Brennan M et al. The effect of intranasal administration of remifentanil on intubating conditions and airway response after sevoflurane induction of anesthesia in children. *Anesth Analg.* 2008;107:1176–1181. [PubMed: 18806024]

210. Benet LZ, Hoener B. Changes in plasma protein binding have little clinical relevance *Clin Pharmacol Therapeut.* 2002;71:115–121.

211. Dershwitz M, Hoke JF, Rosow CE et al. Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease. *Anesthesiology*. 1996;84:812–820. [PubMed: 8638835]

212. Ross AK, Davis PJ, De Lisle Dear G et al. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg.* 2001;93:1393–1401. [PubMed: 11726413]

213. Glass PSA, Hardman D, Kamiyama Y et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). *Anesth Analg.* 1993;77:1031–1040. [PubMed: 8105723]

214. Manullang J, Egan TD. Remifentanil's effect is not prolonged in a patient with pseudocholinesterase deficiency. *Anesth Analg.* 1999;89:529–530. [PubMed: 10439780]

215. Pitsiu M, Wilmer A, Bodenham A et al. Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. *BrJ Anaesth.* 2004;92:493–503.

216. Hoke JF, Cunningham F, James MK et al. Comparative pharmacokinetics and pharmacodynamics of remifentanil, its principle metabolite (GR90291) and alfentanil in dogs. *J Pharmacol Exp Therapeut.* 1997;281:226–232.

217. Pereira e Silva Y, Gomez RS, De Oliveira Marcatto J et al. Early awakening and extubation with remifentanil in ventilated premature neonates.

Pediatr Anesth. 2008;18:176–183.

218. Kamata M, Tobias JD. Remifentanil: applications in neonates. *J Anesth.* 2016;30:449–460. [PubMed: 26758072]

219. Angst MS. Intraoperative use of remifentanil for TIVA: postoperative pain, acute tolerance, and opioid-induced hyperalgesia. *J Cardiothorac Vasc Anesth.* 2015;29:S16–S22. [PubMed: 26025041]

220. Kim SH, Lee MH, Seo H et al. Intraoperative infusion of 0.6-0.9 mcg/kg/min remifentanil induces acute tolerance in young children after laparoscopic ureteroneocystostomy. *Anesthesiology*. 2013;118:337–343. [PubMed: 23241726]

221. Kars MS, Mori BV, Ahn S et al. Fentanyl versus remifentanil-based TIVA for pediatric scoliosis repair: does it matter? *Reg Anesth Pain Med.* 2019;44(6):627–631. [PubMed: 30923248]

222. Buck ML. Is meperidine the drug that just won't die? [Editorial]. *J Pediatr Pharmacol Therapeut.* 2011;16:167–169.

223. Latta KS, Ginsberg B, Barkin RL. Meperidine: a critical review. *Am J Therapeut.* 2002;9:53–68.

224. Glynn CJ, Mather LE. Clinical pharmacokinetics applied to patients with intractable pain: studies with pethidine. *Pain*. 1982;13:237–246. [PubMed: 7122111]

225. Pond SM, Tong T, Benowitz NL et al. Enhanced bioavailability of pethidine and pentazocine in patients with cirrhosis of the liver. *Aust N Z J Med.* 1980;10:515–519. [PubMed: 6937164]

226. Clark RF, Wei EM, Anderson PO. Meperidine: therapeutic use and toxicity. *J Emerg Med.* 1995;13:797–802. [PubMed: 8747629]

227. Beckwith MC, Fox ER, Chandramouli J. Removing meperidine from the health-system formulary: frequently asked questions. *J Pain Palliat Care PharmacoTher.* 2002;16:45–59. [PubMed: 14640355]

228. Benner KW, Durham SH. Meperidine restriction in a pediatric hospital. *J Pediatr Pharmacol Therapeut.* 2011;16:185–190.

229. American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health, American Pain Society Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics*. 2001;108:793–797. [PubMed: 11533354]

230. Lugo RA, Satterfield KL, Kern SE. Pharmacokinetics of methadone. *J Pain Palliat Care PharmacoTher.* 2005;19:13–24. [PubMed: 16431829]

231. Dale O, Sheffels P, Kharasch ED. Bioavailabilities of rectal and oral methadone in healthy subjects. *Br J Clin Pharmacol.* 2004;58:156–162. [PubMed: 15255797]

232. Dale O, Hoffer C, Sheffels P et al. Disposition of nasal, intravenous, and oral methadone in healthy volunteers. *Clin Pharmacol Therapeut.* 2002;72:536–545.

233. Ward RM, Drover DR, Hammer GB et al. The pharmacokinetics of methadone and its metabolites in neonates, infants, and children. *Pediatr Anesth.* 2014;24:591–601.

234. Kharasch ED, Hoffer C, Whittington D et al. Methadone pharmacokinetics are independent of cytochrome P4503A (CYP3A) activity and gastrointestinal drug transport: insights from methadone interactions with ritonavir/indinavir. *Anesthesiology*. 2009;110:660–672. [PubMed: 19225389]

235. Mitchell TB, Dyer KR, Newcombe D et al. Fluctuations in (R, S)-methadone pharmacokinetics and response among long-term methadone maintenance patients. *Addict Biol.* 2006;11:170–174. [PubMed: 16800831]

236. Li Y, Kantelip JP, Gerritsen-van Schieveen P et al. Interindividual variability of methadone response: impact of genetic polymorphism. *Molec Diagn Ther.* 2008;12:109–124.

237. Ansermot N, Albayrak O, Schlapfer J et al. Substitution of (R, S)-methadone by (R)-methadone: impact on QTc interval. *Arch Intern Med.* 2010;170:529–536. [PubMed: 20308640]

238. Ebert B, Thorkildsen C, Andersen S et al. Opioid analgesics as noncompetitive *N*-methyl-d-aspartate (NMDA) antagonists. *Biochem Pharmacol.* 1998;56:553–559. [PubMed: 9783723]

239. Hewitt DJ. The use of NMDA-receptor antagonists in the treatment of chronic pain. *Clin J Pain*. 2000;16:S73–S79. [PubMed: 10870744]

240. Salpeter SR, Buckley JS, Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. *J Palliat Med.* 2013;16:616–622. [PubMed: 23556990]

241. Moulin DE, Boulanger A, Clark AJ et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag.* 2014;19:328–335. [PubMed: 25479151]

242. Bagley SM, Wachman EM, Holland E et al. Review of the assessment and management of neonatal abstinence syndrome. *Addict Sci Clin Pract.* 2014;9:1–10. [PubMed: 24460974]

243. Berde CB, Beyer JE, Bournaki MC et al. Comparison of morphine and methadone for prevention of postoperative pain in 3- to 7-year-old children. *J Pediatr.* 1991;119:136–141. [PubMed: 2066846]

244. Stemland CJ, Witte J, Colquhoun DA et al. The pharmacokinetics of methadone in adolescents undergoing posterior spinal fusion. *Pediatr Anesth.* 2013;23:51–57.

245. Sharma A, Tallchief D, Blood J et al. Perioperative pharmacokinetics of methadone in adolescents. *Anesthesiology*. 2011;115:1153–1161. [PubMed: 22037641]

246. Singhal NR, Jones J, Semenova J et al. Multimodal anesthesia with the addition of methadone is superior to epidural analgesia: a retrospective comparison of intraoperative anesthetic techniques and pain management for 124 pediatric patients undergoing the Nuss procedure. *J Pediatr Surg.* 2016;51:612–616. [PubMed: 26700690]

247. Rasmussen VF, Lundberg V, Jespersen TW et al. Extreme doses of intravenous methadone for severe pain in two children with cancer. *Pediatr Blood Canc.* 2015;62:1087–1090.

248. Kirchheiner J, Keulen JT, Bauer S et al. Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. *J Clin PsychoPharmacol.* 2008;28:78–83. [PubMed: 18204346]

249. Ardakani YH, Rouini MR. Pharmacokinetics of tramadol and its three main metabolites in healthy male and female volunteers. *Biopharmaceut Drug Dispos.* 2007;28:527–534.

250. Lintz W, Barth H, Osterloh G et al. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 3rd communication: suppositories. *Arzneimittelforschung*. 1998;48:889–899. [PubMed: 9793614]

251. Lassen D, Damkier P, Brosen K. The pharmacogenetics of tramadol. *Clin Pharmacokinet.* 2015;54:825–836. [PubMed: 25910878]

252. Bressolle F, Rochette A, Khier S et al. Population pharmacokinetics of the two enantiomers of tramadol and *O*-demethyl tramadol after surgery in children. *Br J Anaesth.* 2009;102:390–399. [PubMed: 19189983]

253. Tzvetkov MV, Saadatmand AR, Lotsch J et al. Genetically polymorphic OCT1: another piece in the puzzle of the variable pharmacokinetics and

pharmacodynamics of the opioidergic drug tramadol. *Clin Pharmacol Therapeut.* 2011;90:143–150.

254. Schnabel A, Reichl SU, Meyer-Friebem C et al. Tramadol for postoperative pain treatment in children. *Cochrane Database Syst Rev.* 2015; (3):CD009574.

255. Taheri R, Shayeghi S, Razavi SS et al. Efficacy of bupivacaine-neostigmine and bupivacaine-tramadol in caudal block in pediatric inguinal herniorrhaphy. *Pediatr Anesth.* 2010;20:866–872.

256. Inanoglu K, Ozcengiz D, Gunes Y et al. Epidural ropivacaine versus ropivacaine plus tramadol in postoperative analgesia in children undergoing major abdominal surgery: a comparison. *J Anesth.* 2010;24:700–704. [PubMed: 20665055]

257. Akkaya T, Bedirli N, Ceylan T et al. Comparison of intravenous and peritonsillar infiltration of tramadol for postoperative pain relief in children following adenotonsillectomy. *Eur J Anaesth.* 2009;26:333–337.

258. Borazan H, Sahin O, Kececioglu A et al. Prevention of propofol injection pain in children: a comparison of pretreatment with tramadol and propofol-lidocaine mixture. *Int J Med Sci.* 2012;9:492–497. [PubMed: 22927775]

259. Neri E, Maestro A, Minen F et al. Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomized, controlled trial. *Arch Dis Childhood*. 2013;98:721–724.

260. Erhan E, Inala MT, Aydin Y et al. Tramadol infusion for the pain management in sickle cell disease: a case report. *Pediatr Anesth.* 2007;17:84–86.

261. Marzulli P, Caligari's L, Barba E. Tramadol can selectively manage moderate pain in children following European advice limiting codeine use. *Acta Paediatr.* 2014;103:1110–1116. [PubMed: 25041277]

262. Palash TJ, Gill CJ. Butorphanol and nalbuphine: a pharmacologic comparison. *Oral Surg.* 1985;59:15–20.

263. Shah B, Ramchandani Y, Misran A. Development and evaluation of oral osmotic pump of butorphanol tartrate. *Pharmaceut Dev Technol.* 2014;19:868–880.

264. Shy WC, Morgenthau EA, Baraiya RH. Pharmacokinetics of butorphanol nasal spray in patients with renal impairment. *Br J Clin Pharmacol.* 1996;41:397–402. [PubMed: 8735680]

265. Shy WC, Morgenthau EA, Pittman KA et al. The effects of age and sex on the systemic availability and pharmacokinetics of transnasal butorphanol. *Eur J Clin Pharmacol.* 1994;47:57–60. [PubMed: 7988625]

266. Vachharajani NN, Shyu WC, Greene DS et al. The pharmacokinetics of butorphanol and its metabolites at steady state following nasal administration in humans. *Biopharmaceut Drug Dispos.* 1997;18:191–202.

267. Singh V, Pathak M, Singh GP. Oral midazolam and oral butorphanol premedication. *Indian J Pediatr.* 2005;72:741–744. [PubMed: 16186674]

268. Pappas AL, Fluder EM, Creech S et al. Postoperative analgesia in children undergoing myringotomy and placement equalization tubes in ambulatory surgery. *Anesth Analg.* 2003;96:1621–1624. [PubMed: 12760984]

269. Bennie RE, Boehringer LA, Dierdorf SF et al. Transnasal butorphanol is effective for postoperative pain relief in children undergoing myringotomy. *Anesthesiology*. 1998;89:385–390. [PubMed: 9710397]

270. Lawhorn CD, Stoner JM, Schmitz ML et al. Caudal epidural butorphanol plus bupivacaine versus bupivacaine in pediatric outpatient genitourinary procedures. *J Clin Anesth.* 1997;9:103–108. [PubMed: 9075033]

271. Singh V, Kanaujia A, Singh GP. Efficacy of caudal butorphanol. *Indian J Pediatr.* 2006;73:147–150. [PubMed: 16514225]

272. Gunter JB, McAuliffe J, Gregg T et al. Continuous epidural butorphanol relieves pruritus associated with epidural morphine infusions in children. *Paediatr Anaesth.* 2000;10:167–172. [PubMed: 10736080]

273. Radvansky BM, Puri S, Sofonios AN et al. Ketamine: a narrative review of its uses in medicine. *Am J Therapeut.* 2016;23:e1414–e1426.

274. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Therapeut.* 2013;19:370–380.

275. Dayton PG, Stiller RL, Cook DR et al. The binding of ketamine to plasma proteins: emphasis on human plasma. *Eur J Clin Pharmacol.* 1983;24:825–831. [PubMed: 6884418]

276. Rao LK, Flaker AM, Friedel CC et al. Role of cytochrome P4502B6 polymorphisms in ketamine metabolism and clearance. *Anesthesiology*. 2016;125:1103–1112. [PubMed: 27763887]

277. Alletag MJ, Auerbach MA, Baum CR. Ketamine, propofol, and ketofol use for pediatric sedation. *Pediatr Emerg Care*. 2012;28:1391–1398. [PubMed: 23222112]

278. Roelofse JA. The evolution of ketamine applications in children. *Pediatr Anesth.* 2010;20:240–245.

279. Fredriksson A, Ponten E, Gordh T et al. Neonatal exposure to a combination of *N*-methyl-d-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. *Anesthesiology*. 2007;107:427–436. [PubMed: 17721245]

280. Dong C, Anand KJS. Developmental neurotoxicity of ketamine in pediatric clinical use. *Toxicol Lett.* 2013;220:53–60. [PubMed: 23566897]

281. Anand KJS, Garg S, Rovnaghi CR et al. Ketamine reduces the cell death following inflammatory pain in newborn rat brain. *Pediatr Res.* 2007;62:283–290. [PubMed: 17551412]