European Journal of Drug Metabolism and Pharmacokinetics (2019) 44:591–609
https://doi.org/10.1007/s13318-019-00552-0

REVIEW ARTICLE

Opioids: A Review of Pharmacokinetics and Pharmacodynamics in Neonates, Infants, and Children

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Published online: 22 April 2019
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Abstract

Pain management in the pediatric population is complex for many reasons. Mild pain is usually managed quite well with oral acetaminophen or ibuprofen. Situations involving more severe pain often require the use of an opioid, which may be administered by many different routes, depending on clinical necessity. Acute and chronic disease states, as well as the constantly changing maturational process, produce unique challenges at every level of pediatrics in dosing and management of all medications, especially with regard to high-risk opioids. Although there has been significant progress in the understanding of opioid pharmacokinetics and pharmacodynamics in neonates, infants, children, and adolescents, somewhat limited data exist from which necessary information, concerning the safe and effective use of these agents, may be drawn. The evidence here provided is intended to be helpful in directing the practitioner to patient-specific reasons for preferring one opioid over another. As our knowledge of opioids and their effects has grown, it has become clear that older medications like codeine and meperidine (pethidine) have very limited use in pediatrics. This review provides pharmacokinetic and pharmacodynamic evidence on the currently available opioids: morphine, fentanyl (and derivatives), codeine, meperidine, oxycodone, hydrocodone, hydromorphone, methadone, buprenorphine, butorphanol, nalbuphine, pentazocin, ketobemidone, tramadol, piritramide, naloxone and naltrexone. Morphine, being the most studied opioid analgesic, is the standard against which all others are compared. Pharmacokinetic parameters of morphine that have been found in neonates, i.e., higher volume of distribution, immature metabolic processes that develop at various rates, elimination that is variable based on age and weight, as well as treated and untreated disease processes, are an example of all opioids in the population discussed in this review. Outside the premature and neonatal population, the use of opioids in infants, children, and adolescents quickly begins to resemble the established values found in adults. As such, the concerns (risks) of these medications become comparable to those seen in adults.

1 Introduction

Although effective pain management is foundational in the care of all children, this area has, historically, not always received the necessary attention. It was only recently (2001) that the American Academy of Pediatrics (AAP) and the American Pain Society (APS) published recommendations on pediatric pain management, following the Joint Commission on Accreditation of Healthcare Organizations that prioritized pain management. In general, the

Key Points

While the information published on the pharmacokinetics and pharmacodynamics of opioids in children has increased, many unanswered questions remain. The most highly studied medications in the pediatric population are morphine and fentanyl.

Pediatric opioid pharmacokinetic data can best be described as highly variable, especially in premature and infant populations: therefore, each patient must be dosed and monitored carefully.

In general, the absorption, distribution, metabolism, and elimination of opioids in children and adolescents are comparable to that of adults.

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pharmacokinetics and pharmacodynamics of opioids are highly dependent on patient's age. Pharmacokinetic variation between children and adults arise from differences in protein binding, volume of distribution, and proportions of fat and muscle stores, as well as maturity of renal and hepatic function. While numerous processes quickly reach adult values within several months of birth, most developments are patient-specific requiring particular attention and dose adjustment during therapy. The general pharmacokinetics of opioids have been studied broadly in most pediatric populations including premature neonates, neonates, infants, children, and adolescents. Additionally, specific pediatric populations (including postoperative cardiovascular and obesity) that have been studied providing more evidence of the patient-specific nature of opioid dosing. As this patient population continues to be extremely difficult to study owing to the requirement of collecting at least some patient subjective data, there remains an overall lack of information on opioid pharmacodynamics. Prospective clinical trials in preterm infants, term infants, children, and adolescents are difficult to perform, time consuming, expensive, and research methods are limited by special ethical considerations [1, 2].

The administration of opioids by the oral route is burdened with many difficulties, including a higher stomach pH seen in newborns, delayed gastric emptying, and palatability of many oral liquid formulations. While stomach pH and gastric emptying are a concern, these parameters reach adult values rather quickly and have little influence on drug absorption. In fact, oral administration of opioids is limited in neonates and infants to a select few, i.e., given for neonatal abstinence syndrome (NAS), and there is little evidence that these factors affect the treatment of this problem. Developmental changes can also alter the absorption of drugs administered via other extravascular routes [3]. Percutaneous absorption, for example, is influenced by the thinner stratum corneum and greater hydration seen in the preterm infant. As neonates grow into infants, the metabolic processes also mature affecting the metabolism of drugs, such as morphine. These differences should be considered in the event that patient response is not as expected and could be explained by patient-specific differences in metabolism.

Practitioners often assume that children need higher doses of opioids by weight when compared to adult patients [4]. As the ratio of total body surface area to body mass in infants and young children far exceeds that observed in adults, the assumption appears correct. However, there are many factors, apart from body weight, that may help to account for the differences in dosage required in children. Preterm neonates and young infants have comparatively larger extracellular and total body water compartments compared to adults which results in lower plasma concentrations of drugs when medications are administered on a weight-based method [3]. Other factors related to maturation or concomitant disease state(s), such as overall organ perfusion, permeability of cellular membranes and blood vessels, local and regional blood flow, acid–base balance, and cardiac function, can all impact drug binding and dispersal [3]. While more is known about opioids than ever before, each patient must be approached individually and carefully monitored while under the influence of these important medications.

Underlying the available knowledge that exists on the pharmacokinetics and pharmacodynamics of opioids in pediatrics is the developing study of the role of pharmacogenetics in the 'behavior' of these medications in the body. Variations in the pharmacokinetics of morphine, for example, may contribute to inter-individual differences in response [5]. Morphine is metabolized by various pathways with approximately 70% of the drug converted via glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), considered the more potent form. Many transport proteins, including organic cation transporter 1 (OCT1), ATP-binding cassette (ABC) *ABCB1, ABCC2*, and *ABCC3* are known to play a substantial role in the disposition of morphine and its metabolites in the animal model. Venkatasubramanian et al. [5] studied nearly 500 plasma samples from 220 children and found that *OCT1* homozygous genotypes were associated with lower morphine clearance. The authors also showed that children with the *ABCC3*-211C > T polymorphism C/C genotype have significantly higher (~ 40%) metabolite transformation than C/T + T/T genotypes. At the level of the blood–brain barrier (BBB), several ABC transporters are involved in the extrusion of compounds into the bloodstream. Current evidence suggests that P-glycoprotein participates in the active brain-to-blood efflux of opioids at the BBB, and thus contributing to the development of central tolerance of these drugs [6]. Up-regulation of these ABC transporters, especially P-glycoprotein, may have an important impact on the development of tolerance of these drugs, with profound implications on the individual. While largely studied in the murine model, these concepts may provide a glimpse into the inter-patient variability seen in many patients [6]. Table 1 provides a list of known opioid substrates, inducers, and inhibitors of ABC transporters at the BBB [7]. In summary, these results suggest that uptake and efflux transporters within hepatocytes impact morphine metabolism and disposition significantly and need further investigation [5]. In order to achieve safe and effective drug therapy in children, it is important that the developmental patterns of transporter gene expression continue to be evaluated [8].

A literature review was performed by searching the Medline database from 1966 to September, 2018. The review focused on the individual medications and search words

including 'pharmacokinetics', 'pharmacodynamics', 'oral', 'parenteral', 'rectal', 'nebulized', 'inhaled', 'topical', 'transmucosal', 'intravenous', 'intrathecal', and 'epidural', among others. Searches were also limited to 'ages 0 to 18' in an attempt to minimize unnecessary reviews. Additional literature was retrieved from other sources (book chapter, online searches) as indicated. Pertinent articles were retrieved and reviewed for content. While this narrative is not a comprehensive review, it is intended to provide the practitioner with an overview of the opioids utilized in the pediatric population and the available pharmacokinetic and pharmacodynamic parameters that influence their clinical use.

Table 1 Known opioid substrates and inducers/inhibitors of ABC transporters at the blood–brain barrier. From [7] with permission

Opioid analgesic	ABC transporter/P-glycoprotein	Inducer or inhibitor of transporter
Alfentanyl	Substrate	
Buprenorphine	Substrate	Inhibitor
Codeine	Non-substrate	
Fentanyl	Substrate	
Hydrocodone	Non-substrate	
Meperidine	Substrate	
Methadone	Substrate	Inhibitor
Morphine	Substrate	Inducer
Oxycodone	Non-substrate	Inducer
Sufentanil	Non-substrate	
Tramadol	Substrate	

ABC ATP-binding cassette

2 Morphine

2.1 History and Pharmacology

Morphine is extracted from the poppy plant *Papaver somniferum*, and is considered the opioid analgesic against which all others are measured [9]. Simply due to the age and accumulated knowledge of the drug, its pharmacokinetics (Table 2) and pharmacodynamics are best studied in pediatric patients compared to all other analgesics. Morphine is a pure agonist with its primary effect at the μ-receptor with some activity at the K-receptor, resulting in analgesia. It may be administered by the intravenous, intramuscular, subcutaneous, oral, rectal, epidural, and intrathecal routes.

2.2 Analgesia and Sedation

A meta-analysis calculated that an initial morphine dose of 7 μg/kg/h is adequate for postoperative analgesia in term neonates [10]. A study published by Lynn et al. recommended morphine infusion rates for postoperative analgesia that advanced from 10 μg/kg/h for infants aged 0–7 days, 15 μg/kg/h for 8–30 days, 20 μg/kg/h for 31–90 days, and 25 μg/kg/h for 91–365 days [11]. In contrast, Olkkola et al. [9] found adequate analgesia parameters were obtained in postoperative cardiac surgery patients at 5 μg/kg/h for those aged between 0 and 30 days, 10 μg/kg/h between 31 and 90 days, 15 μg/kg/h between 91 and 180 days, and 25 μg/kg/h between 181 and 365 days. Rates of infusion were adjusted to achieve a serum level of 20 ng/mL. The difference is thought secondary to reduced renal elimination of the morphine metabolites that is seen in infants undergoing cardiac surgery [9].

Morphine administered intravenously by continuous infusion has been shown to provide a more consistent level of

Table 2 Summary of morphine pharmacokinetics

Age	Bioavailabilty (%)	Distribution (L/kg)	Metabolism	Half-life (h)	Elimination (mL/min/kg)
Preterm	–	1.82–5.2 [13, 29]	Glucuronidation primarily to M3G [1]	6.6–11.1 [13, 29]	2.3–7.8 [13, 20]
Term infants to 1 month	Oral 44.3 [21]	5.15 ± 2.6 [21]	Glucuronidation to M3G, M6G [1]	3.91 ± 1 [10] 6.5 ± 2.8 [20]	9.2 [10] 8.1 ± 3.2 [20]
> 1 month to 1 year	Rectal 35 [25]	2 [19] 2.8 ± 2.6 [19]	–	1.15 ± 2.4 [9]	5.2 [18] 25.8–75.6 [19] 25.3–48.9 [20]
> 1 year	Oral 29.8 [21]	3.17–3.76 [19]	–	0.76 ± 1 [18] 2.0 ± 1.8 [10]	23.6 ± 8.5 [20]
Adults	Oral 19–47 [30]	2.1–4.0 [30]	–	2–4 [30]	20–30 [30]

M3G morphine-3-glucuronide, *M6G* morphine-6-glucuronide

analgesia than morphine administered by intermittent doses [11], but this has been disputed elsewhere [12]. These differences are likely due to large inter-individual variability and immature morphine metabolism into the more active M6G, as well as changes due to increased gestational and postnatal age [13]. Clinical trials studying morphine for postoperative analgesia have shown large inter-individual variability in drug plasma concentrations and a wide range of dosing requirements [13]. Intermittent intravenous doses of morphine are administered at doses ranging from 0.025 to 0.03 mg/kg/dose every 2–4 h in infants aged < 6 months [14]. Opioid-naive children weighing < 50 kg are usually administered doses of 0.05 mg/kg/dose with a maximum of 2 mg per dose, with higher doses administered when pain is not adequately controlled. Opioid-tolerant children may need doses starting at 0.1–0.2 mg/kg/dose with an initial maximum of 4–8 mg. Children > 50 kg should be dosed as adults with 2–4 mg per dose initially with higher doses indicated for tolerant patients [15].

Respiratory depression and potential consequences are the major concern of opioids. Lynn et al. [16] suggested that respiratory depression may be minimalized if serum morphine concentrations are maintained < 20 ng/mL. However, since morphine serum concentrations are not monitored, diligent clinical evaluation remains the mainstay for prevention of respiratory depression. Invasive observation of arterial $PaCO_2$ or non-invasive end-tidal CO_2 monitoring is also an option for patient monitoring. Risk factors for respiratory depression have been described as aged < 1 year, higher than recommended doses, concurrent disease affecting ventilatory reserve (scoliosis, renal insufficiency), concurrent sedatives, and dosing errors [17].

2.3 Intravenous Morphine

2.3.1 Distribution

Morphine has a volume of distribution in preterm neonates that is higher than in term neonates and older infants [1]. This is specifically seen on days 2 to 5, with contributing factors such as organ size, fat and muscle content, binding affinity for serum proteins, and the water/lipid solubility of morphine, all affecting these alterations in volume of distribution. Other contributing and complicating factors include fluid balance in the face of poor renal function, intravenous fluid administration, changes in blood flow due to patent ductus arteriosus, and capillary leak due to sepsis, among others [1]. Disease severity might also play a role in drug distribution, as would be expected. Overall, the volume of distribution of intravenous morphine has been described as increasing exponentially with age reaching adult levels at 6 months [18].

2.3.2 Metabolism

Conversion of morphine by glucuronidation is a crucial metabolic step, producing either M3G or to M6G [1]. M6G is the more highly active form but is not produced in significant amounts until at least two days post-birth, whereas M3G is produced in both preterm and term infants at birth. This difference in the metabolism of morphine in the premature infant explains that while morphine is a widely used opioid in children, it may not be the most appropriate choice to treat acute pain in the premature infant [19], as acute pain effect may not be provided due to unpredictable metabolism during the first few days of life.

2.3.3 Elimination

Clearance of morphine is typically highly variable between individuals but overall it can be described as slower in the youngest patients and approaches adult values by 6 months of age [9]. Morphine clearance has been shown to be decreased in children undergoing cardiac surgery compared to cases of non-cardiac surgery. M3G and M6G, being water soluble, are renally excreted and elimination is similar to the glomerular filtration rate (GFR). The clearance of intravenous morphine, which usually ranges between 80 and 130 min, is more rapid in children than in adults [20], but should be expected to be prolonged (up to 400 min) in children requiring vasopressor support.

2.4 Intramuscular and Subcutaneous Morphine

The use of intramuscular or repeated subcutaneous administration of morphine is no longer recommended. These routes cause local tissue irritation, pain, and induration. The variable absorption of morphine coupled with a lag time to peak effect led to the recommendation to not use these routes in children, as more reliable and less painful options are available [2].

2.5 Oral Morphine

Liu et al. evaluated 34 neonates with NAS who received diluted tincture of opium, which contained 0.04 mg morphine equivalent per 1 mL [21]. They found an oral bioavailability of 46.3%, which is higher than the oral bioavailability (23.9%) seen in adults. Velez de Mendizabal et al. [22] evaluated 40 children aged from 2 to 6 years and found that the disposition of morphine, M3G, and M6G was best described by a one-compartment model. Additionally, the metabolites M3G and M6G were described by a delay transit compartment, demonstrating a delay in the appearance of these metabolites [22]. Dawes et al. studied single doses of

oral morphine syrup ranging from 0.1 to 0.3 mg/kg/dose, measuring blood concentrations at 30, 60, 90, 120, 180 and 240 min [23]. Doses of 0.1 mg/kg/dose provided consistently low values < 10 μg/mL at 60 min. Children given doses of 0.2 and 0.3 mg/kg/dose had higher observed maximum concentration (C_{max}) of 16.4 μg/mL, but with considerable variability. Oral bioavailability was 29.8% and an oral initial (loading) dose of 0.2 mg/kg/dose followed by 0.1 mg/kg/dose every 4 h consistently provided a target concentration of 10–20 μg/mL, while minimizing adverse effects [22]. Hunt et al. found an average half-life of 2.3 h in 40 children ($n = 18, < 11$ years and $n = 22, > 11$ years), an apparent volume of distribution of 5.2 L/kg, and an area-under-the curve $(AUC)_{12h}$ of 86 [24]. They found a linear relationship between dose and plasma concentration within the range of 0.3–4 mg/kg/day. This study was performed in cancer patients, who often required higher doses to achieve adequate pain control. However, the study did suggest that plasma concentrations < 12 μg/L were unlikely to provide adequate pain control, similar to previous values [23].

2.6 Rectal Morphine

Lundeberg et al. studied the rectal administration of a single morphine dose in 20 preoperative children with a mean age of 15 months (combined groups) and found a bioavailability between 27 and 35% in the two dosage forms [25]. Rectally administered morphine undergoes first-pass metabolism, resulting in higher concentrations of M3G and M6G than intravenous administration. As rectally administered morphine may not be a common dosage form, extra attention should be used in those unfamiliar with these products, as variable patient effects could be encountered with potential negative outcomes [26].

2.7 Epidural and Intrathecal Morphine

Nichols et al. studied the disposition and respiratory effects of 0.02 mg/kg of intrathecal morphine in 10 children (aged 4 months to 15 years) and found it depressed the ventilatory response to carbon dioxide for up to 18 h [27]. This is thought to be due to the rostral spread of morphine in the cerebrospinal fluid, rather than systemic absorption. Eschertzhuber et al. reviewed the use of lower doses of intrathecal morphine (0.005 and 0.015 mg/kg) and showed similar results, with prolonged time to extubation seen with the high-dose group [17]. Jones et al. found that respiratory depression was more likely in children receiving doses > 0.02 mg/kg intrathecal morphine and is most often encountered at 3.5–4.5 h after administration [28]. While intrathecal morphine provided sufficient pain relief, the increased risk of respiratory depression, especially with doses > 0.02 mg/kg, should limit the use of this route to specific patient populations [28].

2.8 Summary of Information Pertaining to Morphine

Morphine will remain the standard by which all other opioids are compared. Premature neonates remain the least-studied group in pediatrics, and one should expect significant variability within this population due to the complex developmental and disease-induced factors. As the neonate becomes an infant, the pathways for the metabolism and elimination of morphine mature rapidly, usually reaching adult values by 6 months. As with older children and adults, forces that lead to decreased renal function may also lead to reduced drug elimination. The dosing of morphine for analgesia and sedation varies widely, with expected higher doses needed as the infant matures during the first year of life. As discussed in Sect. 2.2 [13], due to the inconsistent conversion of morphine to the metabolites M3G and the more active M6G, especially in premature neonates, medications that do not require conversion, such as fentanyl, would be preferred for intermittent or acute pain management. Appropriate clinical monitoring, while important, is critical during infancy in order to maintain adequate analgesia while minimizing adverse effects. As will be discussed in later sections, there are situations in pediatrics where other opioids may be preferred over morphine, especially in the neonate.

3 Codeine

Codeine is a naturally occurring derivative of opium and is a prodrug that is converted to morphine and is considered to have a potency of one-tenth that of morphine. The metabolism to morphine is dependent on the highly polymorphic cytochrome P450 (CYP) 2D6 pathway. Polymorphisms have been identified in this gene that have been called poor metabolizers, extensive metabolizers, and ultra-rapid metabolizers, that result in varied amounts of morphine produced from the standard codeine dose [31]. In the general population, approximately 10% of codeine is converted to morphine. When a patient is a poor metabolizer, almost no codeine is converted, leading to poor or nonexistent pain relief. A patient that is considered an ultra-rapid metabolizer can produce 50–75% more morphine than a CYP2D6 extensive metabolizer. There have been numerous case reports of fatalities following the administration of codeine to children who were later found on autopsy to be an ultra-rapid metabolizer of codeine [31]. Because CYP2D6 and other polymorphic genes are not routinely screened before prescribing codeine, many agencies consider the risk of codeine to be greater than the benefit and consider it contraindicated in children aged

< 12 years and only used for those aged < 18 years for acute mild-moderate pain uncontrolled by acetaminophen (paracetmol) or ibuprofen. This regulation has been endorsed by the United States Food and Drug Administration (FDA), European Medicines Agency, and the United Kingdom Medicines and Healthcare Products Regulatory Agency [32].

In the United States, codeine is a Schedule III controlled substance which allows more prescribing flexibility. A population where this flexibility is particularly useful is in sickle cell disease, where intermittent use of opioids is necessary. Gammal et al. studied the pharmacogenomics of codeine in 830 patients with sickle cell disease, finding 75% with the CYP2D6 genotype result; 7.1% were ultra-rapid or possible ultra-rapid metabolizers, and 1.4% were poor metabolizers [14]. Through a system of interruptive alerts recommended for the high-risk patients, codeine can still be useful. Since approximately 10% of the population are CYP2D6 poor and intermediate metabolizers at risk of failing codeine therapy, pharmacogenetic testing can also be utilized to direct appropriate therapy.

4 Meperidine

Meperidine (pethidine), a synthetic phenylpiperidine, is a μ-receptor agonist that is *N*-demethylated to normeperidine [33]. This metabolite has a significantly longer half-life, approximately 15–30 h in adults, than the parent drug [34]. When accumulation occurs secondary to renal or hepatic dysfunction or with large doses, an excitatory syndrome can occur that includes hallucinations, tremors, hyperactive reflexes, and convulsions [33]. The pharmacokinetics of intravenous meperidine in neonates and children have been described by Pokela et al. [33], who reported a great inter-individual variability of median half-life of 10.7 h (range 3.3–59.4 h), median clearance of 8 mL/kg/min (range 1.8–34.9 mL/kg/min), median volume of the central compartment of 2.4 L/kg (range 0.5–4.8 L/kg), and median steady-state volume of distribution 7.2 L/kg (range 3.3–11). Since only six of the 21 patients studied were not receiving mechanical ventilation, no conclusions on the effect of meperidine on respiratory efforts were reported. Mather et al. summarized the use of meperidine in newborns and described performance effects for up to 60 h after exposure from the mother [35]. Oral meperidine has poor bioavailability [36], even though it still finds its way into use in pediatric dentistry [37], when combined with sedative/hypnotics. Reports of adverse effects of meperidine in children have accumulated and include orofacial dyskinesias in a 6-week-old child [38], muscle rigidity [39], and seizures [40]. This has led to a joint statement from the AAP and the APS that recommends against the use of meperidine for the management of pain in infants, children, and adolescents, as other, safer opioids are available [41].

5 Oxycodone

Oxycodone hydrochloride is a semisynthetic opioid that is structurally similar to codeine but does not have to be metabolized to an active form and should be considered pharmacodynamically similar to morphine [42]. Oxycodone has a higher bioavailability, longer half-life, and is hepatically metabolized by CYP2D6 and CYP3A4, compared to morphine, which undergoes glucuronidation [43] (Table 3).

5.1 Pharmacokinetics

The pharmacokinetics of oxycodone were studied in 40 children aged 6 months to 8 years who were undergoing surgery and given oxycodone via the intravenous, buccal, intramuscular, and gastric route [42]. Many of the evaluated parameters were similar to those seen in older children and adults [42]. They found the mean clearance of oxycodone following intravenous administration to be 16 mL/kg/min, similar to a previously reported 15 mL/kg/min [44]. They also determined the volume of distribution at steady state to be 3.2 L/kg, compared to 2.5 L/kg reported for adults [45]. The elimination half-life was 2.7 h via the intravenous route, which is similar to adults (2.6 h) [46]. The authors also found that intramuscular administration of oxycodone only achieved 68% of the mean AUC compared to the intravenous route. Buccal administration provided a faster rate of absorption compared to gastric administration, as oxycodone is absorbed mainly in the small intestine. The mean estimated bioavailability of buccal oxycodone is 55%, which is similar to that reported in adults administered oxycodone by the intranasal route [47]. The estimated bioavailability of gastric oxycodone was 37%, which is also similar to that reported in adults [45]. Pokela et al. studied intravenous oxycodone in 22 infants aged between 1 week and 6 months [48]. The clearance and half-life of oxycodone varied between the age groups, with the most significant differences observed in the youngest infants. Clearance values ranged from 9.9 ml/min/kg in infants aged < 1 week, 20.1 mL/min/kg in those aged 1 week to 2 months, and 15.4 mL/min/kg in those aged 2–6 months, which is similar to the results found by Kokki et al. [42]. The half-life of the drug in infants aged < 1 week was 4.4 h versus 2 h for those aged between 2 and 6 months. Both clearance and half-life were correlated with age [48]. The variations seen between these groups (all aged < 6 months) is considerable and makes routine dosing in this age group potentially treacherous. Each patient must be dosed individually and carefully monitored.

Table 3 Pharmacokinetics of oxycodone and hydrocodone

Drug	Bioavailabilty (%)	Distribution	Metabolism	Half-life (h)	Elimination
Oxycodone	50 (solution) [42] 68 (buccal) [42] 60–87 (tablet) [45]	3.2 (children) [42] 2.5 (adults) [45]	CYP2D6[a], 3A4	4.4 (term newborns) [42] 2 (2–6 months) [42] 2.7 (children) [42] 2.6 (adults) [45]	9.9 mL/kg/min (term newborns) [42] 20.1 mL/kg/min (1 week to 2 months) [42] 15.4 mL/kg/min (2–6 months) [42] 16 mL/kg/min [45] 15 mL/kg/min [45]
Hydrocodone	–	4.57 ± 1.33 [52]	CYP2D6	3.45 ± 1.05 (6–17 years) [52] 4.57 ± 0.79 (adults) [52]	0.92 ± 0.38 L/h/kg (6–17 years) [52] 0.65 ± 0.22 L/h/kg (adults) [52]

CYP cytochrome P450

[a]Phenotypes include poor, intermediate, extensive, and ultrarapid metabolizers [42]

5.2 Pharmacogenomics

As knowledge of the hepatic metabolism of medications has grown, the pharmacogenomics of oxycodone metabolism in children has been studied [43]. While oxycodone itself is therapeutically active, it is also partly metabolized to the active metabolite oxymorphone by CYP2D6, which has significant genetic variability. Those patients with more active CYP2D6 activity had higher concentrations of oxymorphone in comparison to phenotypes with less activity [43]. Patients classified as poor metabolizers are more likely to experience less effective pain relief while those classified as extensive metabolizers may be at risk of toxicity. Certain populations have a higher prevalence of CYP2D6 ultra-rapid metabolizer phenotype (20% in Saudi Arabians and 29% in Ethiopians), compared to 1–7% in Caucasians [49–51] and therefore would be more likely to experience toxicity. Greater research into pharmacogenomics will hopefully allow for more personalized opioid selection that will benefit the patient in both improved pain management and fewer dangerous adverse effects [43].

5.3 Dosing

Oxycodone given for moderate to severe pain and as a single agent has been dosed at 0.025–0.05 mg/kg/dose every 4–6 h in infants aged < 6 months [15]. Infants aged > 6 months, children, and adolescents have been given doses of 0.1–0.2 mg/kg/dose every 4–6 h, with a maximum dose of 5–10 mg. Doses of oxycodone must be adjusted for renal impairment and therapy should be initiated at the low end of the dosing range. Dosage reductions are indicated for those with a GFR of 10–50 mL/min/1.73 m^2 where 75% of the dose is administered; while those with a GFR < 10 mL/min/1.73 m^2 or on dialysis should receive a 50% dose reduction.

6 Hydrocodone

Hydrocodone is approximately 12 times more potent at the μ-receptor than codeine and nearly half of hydrocodone clearance is metabolized by CYP2D6 into hydromorphone or by CYP3A4 into norhydrocodone. The pharmacokinetics of hydrocodone were addressed by Liu et al. [52], who studied acetaminophen/hydrocodone in 17 healthy children aged 6–17 years. They found hydrocodone concentrations peaked between 2 and 4 h and mean hydrocodone C_{max} levels ranged from 10 to 16 mg/mL (Table 3). The elimination half-life for hydrocodone was found to be 25% shorter than adult values. After body weight normalization, the total plasma clearance values

were found to be approximately 42% higher than adult values. However, when normalized to body surface area, the clearance was very similar between pediatric patients and adults. The authors postulated that a body surface area approach to dosing may provide a systemic exposure that has been shown effective in adults. Unfortunately, the study was not designed to assess efficacy and no efficacy data were collected [52]. Sauberan et al. studied 30 postpartum women receiving hydrocodone and found fully breastfed neonates received 1.6% (range 0.2–9%) of the maternal weight-adjusted dose of hydrocodone, equating to a total median opioid dosage from breast milk of 0.7% of a therapeutic dose for infants [53].

The therapeutic response of patients with sickle cell disease to hydrocodone was studied by Yee et al. [54], leading to several important considerations for practitioners. The authors found a high frequency of variant CYP2D6 genotypes in the studied patients, possibly contributing to failure of analgesic response. It was recommended that patients with repeated episodes of failed outpatient pain management be genetically tested for CYP2D6 variants, leading to either an inability to convert hydrocodone to hydromorphone (poor metabolizers), rapid drug toxicity, or ineffective analgesia (ultra metabolizers) [54]. As reviewed earlier with codeine [14], genetic testing for CYP2D6 activity for patients with sickle cell disease could provide vital information that would assist the prescriber in choosing and dosing the most effective hydrocodone regimen, or the selection of another opioid altogether, if indicated.

6.1 Hydrocodone Dosing

Hydrocodone, as a single agent, is administered in recommended doses of 0.1–0.2 mg/kg/dose every 4–6 h in infants and children weighing < 50 kg. Children > 50 kg are administered 5–10 mg every 4–6 h, similar to doses used in adults [15]. As hydrocodone is currently combined with acetaminophen in all available forms, the maximum recommended acetaminophen dose is a limiting factor on the oral hydrocodone maximum dose [15].

7 Fentanyl

Fentanyl is a pure synthetic opioid and is widely used in pediatrics, especially neonates. Fentanyl binds to the μ- and κ-opioid receptors and has analgesic, sedative, and anesthetic properties [55]. Fentanyl is considered to be 50–100 times more potent than morphine. Derivatives of fentanyl used in humans include alfentanil, remifentanil, and sufentanil. Table 4 summarizes pharmacokinetic parameters of these compounds.

7.1 Intravenous Pharmacokinetics

The time to distribution of fentanyl following an intravenous dose is very short (1–1.7 min). Fentanyl is rapidly distributed to fat and muscle and crosses the BBB by simple diffusion as well as active transport. The elimination half-life is highly variable, with reports in infants with means ranging from 4.6–17.7 h, compared to 3.7 h for adults [29]. A similar variation has been found with volume of distribution in infants, where values range from 5.1 to 17 L/kg. This same level of variation is seen in clearance where younger patients (< 6 months) had a mean clearance of 8 mL/min/kg, those aged between 6 months and 6 years displayed a mean clearance of 18.8 mL/min/kg, and those aged > 6 years had mean clearance values of 8.1 mL/kg/min [56]. Fentanyl has also been used extensively in infants and children on extracorporeal membrane oxygenation (ECMO) therapy due to its rapid onset of action and relative minimal effect on hemodynamics. Due to adsorption to components of the ECMO circuit, it is common to see significant increases in dose requirements [57].

Vaughns et al. [58] evaluated six adolescent females with a mean total body weight of 137.4 kg and body mass index of 49.6%. Fentanyl was dosed intravenously, based on ideal body weight and blood samples were drawn over a 24-h period. Fentanyl clearance was found to be 11.2 ± 2.6 mL/kg/min when normalized to total body weight, which is higher than reported in lean patients. The volume of distribution was 4.7 ± 2.1 L/kg when normalized to weight, which is in the upper range of normal [58]. The increased fentanyl clearance seen in this population was attributed to an increased hepatic blood flow. Clinically, severely obese patients are more at risk for respiratory adverse effects of fentanyl. Thus, pharmacokinetics should be taken into consideration during dosing.

7.2 Transmucosal Pharmacokinetics

Fentanyl has been formulated into an oral form in which fentanyl citrate was mixed with sucrose and formed into a lozenge on a stick. This formulation is rapidly absorbed through the oral mucosa. The bioavailability of the transmucosal fentanyl has been found to be 50%, exceeding that of oral fentanyl (30%) because fentanyl that is swallowed undergoes moderate first-pass extraction in the liver [59]. Another study reported transmucosal fentanyl to have a bioavailability of 36.1% leading the authors to speculate that a large portion of the dose was swallowed [60]. However, the clinical use of this formulation has many practical disadvantages when used in children, i.e., the lozenge could be chewed, have variable consumption time, the need for supervision, patient refusal to complete the dose, disposal of unused controlled substance, and uncertainty of mucosal

Table 4 Pharmacokinetics of fentanyl and derivatives

Drug	Bioavailabilty (%)	Distribution	Metabolism	Half-life	Elimination (mL/min/kg)
Fentanyl	–	5.1 ± 1 L/kg [55]	CYP3A4, 3A5, 3A7 to norfentanyl (inactive) [55]	5.3 ± 1.2 h [55]	17.9 ± 4.4 [53]
Preterm					
Term infants to 1 month	–	5.1–17 L/kg [55]	–	4.6–17.7 h [55]	8 [55] 11.5 ± 4 [55]
>1 month to 1 year	–	4.5 L/kg [56]	–	21 h (range 11–36) *Critically ill [20]	8 [55] 18.8 [55]
>1 year	30–36 (intravenous form) [59] 50 (lozenge) [58, 60]	3.1 L/kg [56]	–	21 h (range 11–36) *Critically ill [61]	8.1 [56] 13.2 ± 2 [56]
Adolescents	20 (nebulized) [61]	4.7 ± 2.1 L/kg [58] (obese)	–	3.5 ± 2.2 h [57] 4.8 ± 2 h (obese) [58]	11.2 ± 2.6 [58] (obese)
Adults	52 (lozenge) [58]	1.6–4 L/kg [65]	–	3.7 h [53]	13.2 ± 2 [56]
Alfentanil	–	0.82 ± 0.3 L/kg (infants) [76] 1.03 ± 0.71 L/kg [76] (adults)	67% bound to alpha$_1$-acid glycoprotein [77]	321 min (critically ill preterm) [77] 63 ± 24 min (infants) [77] 95 ± 20 min (adults) [78]	0.87 [77] 11.1 ± 3.9 (children) [77] 5.9 ± 1.6 (adults) [78]
Sufentanil	–	2.9 L/kg [77]	79% bound to alpha$_1$-acid glycoprotein [79] demethylated, dealkylated	7.2 ± 2.7 h [79] (neonates) 97 ± 42 min [79] (2–8 years) 76 ± 33 min [79] (adolescents)	6.7 ± 6.1 (preterm) [79] 18.1 ± 2.7 [79] (infants) 16.9 ± 3.2 [79] (children) 13.1 ± 3.6 [79] (adolescents) 30.5 ± 8.8 [79] (adults)
Remifentanil	–	0.452 L/kg (<2 months) [84] 0.22–0.38 L/kg (>2 months) [84]	Rapidly metabolized by plasma esterase [84]	3.4–5.7 min [84]	90–92 (2 months to 2 years) [84] 46–76 (>2 years) [84]

CYP cytochrome P450

versus swallowed dose [61]. When comparing the time needed to reach a desired concentration of 0.6 ng/mL, the orally administered fentanyl and the fentanyl lozenge displayed nearly identical values (0.64 h vs 0.55 h) [61]. Other similar variables include half-life, volume of distribution, and clearance.

7.3 Nebulized Pharmacokinetics

Fentanyl has been delivered by nebulization and compared to intravenous morphine in children aged between 4 and 13 years [62]. The bioavailability of opioids via the inhalation route has been shown to be approximately 20% of the intravenous dose but with wide variations [63]. Fentanyl 4 µg/kg delivered via nebulization provided comparable analgesia to 0.1 mg/kg intravenous morphine [62]. Miner et al. [64] studied 41 children (aged 6 months to 17 years) comparing 3 µg/kg fentanyl via nebulizer to intravenous fentanyl 1.5 µg/kg and found similar effects on pain relief, but was less effective in those aged < 3 years. This was believed to be due to limitations of the younger patients to trigger the nebulizer system.

7.4 Transdermal Pharmacokinetics

Transdermal fentanyl patches have been in clinical use since the 1990s. The newer-generation patches contain fentanyl dissolved in a semisolid polyacrylate matrix [65]. The drug is released from the patch at a constant rate and absorbed into the skin. Release from the skin depot has been described as first-order elimination in adults [66]. In one study, children aged 7–16 years took longer to reach steady state than adults, with some taking as long as 66 h [67]. Even younger children (aged 1.5–5 years)

have been evaluated with transdermal fentanyl and had a higher clearance than adults [68]. Transdermal fentanyl has been studied in children with chronic pain secondary to malignancy and non-malignant disease and proven to be an effective alternative to more invasive drug delivery [69]. It is recommended that a child receives a minimum of 60 mg oral morphine equivalent before transdermal fentanyl is considered an option [69]. Children often require more frequent patch changes (36–48 h vs 72 h) for most effective pain control. This is most likely due to poor patch adhesion, along with greater drug clearance seen in the younger patients [69].

7.5 Fentanyl Dosing

7.5.1 Intravenous Dosing

Opioid-naive neonates should be initially given intravenous fentanyl doses of 0.5–3 μg/kg/dose, repeated every 2–4 h or a continuous infusion of 0.5–2 μg/kg/h [70]. When fentanyl is given in neonates during ECMO, initial doses of 5–10 μg/kg slow intravenous push over 10 min then 1–5 μg/kg/h and higher doses (up to 20 μg/kg/h) may be required [57].

Doses of fentanyl in infants, children, and adolescents for acute pain (opioid naive) are 1–2 μg/kg/dose, given at 2–4 h intervals [15]. In opioid-tolerant or younger patients higher doses may be required. Adolescents who weigh < 50 kg should be dosed at 0.5–1 μg/kg/dose, repeated every 1–2 h, but administration of a second dose after 30 min may be necessary in cases of severe pain [15]. Children > 50 kg should be given fentanyl at doses of 25–50 μg. Doses that are administered prior to procedures or for sedation remain at 1–2 μg/kg/dose (for infants and children) and 0.5–1 μg/kg/dose for adolescents, administered 3 min prior to the procedure. Fentanyl is also utilized as an adjunct for general anesthesia in doses ranging from 2 to as high as 20 μg/kg/dose, depending on the level of sedation/anesthesia to be achieved [71].

7.5.2 Transmucosal Dosing

Fentanyl provided in the oral lozenge form is only available at a dose of 200 μg and is intended for use in adolescents aged ≥16 years. It is meant to be consumed over a period of 15 min. A second 200 μg dose can be administered 15 min after completion of the initial dose if pain is unrelieved. A 4-h interval is required before treating a second pain episode [72].

Intranasal administration of fentanyl is accomplished using the intravenous formulation. Doses of 1.5 μg/kg/dose (range of 1–2 μg/kg with 100 μg maximum) have been studied [73, 74]. Initial doses of 1.5 μg/kg/dose allow for additional doses of 0.3–0.5 μg/kg/dose to be administered every 5 min, not to exceed 3 μg/kg total dose) until successful pain control is achieved [73, 74].

Nebulized fentanyl has been given effectively in infants and children weighing > 10 kg at doses of 1.5 μg/kg (maximum of 100 μg) with a reported range of 1–2 μg/kg with additional doses of 0.3–0.5 μg/kg up to a total dose of 3 μg/kg. Furyk et al. [62] administered 4 μg/kg of nebulized fentanyl in a total volume of 5 mL of normal saline via a standard nebulizer in children (aged 4–13 years) with limb fractures and found it to be equally effective as intravenous morphine.

7.5.3 Transdermal Dosing

Fentanyl transdermal patches should only be used in children aged ≥ 2 years who are opioid tolerant and receiving at least 60 mg oral morphine equivalents per day [75]. Dose conversion from oral morphine equivalents to fentanyl dosage may be approximated by the 24-h morphine dose equivalents. Due to substantial inter-patient variability, it is safer to underestimate a patient's daily fentanyl requirement and provide breakthrough pain relief with an immediate-release opioid [75]. With the initial application, the absorption of fentanyl required several hours to reach steady state. Transdermal fentanyl is always inappropriate for the management of acute pain and is considered contraindicated.

8 Alfentanil

Intravenous alfentanil is an analog of fentanyl with around 10–25% of the potency but with a more rapid onset. Marlow et al. studied the pharmacokinetics of alfentanil in 22 ventilated preterm infants with a single dose of 20 μg/kg [76]. The median clearance was 0.87 mL/kg/min and the median elimination half-life was 321 min, each with a wide variation. Roure et al. determined the pharmacokinetics of 20 μg/kg alfentanil in 20 children, aged 10 months to 6.5 years [77]. They found a similar volume of distribution of 0.82 ± 0.3 L/kg and 1.03 ± 0.71 L/kg and plasma protein binding of 11.5 ± 0.9% and 11.8 ± 3.9% in children and adults, respectively. The elimination half-life was significantly shorter (63 ± 24 min vs 95 ± 20 min) in children than adults [77].

9 Sufentanil

Sufentanil is between 5 and 10 times more potent than fentanyl but with a shorter duration of action [78]. The mean distribution half-life is 5.2 ± 2.2 min and the mean elimination half-life is 97 ± 42 min. The volume of distribution at steady state is 2.9 L/kg/min and the mean clearance is

30.5 ± 8.8 mL/kg/min. In adolescents with chronic renal failure [79], the pharmacokinetic parameters (half-life and clearance), while variable, were not found to be different than those with normal renal function. Greeley et al. studied 28 patients ranging from neonates to adolescents undergoing cardiovascular procedures [80]. Clearance was determined to be lower in the neonatal group (6.7 ± 6.1 mL/kg/min) than the values of 18.1 ± 2.7, 16.9 ± 3.2, 13.1 ± 3.6 in infants, children, and adolescents, respectively. The volume of distribution was significantly greater in neonates when compared to children and adolescents [80]. Finally, the elimination half-life was also significantly longer in the neonatal group than in the others. Sufentanil is also highly protein bound to alpha$_1$-acid glycoprotein in plasma. Even though this has not been shown to be clinically relevant, the mean free fraction was significantly higher in newborns compared to older infants, children, and adults. This is in accordance with the lower concentrations of alpha$_1$-acid glycoprotein found in newborns [78]. Sufentanil has also been studied in 41 critically ill children and was found to have high inter-individual variability in all pharmacokinetic parameters [81].

Sufentanil has also been administered intranasally as a preoperative/preinduction medication and obtained plasma concentrations were correlated to clinical effects [82]. A dose of 2 μg/kg of sufentanil was administered as a nasal drop 10 min prior to general anesthesia. Venous blood samples drawn at 15, 30, 60, 90 and 150 min showed a peak plasma sufentanil concentration occurring between 15 and 30 min and persisting well into the operative period. While the onset (10 min) was rapid, the longer duration of effect may severely limit the use in short diagnostic procedures where other medications may be more advantageous [82].

10 Remifentanil

Remifentanil is an ultra-short-acting piperidine derivative that is rapidly metabolized by plasma esterases, with a potency of twice that of fentanyl [83]. This unique metabolism results in a predictably rapid elimination despite prolonged administration and decreased hepatic function. Ross et al. [84] studied 42 children (aged 0–18 years) undergoing elective surgery, and found the largest volume of distribution in infants aged < 2 months (0.452 L/kg) compared to means of 0.223–0.308 L/kg in those aged > 2 months. Infants aged < 2 months and those aged between 2 months and 2 years also had more rapid clearance of remifentanil at 90 mL/kg/min and 92 mL/kg/min, respectively, compared to the means of all other groups (46–76 mL/kg/min). The half-life was similar in all age groups (3.4–5.7 min) [84]. Standing et al. studied seven infants (aged 3 months to 1 year) undergoing cranioplasty surgery, specifically looking at the hypotensive effect of the drugs [85]. During pediatric neurosurgical procedures, anesthetic techniques that induce a moderate degree of hypotension [a 30% reduction in mean arterial blood pressure (MAP)] lead to less blood loss and fewer blood transfusions. They found a clearance of 2.22 L/min/70 kg, similar to those values mentioned above [84]. They also determined that a steady-state concentration of remifentanil of 14 ng/mL should lead to a 30% reduction in MAP. This would require a typical 7.5-kg infant to receive a loading dose of 36 μg/kg followed by a continuous infusion of 8 μg/min.

11 Summary on Information Pertaining to Fentanyl and Derivatives

The accumulated knowledge of the pharmacokinetics and pharmacodynamics of fentanyl in the premature, neonate, infant, children, and adolescent make it the favored choice of the synthetic opioid fentanyl and its derivatives. While there has been some research into the use of alfentanil and sufentanil in these age groups, there lacks sufficient reason to recommend their use over fentanyl. As outlined in Sects. 7.1–7.4 [62, 71–75], the various routes of administration and the accumulated evidence on the use of fentanyl favor its use over the other derivatives. Remifentanil, with its rapid metabolism by plasma esterases, makes it attractive for use in patients with reduced hepatic function and those requiring prolonged use. As more research is performed with remifentanil and the other fentanyl derivatives, clinical situations may be identified that may favor the use of alfentanil, sufentanil or remifentanil over the more widely used fentanyl.

12 Methadone

Methadone is also a μ- and κ-receptor agonist but also has weak *N*-methyl-D-aspartate (NMDA) receptor antagonist properties. Its action at the NMDA receptor is believed to prevent or at least attenuate opioid tolerance, which is more common to other opioids [86]. In the pediatric population, it is primarily used in the treatment of neonatal abstinence syndrome (NAS, weaning children from chronic opioids) and in cancer pain. With a longer duration of action, methadone is useful in these clinical situations.

Methadone has an oral bioavailability of 0.86 [87] and a clearance similar across neonates, children, teenagers, and adults [88]. Methadone is metabolized by CYP3A4, CYP2B6 and CYP2D6, all of which are immature at birth. It is believed that CYP3A7 is increased at birth through to 6 months of age, at which time CYP3A4 levels rise to

accommodate [89]. Methadone has a high lipid solubility, similar to that of fentanyl and sufentanil, leading to rapid distribution into fat tissues and the central nervous system [90].

Methadone has good bioavailability, reported to be 70–80% (reported range is 36–100%) and a maximum concentration following oral dosage of 2.5–4 h (range 1–5 h) [91].

Wiles et al. characterized the population pharmacokinetics of oral methadone in NAS [89]. They found considerable inter-individual variability in methadone drug concentrations which were best described by a one-compartment model with first-order absorption. Twenty neonates had population mean values for volume of distribution of 2.53 L/kg, whereas Berde et al. [92] found this value to be 7.1 ± 2.5 L/kg in children. The terminal half-life was found to be 19.2 ± 13.6 h with a range of 3.8–62 h. These values correspond well with adult data when the bioavailability of the oral form is considered [86]. Intravenous methadone and its metabolites were studied in 5–18-year-old patients undergoing major spine surgery [93]. Methadone pharmacokinetics were found to be linear over the dose range of 0.1–0.3 mg/kg. The study found that perioperative methadone disposition in adolescents was similar to that in adults. It should be noted that methadone may persist in the liver and other tissues and that slow release from these tissues may prolong the pharmacologic effect, even in the setting of low serum concentrations. Thus caution must always be employed during methadone therapy as it may accumulate, leading to sedation and potentially respiratory depression.

12.1 Methadone Dosing

When methadone is used for NAS, initial doses are usually 0.05–0.1 mg/kg/dose administered every 6 h [94]. When methadone is to be tapered, the dose should be reduced by 10–20% of the effective dose every 1–2 days, based on patient response. Alternatively, the effective dose may be maintained and the dosing interval may be extended, or a combination of dose and interval taper may be employed [94].

When methadone is employed for severe pain in infants aged < 6 months, doses of 0.025 mg/kg/dose should be administered every 4–6 h intravenously compared to 0.025–0.05 mg/kg/dose every 4–8 h orally [95]. Infants aged > 6 months, children, and adolescents have been administered 0.1 mg/kg/dose intravenously every 4–8 h if < 50 kg. Patients weighing > 50 kg have been treated with doses of 5–8 mg every 4–8 h. Oral methadone is dosed at 0.1–0.2 mg/kg/dose every 4–8 h in those weighing < 50 kg and 5–10 mg every 4–8 h in those > 50 kg [95]. Methadone is often used to treat iatrogenic opioid dependency and the recommended dose is 0.05–0.1 mg/kg/dose every 6 h, increasing the dose by 0.05 mg/kg/dose until withdrawal symptoms are controlled. This is followed by a regimen of interval lengthening to every 12–24 h and/or a dose taper until a final dose of 0.05 mg/kg/day is reached, then discontinued [96].

13 Buprenorphine

Buprenorphine is a semi-synthetic opioid derived from thebaine, an opium alkaloid [97]. It is a partial agonist–antagonist at the μ-receptor, with slow dissociation from the receptor. It has very low oral bioavailability due to extensive first-pass metabolism. Barrett et al. [98] studied the pharmacokinetics of buprenorphine in 12 premature neonates (27–32 weeks gestational age) given a continuous infusion and found a clearance of 0.23 ± 0.07 L/h/kg, an elimination half-life of 20 ± 8 h and a volume of distribution of 6.2 ± 2.11 L/kg (Table 5). Although direct measurements of analgesia and sedation were not made, 25% of patients required additional buprenorphine doses and led the authors to recommend that buprenorphine by continuous infusion should not be utilized in neonatal intensive care [98]. Ng et al. [99] analyzed 24 neonates and 5 adults and found a two-compartment model with first-order absorption best described the pharmacokinetics of sublingual buprenorphine in neonates. They described the 'typical neonate' with NAS (2.9 kg, postnatal age of 5.4 days) to display a clearance of 3.5 L/kg/h and elimination half-life of 11 h (Table 5). The clearance of buprenorphine was linear with body weight and age [99]. Moore et al. [100] recently studied 28 neonates with NAS who received buprenorphine and found a negative linear relationship between average concentration (C_{ave}) and time to NAS stabilization (TNS), which provides evidence that increasing the buprenorphine C_{ave} can decrease TNS. They determined that a C_{ave} of 0.8 ng/mL provided the best opportunity for success in treating NAS [101]. This is similar to adult data that suggested control of withdrawal symptoms at a buprenorphine concentration of 0.7 ng/mL [102]. Moore et al. estimated a pharmacokinetic target for NAS stabilization was an AUC_{0-inf} of 40 ng·h/mL [100]. This appeared to be required in order to achieve a shorter time to stabilization and control of symptoms. They estimated that an initial dose of 15 μg/kg every 8 h reached the 0.8 ng/mL target within 2 days for the majority of patients [101].

13.1 Buprenorphine Dosing

When buprenorphine is used for the treatment of NAS, the initial dose employed has been 5.3 μg/kg/dose every 8 h,

Table 5 A summary of pharmacokinetics of methadone and buprenorphine

Drug	Bioavailabilty (%)	Distribution	Metabolism	Half-life (h)	Elimination
Methadone	86 [87]	2.53 L/kg [89] 7.1 ± 2.5 L/kg [88] (adults)	CYP3A4, 2B6, 2D6, 3A7[a] [87]	19.2 ± 13.6 [89]	8.94 L/h/70 kg [89]
Buprenorphine	46–65 [100] (buccal film)	6.2 ± 2.11 L/kg [100] 3.2 ± 2 L/kg [99]	CYP3A4 to norbuprenorphine [98]	20 ± 8 [98] 11 [99] (term)	0.23 ± 0.07 L/kg/h [99] 3.5 L/kg/h [100]

CYP cytochrome P450

[a]Increased from birth to 6 months

with the dose increasing by 25% increments based on NAS scores. A rescue dose of 50% has been used between scheduled doses [103]. Similar to the use of morphine for NAS, buprenorphine is weaned after two days of stable symptoms at a recommended dose reduction of 10% per day [103].

Buprenorphine can be utilized for the treatment of moderate to severe acute pain and has been used in doses of 2–6 µg/kg/dose every 4–6 h in children aged 2–12 years [104]. A transdermal patch is also available that has been used for chronic pain and initial dosing is based on morphine equivalents, with patch sizes ranging from 5 to 20 µg/h.

The use of buprenorphine for opioid dependence has been used in adolescents aged 16 years and adults [105]. Doses begin at 2–4 mg initially, given after mild to moderate withdrawal symptoms appear. Doses are increased until a clinically effective dose is reached. Daily doses of at least 8 mg/day are usually necessary with a maximum considered to be 24 mg/day. Oral buprenorphine should be administered with naloxone in order to reduce the abuse potential of the drug.

14 Nalbuphine

Nalbuphine is a synthetic opioid agonist–antagonist that is actually structurally similar to the pure antagonist naloxone [106]. Nalbuphine was administered to 20 children (8–15 kg, mean age 3–4 years) as a loading dose (0.2 mg/kg over 10 min) followed by a continuous infusion of 0.8 mg/kg over 24 h. Population parameters included a clearance of 41 L/h, mean volume of distribution of 5.5 L/kg, and elimination half-life was 2.7 h. The total body clearance decreased significantly as age increased [106]. Jaillon et al. [107] found similar changes in clearance with age. However, the elimination half-life reported by Jaillon et al. was 1.5–2 times higher than reported by Bressolle et al. [106].

15 Pentazocine

Pentazocine is a κ-opioid agonist and µ-receptor antagonist that was released for human use in 1967. It has been used very little in pediatrics, thus relevant pharmacokinetic and pharmacodynamic data are limited. Hamunen et al. [108] described the use of pentazocine in 10 children following a single intravenous dose after ophthalmic surgery. They described an elimination half-life of 3 ± 1.5 h and clearance of 21.8 ± 5.9 mL/min/kg, which were similar values to those of adults. The authors did report a significant impact on ventilatory rate, oxygen saturation, and end-tidal carbon dioxide [108].

16 Butorphanol

Butorphenol is a competitive µ-receptor antagonist that provides analgesia through an agonist effect at the κ-receptor. Although the drug was initially marketed in an intravenous and nasal formulation, only the nasal form is currently available. While pediatric information is lacking for butorphenol, pharmacokinetic information is available for adults. Davis et al. [109] (Table 6) determined that intranasal butorphenol had a mean bioavailability of approximately 80% and rapid absorption led to a median time to reach maximum concentration of 20 min. Half-life was 4.63 ± 1.2 and 4.39 ± 0.91 h, for the 1 mg and 2 mg doses, respectively. Clearance was nearly identical, at 141 ± 34.8 and 140 ± 30 L/h for 1 and 2 mg doses, respectively [110].

17 Tramadol

Tramadol is a synthetic 4-phenyl-piperidine analog of codeine that is a racemic mixture where the (+) enantiomer as well as the metabolite (+)-O-desmethyl-tramadol (M1) binds to µ-opioid receptors [111] (Table 6). The (+) enantiomer inhibits serotonin uptake and a direct serotonin-releasing action; while the (−) enantiomer inhibits norepinephrine uptake and increases its release [111]. Tramadol is metabolized to the M1 form by CYP2D6 and has been described in the neonatal population by Allegaert et al. [112, 113]. Tramadol is described as increasing from the youngest (25 weeks post-conception age; PCA) to reach 84% of adult values at only 44 weeks PCA. Clearance was found to be 5.52 L/h/70 kg, and central volume of distribution at

Table 6 Pharmacokinetic parameters of butorphanol and tramadol

Drug	Bioavailabilty (%)	Distribution (L/kg)	Metabolism	Half-life	Elimination
Butorphanol	80 (nasal) [110]	–	–	4.63 ± 1.2-h [111]	141 ± 30 L/h/kg [111]
Tramadol	75 [112]	4.1 ± 1.2 [112]	CYP3A4, 2D6, active metabolite O-desmethyl tramadol [112]	3.6 ± 1.1 mL/kg/min [115]	12 mL/min/kg (children) [115] 7.3 mL/min/kg (adults) [115]

CYP cytochrome P450

25 weeks of 256 L/70 kg was found to be 120% of adult value at 87 weeks PCA. The formation of the M1 metabolite (i.e., the impact of the CYP2D6 activity) was not related to the PCA and is highly variable [112, 113]. Payne et al. [114] gave oral tramadol drops to 24 dental surgery patients (mean age 5.3 ± 1.1 years) and found rapid absorption (30 min), a half-life of 3.6 ± 1.1 h, serum clearance of 5.6 ± 2.7 mL/min/kg, and volume of distribution of 4.1 ± 1.2 L/kg. Garrido et al. [115] found an increased clearance of 12 mL/min/kg in younger children (2–8 years) versus an adult value of 7.3 mL/min/kg. Vandenbossche et al. [116] studied oral tramadol in 38 children aged 7–16 years who received a single dose of immediate-release tramadol (1–2 mg/kg, average dose 1.4 mg/kg). The half-life of tramadol and M1 was shorter in children and adolescents compared to adults as well as the normalized clearance. Furthermore, the apparent oral clearance was higher in pediatric patients with lower body weight [116]. The pharmacokinetics of rectal tramadol in postoperative pediatric patients were studied by Zwaveling et al. [117]. The authors found an elimination half-life of 4.3 ± 0.2 h and an apparent clearance of 16.4 ± 1.5 L/h. Their data suggested that a rectal dose of 1.5–2 mg/kg is therapeutic.

In 2017, the FDA added to the warning labels of tramadol, making it contraindicated for use in treating pain in children aged < 12 years. This also included a contraindication on the use of tramadol in children aged < 18 years to treat pain after surgical removal of the tonsils and adenoids, as well as use in breastfeeding women [118]. Tramadol is extensively metabolized in the liver by CYP2D6 and CYP3A4 [119]. CYP2D6 metabolism leads to the O-demethylation to the analgesic metabolite, desmethyltramadol, which has a 200-fold higher affinity for the μ-opioid receptor than the parent drug. Ultra-rapid metabolizers, like those described earlier with codeine (Sect. 3), which affects 5.5% of the population in western Europe, are at an increased risk of respiratory depression from tramadol [119]. Additionally, the European Society for Paediatric Anaesthesiology (ESPA) issued a statement in 2018 addressing tramadol use in children [120]. While these guidelines do not list tramadol as contraindicated, the ESPA has placed strict recommendations on the use of tramadol in children, limiting its use to acute postoperative pain in a monitored setting.

18 Ketobemidone

Ketobemidone is a phenylpiperidine, structurally related to meperidine, and a full agonist at the μ-receptor. It has also been shown to inhibit the excitatory effect of the NMDA receptor agonists [121]. It has been used in adults and children in Scandinavian countries for > 50 years. Lundeberg et al. [122] studied 24 children (5 aged < 90 days, 10 aged 1–2.5 years, and 9 aged 7–10 years) and found the shortest half-life (2 h) in the 1–2.5-year-old group, followed by 3 h (0–90 days) and 3.7 h in those aged 7–10 years. Clearance ranged from 0.74 to 0.89 L/h/kg. The authors determined that the pharmacokinetic parameters of ketobemidone in children aged > 1 month appear similar to those in adults [122]. Lundeberg et al. [121] also published data on the pharmacokinetics of ketobemidone in 15 full-term neonates who were administered a single intravenous bolus dose. The median (range) values of ketobemidone clearance, apparent volume of distribution, distribution half-life, and elimination half-life were 0.46 (0.23–0.84) L/h/kg, 4.64 (3.5–7.31) L/kg, 1.17 (0.16–3.47) L/kg, 2.85 (1.04–10.78) min, and 7.26 (3.5–11.3) h, respectively [121]. The prolonged elimination half-life was thought to be due to a reduced metabolic capacity in the neonatal population, as ketobemidone is a substrate for cytochrome P450 enzymes 2C9 and 3A4 and metabolic capacity for these substances may still be immature [123].

19 Piritramide

Piritramide, considered a morphine equivalent, is a 4-amino piperidine derivative that acts as an agonist at the μ-receptor. Muller et al. [124] studied the pharmacokinetics of piritramide in 25 children (newborns to 4 years), administering a single bolus injection of 50 μg/kg. Subsequent doses of 15 μg/kg were administered in the case of inadequate pain control. The median half-life of distribution was longer in the newborn group (37 min, range 15–189) compared to infants aged between 2 and 4 months (8.4 min, range 3.6–18.1), infants aged between 5 and 12 months (13.2 min, range 2–34.7), and children aged 2–4 years (17.8 min, range 7.5–38). The volume of distribution and total clearance were small in the newborn and young infant groups (2.0 ± 4.93 L/

kg and 15.9 ± 16.7 mL/min) compared to the older infants and young children (7.0 ± 5.2 and 6.7 ± 2.2 L/kg, respectively. The values in the older infants and children compare to adult values of 7 L/kg [124]. Despite the fact that piritramide has been in clinical use for > 30 years, there is a general lack of published information on use in children.

20 Naloxone

Naloxone, a synthetic derivative of oxymorphone, is a pure opioid antagonist with a great affinity for the μ-receptor [125]. In doing so, naloxone reverses opioid-induced respiratory depression, sedation, and hypotension. Naloxone is metabolized by glucuronide conjugation, N-dealkylation, and reduction to the 6-ketone group [125]. It is important to remember that the umbilical vein administration of naloxone in the neonate might reduce the bioavailability of the drug since as much as half of the venous blood flow from the umbilical cord passes through the liver before reaching the general circulation [125]. Infants administered 70 μg naloxone were reported to have a mean plasma half-life of 2.65 ± 1.3 h, apparent volume of distribution of 1.78 ± 0.73 L/kg, and plasma clearance of 576 ± 372 mL/h/kg. This is compared to infants receiving 35 μg naloxone with a half-life of 3.53 ± 2.2 h, volume of distribution of 2.2 ± 1.18 L/kg, and clearance of 564 ± 488 mL/h/kg [125]. Intramuscular administration of 200 μg naloxone resulted in peak concentrations similar to those obtained with 70 μg intravenous but significantly higher than those obtained with 35 μg. The half-life of naloxone in neonates following intravenous dosing was two to three times longer than that reported in adults. This is believed to be secondary to a diminished ability of the newborn to conjugate naloxone with glucuronic acid [126].

Due to the increase in deaths due to opioid overdose, naloxone by intramuscular auto-injector (in 2014) and nasal spray (in 2015) have been introduced. Both products are approved for emergency use in children and adults for suspected drug overdose. The pharmacokinetics of intranasal naloxone have not been studied in children. Intranasal naloxone in doses of 4 mg and 8 mg were compared to 0.4 mg intramuscular and maximum plasma concentrations were reported as 4.83 ng/mL, 9.7 ng/mL and 0.88 ng/mL, respectively. Time to C_{max} was similar among the groups, as were half-lives [127]. The intranasal dose is 4 mg for children as well as adults. If there is no response to the initial dose or if symptoms return, additional doses may be administered every 2–3 min while awaiting emergency assistance or during transport to a hospital.

21 Naltrexone

Naltrexone, an opioid antagonist with high affinity for the opioid receptor, has been proven to be an effective treatment for opioid addiction [128]. It is not utilized for opioid reversal but for alcohol use disorder and for opioid dependence in order to block the effects of exogenously administered opioids. The pharmacokinetics and pharmacodynamics of naltrexone have not been studied in children and current available information is pertinent only to adults. Orally administered naltrexone is well absorbed and has a large volume of distribution of 1350 L. Naltrexone is metabolized via dehydroxygenase conversion to 6-beta-naltrexol. The long-acting intramuscular form is bound to a polymer that erodes and releases the drug, leading to a half-life of 5–10 days. The adult dose of intramuscular naltrexone for alcohol use disorder is a 50-mg loading dose followed by either a 190 mg or 380 mg dose every 28 days [129]. The use of naltrexone could be considered for adolescents and young adults with co-occurring alcohol use disorder.

22 Conclusions

There has been a significant amount of research effort invested into the pharmacokinetics and pharmacodynamics of the various opioid analgesics in the wide pediatric population. As the evidence indicates, the elimination of all opioids is slower in the neonatal population when compared to children and adults. However, this is somewhat temporary as the rate of elimination usually reaches adult values within the first year of life. As metabolic processes may be reduced in the premature and neonatal period, most of these mechanisms mature and may exceed adult values during childhood. In consideration of these variables, as well as weight-based dosing adding to these complexities, it remains critical that each pediatric patient be managed individually, as most of these markers have a high degree of variability.

Funding James C. Thigpen declares that no source of funding was used to prepare this article. Brian L. Odle declares that no source of funding was used to prepare this article. Sam Harirforoosh declares that no source of funding was used to prepare this article.

Compliance with Ethical Standards

Conflict of interest James C. Thigpen declares no conflicts of interest. Brian L. Odle declares no conflicts of interest. Sam Harirforoosh declares no conflicts of interest.

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