Chapter 4: Neonatal Considerations

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INTRODUCTION

FOCUS POINTS

1. Review of pharmacokinetics—developmental principles of absorption, distribution, metabolism, and elimination
2. Review of pharmacodynamics
3. Review of anesthesia-specific medications with a neonatal perspective

As one considers the anesthetic to be delivered to a neonatal patient, it is prudent to give special attention to the ontogeny that will affect this plan. Neonates are children typically defined as age birth to 1 month. However, if born prematurely, as early as 24 weeks, this "neonatal" period is extended. Since neonates are not simply small adults, one must review the developmental aspects of pharmacokinetics and pharmacodynamics prior to administering anesthesia.

The emphasis on a neonatal tailored anesthetic originates from the very basic facts. Start with growth and maturation. Compared with adults, neonates have larger heads, shorter extremities, and larger torsos. Their skin as a vital organ accounts for a much larger percentage of body weight playing a significant role in pharmacokinetics. The rest of their organs are immature in function affecting a drug's ultimate action. With advances in neonatal critical care, infants are born at birth weight of 500 g and gestational age of 24 weeks creating a different physiologic state than previously seen.

PHARMACOKINETICS

When caring for a premature infant, a clinician must respect developmental nuances that make essential a thorough review of neonatal pharmacology prior to anesthetic administration. All infants, but especially premature ones, undergo rapid developmental changes in the postnatal period, which affect each aspect of pharmacokinetics. Pharmacokinetics refers to the disposition of a drug in the body and the processes that affect its course. These processes include drug absorption, distribution, metabolism, and elimination. We will review each process through the neonatal perspective. Fundamental parameters common among these processes include volume of distribution (V_d), clearance, and **half-life**.[1]

a. V_d is a concept used to define the volume required to contain the total amount of a drug at a concentration equal to that in plasma. This "volume" is affected by hydrophilicity and lipophilicity. When a drug is highly water-soluble, it will have a small V_d because it must remain in the intravascular space only. Conversely, when a drug is lipophilic, it is distributed to the entire body and its V_d is much larger. Neonates are considered to have a much larger volume of distribution for hydrophilic drugs compared to a smaller volume of distribution for lipophilic drugs.

b. Clearance is the organ's ability to clear or eliminate a drug from an amount of fluid (blood or plasma). This is a concept that will be further elaborated in the section on elimination. This capability is also affected by the eliminating organ's maturity, whether it will be the liver or the kidney.

c. Half-life is the time required for half the amount of a drug in the blood to be removed from the body[2]

Absorption

The first process in the pathway of pharmacokinetics is absorption, that is, the transfer of a drug from the site of administration into the circulation.[3] There are many factors that can affect the rate of absorption just like there are many modes of medication administration to consider. Possible routes for a neonate include oral (or via a feeding tube), rectal, intramuscular, subcutaneous, and topical. There is a great variability in drug absorption into a neonate's circulation, as their fat, muscle, fluid, and skin compartments are all underdeveloped and not taken into consideration when the initial drug studies are designed. While in the operating room, absorption is not commonly a concern as most of our medications are administered intravenously. However, anesthesia providers must consider alternative modes of administration should the need arise.

Enteral absorption is not reliable in a neonate for two main reasons. Neonates are susceptible to delayed gastric emptying and venous congestion. Delayed gastric emptying and poor intestinal absorption are multifactorial related to gastroesophageal reflux, poor perfusion due to illness, disease of the intestines (short-gut syndrome), irregular peristalsis, and the composition of breast milk or formula consumed.[2] Gastric emptying will reach adult rates by 6 to 8 months of life. Drugs administered via the rectum will also be affected by similar factors though the mechanism proposed is passive diffusion. If the drug is placed in the superior aspect of the rectum it will enter the portal circulation and undergo hepatic first-pass metabolism as compared to a lower rectal placement that will initially bypass the liver.[2]

Intramuscular (IM) absorption depends primarily on blood flow which can be compromised in states of low perfusion such as respiratory distress and hypoxemia, cardiac dysfunction, and sepsis all more frequently seen in premature neonates. Absorption also depends on skeletal mass which is less in neonates than in adults; medication contact time is decreased resulting in reduced absorption. Lack of muscle movement/activity from illness or a muscle relaxant agent may also affect absorption and thus peak serum concentration. Higher density of skeletal muscle capillaries has a theoretical increase in absorption after IM injection in neonates.[1] Medications commonly used intramuscularly in the operating room include atropine, glycopyrrolate, opioids, ketamine, and succinylcholine.

Percutaneous absorption has clinical significance but is often overlooked. It is related to skin hydration and surface area, but inversely related to the thickness of the stratum corneum.[2] A neonate has a larger ratio of surface area to body weight and a thinner stratum corneum, and when combined with better perfusion as seen in full-term infants,[1] topical medication bioavailability may be increased. It is estimated that when a medication is applied topically, neonates are *exposed* to 2.7 times the amount intended as compared to a similar application to an adult or child.[4] For example, in the operating room when cleansing solutions are used before a peripheral nerve block or an epidural catheter is placed, and prior to venous or arterial catheterization, toxic exposure can be a real risk. Similarly, when topical local anesthetics (EMLA, LTA, lidocaine gel) of various concentrations are used prior to procedures (ENT procedures, orogastric tube placement, nasotracheal intubation) clinicians need to be cognizant of their potency to prevent toxicity.

Other risk factors associated with toxicity include damaged skin due to trauma, burn, or infection and prematurity due to immature barrier.

Distribution

Distribution is the next step in the process of pharmacokinetics and involves medication distribution into compartments of the body. A key factor in this process is the age of the patient and its related physiologic changes—circulating binding proteins, compartment sizes, and membrane permeability. Other factors include affinity to circulating proteins, available binding sites, disease states, hemodynamics and presence of endogenous compounds such as bilirubin.

Protein binding becomes significant because it limits the amount of active drug available in circulation. Total drug in the body is the sum of bound drug (drug + protein) and unbound drug. The "bound" drug molecules are not active and not capable of crossing membranes or binding to receptors to trigger pharmacologic action, metabolism, and excretion. Binding to serum proteins is a rapidly reversible process that creates a dynamic system of drug availability to transfer across membranes.[1] The amount of unbound drug is much larger in neonates who have an altered ratio and affinity of proteins. Plasma proteins that most commonly bind to medications include albumin and alpha-1-acid glycoprotein. Albumin binds acidic medications and the affinity between the two is not at adult levels at birth, nor are total plasma protein levels. Albumin levels at birth are approximately 75% to 80% of adult levels which they reach at about a year of age.[1,2] Alpha-1-acid glycoprotein is at 50% of adult levels at birth.[1] Although the total amount of drug concentration appears to be in the therapeutic range for adults and older children, the free-drug concentration may in fact lay in a toxic range for the premature patient.

When cord blood has been studied and tested for protein binding, it is shown that there is a significant reduction in binding medications such as lidocaine and propranolol as compared to the serum of an adult.[2]

Aside from protein availability to determine distribution, total body water also makes a significant contribution. Composition of body compartments, such as total water and total fat varies with gestational age (Table 4-1), alter the volume of distribution for each drug and will theoretically influence medication concentration available for distribution and effect.

Table 4-1

Percentage Fat Based on Gestational Age[3]

Gestational Age	% Body Weight	% Fat
24 wks	89	0.1–0.5
40 wks	75	15
6 mos	60	30
Adult	65	20

Source: Data from MacDonald MG, Seshia MMK, Mullett MD, eds. *Avery's Neonatology*, 6th ed. 2005. Copyright © Lippincott Williams & Wilkins. All rights reserved.

Hydrophilic drugs such as acetaminophen or vancomycin have a larger volume of distribution in a newborn per kilogram of body weight compared with an adult. Theoretically, neonates and infants could require larger doses per weight to reach therapeutic serum concentrations. Conversely, for a full-term healthy baby, his or her fat content is large enough to make the assertion that lipophilic drugs will have a large volume of distribution, similar to hydrophilic medications. The low-fat content of the extremely premature infants' brain may affect distribution of centrally acting medications as outlined in Table 4-2 as compared to their adult counterpart in Table 4-3. For example, propofol is a lipophilic drug routinely administered in the pediatric operating room. Neonates have lower total body fat compared to an adult, which allows propofol to have a smaller volume of distribution in the central compartment and higher plasma concentrations. This scenario places the neonate at risk for toxicity that is unique to their population.

Table 4-2

Pharmacology of Intravenous Anesthetic Agents in Extremely Premature Infants[5]

Medications	Dose (mg/kg)	V_d (L/kg)	Elimination Half-Life (h)
Propofol	2.5	9.5	
Phenobarbital	2 PO TID	0.8–1.2	60–180
Fentanyl	0.001–0.005	1.0	4.2
Morphine	0.05–0.1		6.8
Acetaminophen	10–15 PO (60 mg/d max)	1.0	4.8
Rocuronium	0.6–1.2		
Midazolam	0.1	1.15	14.1

Source: Data from Khan KS, Hayes I, Buggy DJ. Pharmacology of anaesthetic agents I: intravenous anaesthetic agents. *Cont Ed Anaesth Crit Care Pain.* 2014;14:3. https://www.journals.elsevier.com/british-journal-of-anaesthesia

Table 4-3

Pharmacology of Intravenous Anesthetic Agents in Adults[5]

Medications	Dose (mg/kg)	V_d (L/kg)	Elimination Half-Life (h)
Propofol	1–2	4.6	4–7
Phenobarbital	30–120 PO TID	0.5–0.6	53–118
Fentanyl	—	4.0	3.7
Morphine	0.05–0.1		
Acetaminophen	12.5	0.9	2
Rocuronium	0.6–1.2		
Midazolam	—	1.1	1.9

Source: Data from Khan KS, Hayes I, Buggy DJ. Pharmacology of anaesthetic agents I: intravenous anaesthetic agents. *Cont Ed Anaesth Crit Care Pain.* 2014;14:3. https://www.journals.elsevier.com/british-journal-of-anaesthesia.

Membrane permeability of the newborn blood-brain barrier (with incomplete myelinization) is increased, thus creating a higher drug concentration in the central nervous system with possible perioperative effects.[4]

Increased presence of unconjugated bilirubin and free fatty acids can compete with medications that are protein bound, displacing those drugs and

creating an increase in free drug concentration. Hyperbilirubinemia as seen in the jaundiced neonate can reduce protein binding of penicillin, ampicillin, and phenobarbital necessitating dose adjustments. In combination with an increase in unbound drug, by nature of immature plasma proteins, hyperbilirubinemia creates a scenario in which the amount of drug now free for distribution to the tissues may place the infant at risk of toxic exposure. Presence of certain medications such as diazepam and phenytoin can displace bilirubin from albumin binding sites, increasing the risk of kernicterus.[6] Otherwise known as bilirubin encephalopathy, kernicterus results from deposition of bilirubin in the brain potentially leading to cerebral palsy, hearing loss, vision problems, or mental retardation. The binding affinity of albumin for bilirubin increases with age and does not reach adult levels until approximately 5 months of age. If a neonate is on one of these bilirubin-displacing medications, preoperative discussion should ensue to avoid perioperative morbidity.

Metabolism

Metabolism encompasses bioactivities by which a drug may get activated, inactivated (for elimination), or converted into a toxic metabolite. These reactions are identified as phase I, oxidation, reduction, or hydrolysis; or phase II, conjugation reactions which are glucuronidation, sulfation, and acetylation.[3] Phase I reactions modify the structure of the drug, altering a functional group and causing it to become polar(water-soluble). This results in activation or inactivation of the parent drug. Phase II reactions add an endogenous molecule to the drug or its metabolite. This process makes the product further water-soluble allowing it to be eliminated via bile or urine.[1] These transformations occur primarily in the liver. Other sites of metabolism include the kidneys, red blood cells, intestines, lungs, and skin. Phase I reactions in the liver are supported by the cytochrome P-enzymes (CYP). Many of the medications administered in the operating room during a general anesthetic are metabolized by these two reactions. Each site of metabolism plays a role and it is important to remember that during compromised perfusion states in the operating room the overall ability of the body to activate and eliminate medications may be altered. Specifically for newborns, hepatic blood flow is increased at birth as the ductus venosus is eliminated. This change occurs during the first week of life. However, it is not fully mature until age three.

Phase I Enzymes

Newborns have a reduced total quantity of cytochrome P450 microsomes and at term will only reach 50% of adult values.[3] It can be assumed that a reduced enzyme concentration in neonates will dictate prolonged half-lives of medications such as caffeine, phenytoin, and phenobarbital. However, due to the complexities of the developmental patterns of cytochrome enzymes, one cannot make broad generalizations regarding a neonate's metabolizing capabilities. CPY3A, an important such enzyme associated with many substrates such as acetaminophen, alfentanil, diazepam, lidocaine, midazolam, verapamil, and R-warfarin, is functionally active in the fetus mainly as CYP3A7 with activity reaching 75% of adult levels by 30 weeks' gestation. Postnatal activity has been found to be low but is near adult level by 6 to 12 months. It is also induced by dexamethasone, phenobarbital, and phenytoin requiring adjustment of substrate medication dosing.[3]

Phase II Reactions

The purpose of phase II reactions is to change the substrate to make it easier to be eliminated through the kidneys. The enzymes associated with phase II conjugation reactions include glucuronosyltransferase, sulfotransferase, *N*-acetyltransferase, glutathione *S*-transferase, and methyl transferase. There isn't as much known of these reactions, but there are some developmental changes that will affect drug clearance.

Morphine is metabolized via glucuronidation to morphine-3-glucuronide and morphine-6-glucuronide. Its metabolism takes place in the liver and kidney, while its elimination is dependent on urine and bile. It is the M6G metabolite that competes for the mu receptor and potentially contributes to the overall analgesic effect of morphine, whereas M3G does not appear to compete for opioid receptor binding. A neonate's ability to glucuronidate morphine is limited and thus its clearance may be limited[7] necessitating a dose adjustment to avoid complications with respiratory depression. Maturation of function of this enzymatic process may not be complete until 6 to 18 months of age.

Acetaminophen appears to be preferentially metabolized in neonates and children. It is metabolized by three phase II reactions: sulfation, glucuronidation, and through cytochrome P450-2E1. The sulfotransferase system is mature in the neonate as compared to the glucuronosyltransferase system previously discussed in the context of morphine. The excretion of acetaminophen is not significantly prolonged in an infant likely due to the formation of the acetaminophen-sulfate conjugate which compensates for the other immature enzyme system. This will become the nondominant product as the liver matures and glucuronidation takes over in the adult. Toxicity is a risk with acetaminophen administration in all humans when glutathione stores cannot compete with frequent dosing. The mechanism of this relates to the P450 pathway which

produces *N*-acetyl-*p*-benzoquinone imine (NAPQI), a toxic metabolite. NAPQI is then metabolized via glutathione to nontoxic cysteine and mercapturic acid. If NAPQI is not metabolized, hepatocyte damage and necrosis of the liver can occur. Acetaminophen's elimination half-life is prolonged in infants from approximately 2 hours in adults to 3.5 hours. While this may not be of concern after a single dose in the operating room, repeated dosing at shorter intervals may lead to potential toxicity in this patient population.[8]

Pharmacokinetics: Elimination

Elimination is the final step in the life of a drug in the human body and refers to processes that remove a drug from the body. Metabolism via biotransformation, as discussed in the section above, with inactivation of the end-product, facilitates elimination. Routes available for excretion and elimination include biliary tract, lungs, and kidneys. Renal elimination plays the largest role in the body's ability to eliminate medications. Drug elimination half-life describes medication removal from the blood and is the time required for half the amount to be removed.[2] Renal clearance is described as the volume of plasma that is cleared of a drug per unit of time through the kidneys.[4] Glomerular filtration, tubular secretion and tubular reabsorption collectively are responsible for renal clearance. If a drug is nonvolatile, water soluble, and has a low molecular weight it will most likely be eliminated by the kidney.

Each of these processes may mature at different times and with a different pattern. Renal function maturation is complete in early childhood. Nephrogenesis is complete after 34 weeks' gestation, which means a premature patient will have difficulty concentrating his or her urine. Any insult to the development of the fetus will affect renal function, for example, growth retardation and nephrotoxic drugs administered to the mother. Similarly, any insult in the postnatal period such as hypoxemia, hypoperfusion, or nephrotoxic drugs will cause renal injury and alter rates of drug elimination for the newborn. Regarding glomerular filtration, this function is not fully developed until 8 to 12 months of age. In a premature infant it can be as low as 0.6 to 0.8 mL/min. Postnatal decrease in renal vascular resistance coupled with an increase in renal blood flow allow for a dramatic increase in GFR within the first 2 weeks of life. Tubular secretion is an active process that is also immature at birth and reaches adult values similarly to the GFR, at 7 to 12 months of age. This activity will alter the course of medications such as antibiotics (penicillins and cephalosporins) which are frequently administered in the operating room. Lastly, tubular reabsorption is a passive process that depends on the characteristics of the drug and fluids present within the proximal and distal tubule.[4] The maturation of this last eliminating process is continual with a peak occurring between 1 and 3 years of age.

Upon conclusion of a review of the principles of pharmacokinetics it should be clear to the reader that when assuming care of a neonate who is either premature or full-term, the practitioner should bear in mind anatomic and developmental differences that may alter the anesthetic plan. Preoperative assessment should include discussion with the neonatologist and pediatric pharmacist for proper dosing strategies in light of renal and hepatic limitations.

PHARMACODYNAMICS

Pharmacokinetics takes into consideration how the body processes a drug, whereas pharmacodynamics (PD) encompasses what actions that drug has on the human body. It is the relationship between the drug's concentration at the receptor and the response evoked. It is that concentration which is dependent on the pharmacokinetic processes that determine if the result will be therapeutic or toxic. Therefore, the concepts to understand when reviewing pharmacodynamics include receptor binding, post-receptor effects, and chemical interactions.[4] With the interaction between these two systems, proper management of medications for the newborn and premature patient can be established. Unfortunately, pharmacodynamics of neonates is not something that has been well studied to the extent of pharmacokinetics. What has been explained is that the PD response should be different in a neonate due to immature receptors and has been studied with a focus on specific medications. An increased sensitivity and risk for toxicity is the overall outcome associated with a neonate's receptors.[9]

An explanation as to the effect of ontogeny on the drug-response dynamic can be extrapolated by examples from the literature. Mu opioid receptors have been shown to have an increased expression in neonates as compared to adults. This would then place the patient at increased risk of narcotics commonly administered in the pediatric operating room, such as morphine or fentanyl.[10] Similarly, a neonate's dose-response to calcium channel blockers is more profound compared to an adult's response with regard to bradycardia and hypotension. Alternatively, a neonatal heart has reduced calcium stores and their myocardium is sensitive to administration of calcium, causing an enhanced contractility response.[11]

DRUG-SPECIFIC CONSIDERATIONS

This section focuses on commonly administered anesthetics and effects seen in the neonatal population. The first is *inhaled anesthetics* which have effects on several biologic systems including the cardiovascular, respiratory, and central nervous systems. The PD response observed in the neonatal cohort frequently in the operating room is a dose-dependent decrease in mean arterial pressure and systemic vascular resistance due to direct myocardial depression and depression of baroreceptor reflex, respectively. Other attributes are shared with adults, such as an increase in the respiratory rate and reduction in tidal volume and functional residual capacity. Dose-dependent increases in cerebral blood flow is coupled with a decrease in cerebral metabolic oxygen consumption.[12]

Morphine is considered the gold standard of narcotics by which other *opioids* are compared. Concerns arise due to an infant's risk of increased sensitivity, specifically to the respiratory depressant properties, as described in the pharmacodynamics section. From a cardiovascular point of view, there is a wide margin of safety for narcotics when used as an anesthetic though depressant effects are observed when used in combination with other medications such as volatile anesthetics and benzodiazepines. Of additional concern is the prolonged elimination half-life of opioids which is significant in a neonate and compounded by changes in hepatic blood flow.[12] An exception is with remifentanil which when studied was found to have a more rapid clearance with a comparable half-life to adults.[13] The most likely explanation for this phenomenon is remifentanil's degradation by red blood cell and tissue esterases which quickly render it inactive.

Benzodiazepines are used routinely in the perioperative period. Their function is multifold: alleviating preoperative anxiety and providing perioperative amnesia, as an adjunct to a balanced anesthetic, as well as for reduction in pain caused by muscle spasm associated with surgical procedures. Their cardiovascular effects are minimal when used alone. The receptors for this class of medications, gamma-aminobutyric acid (GABA), are located in the cerebral cortex, hypothalamus, cerebellum, corpus striatum, and medulla oblongata. These medications have been safely used in the neonatal population; however, studies have shown a prolonged elimination half-life of diazepam and its active metabolites.[14]

Sedative-hypnotic agents such as ketamine have a long history in anesthesiology providing reliable effects for general anesthesia as well as for sedation. Ketamine is an amnestic and holds analgesic properties but is associated with dysphoria and increased secretions. It is also emetogenic, discouraging practitioners from using it more frequently. Ketamine's cardiopulmonary profile is relatively safe as it does not cause the significant respiratory depression and hypotension as predictably as does propofol. The caveat to this is that its effects on the myocardium are indirect via the central nervous system causing increased sympathetic tone. The result is an increased heart rate, systemic blood pressure, and cardiac output. It is important to remember that ketamine directly stimulates the myocardium with a negative inotropic effect. In the chronically ill patient who cannot mount a sympathetic surge, its direct negative effects on the heart will be revealed. Focusing on the neonates, its half-life is significantly prolonged as compared to older children and adults, thus cautious administration at longer intervals should be considered.[15]

Lastly, added in the armamentarium for anesthesiology, sugammadex is now used at hospitals across the United States for the purpose of rapid reversal of nondepolarizing muscle relaxants such as rocuronium and vecuronium. Its reported use in the neonatal and pediatric population is in its infancy at this point. Sugammadex works as a selective relaxant binding agent and its chemical structure is a ring formation. It forms a complex with aminosteroid muscle relaxants such as rocuronium and vecuronium. By binding these drugs at the neuromuscular junction the amount available for action at the receptor is reduced. Metabolism of sugammadex is limited and it is excreted via the kidneys unchanged. The paralytic–sugammadex complex is eliminated via the urine. This process is rapid with approximately 70% of the dose administered excreted in 6 hours. Due to the dependence on the renal elimination, it should not be used in patients with significantly reduced renal function. One study demonstrating its use in neonates dosed sugammadex at 4 mg/kg ($N = 23$) with residual neuromuscular blockade following surgery. Time to recovery of TOF to 0.9 ranged from 1.2 to 1.4 minutes. Recurarization was not observed in this study.[16] Similar rapid results were reported in a premature infant with residual weakness after a vecuronium infusion. In this infant though, reoccurrence of weakness was seen but was attributed to the infant's chronic illness.[17]

REFERENCES

1. Tofovic S. Developmental pharmacology. In: Davis PJ, Cladis FP eds. *Smith's Anesthesia for Infants and Children*. Elsevier; 2016:168–175.

2. Blumer J, Reed MD. Principles of neonatal pharmacology. In: Yaffe SJ, Aranda JV eds. *Neonatal and Pediatric Pharmacology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:179.

3. Ward RM, Lugo RA. Drug therapy in the newborn. In: MacDonald MG, Seshia MMK, Mullette MD eds. *Avery's Neonatology.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:1508–1557.

4. Tayman C. Neonatal pharmacology: extensive interindividual variability despite limited size. *J Pediatr Pharmacology*. 2011;16(3):170–184.

5. Kahn K et al. Pharmacology of anaesthetic agents I: intravenous anaesthetic agents. *Br J Anesthes.* 2014;14(3):100–105.

6. Volpe JJ. Bilirubin-induced brain injury. In: Volpe JJ ed. *Neurology of the Newborn*. 5th ed. Philadelphia, PA: Elsevier Saunders; 2008, pp. 619–649.

7. Christrup LL. Morphine metabolites. *Acta Anaesth Scand.* 1997;41(1 pt 2):116–122.

8. Baker CF. Acetaminophen-induced hepatic failure with encephalopathy in a newborn. *J Perinatol.* 2007;27:133–135. [PubMed: 17262050]

9. Ku L. Dosing in neonates: special considerations in physiology and trial design. *Pediatr Res.* 2015;77:2–9. [PubMed: 25268145]

10. Mulla H. Understanding developmental pharmacodynamics: importance for drug development and clinical practice. *Paediatr Drugs*. 2010;12:223–233. [PubMed: 20593907]

11. Anderson BJ. Pharmacology in the very young: anesthetic implications. *Eur J Anaesth.* 2012;29:261–270.

12. Vitali SH, Camerota AJ, Arnold JH. Anesthesia and analgesia in the neonate. In: MacDonald MG, Seshia MMK, Mullette MD eds. *Avery's Neonatology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:1558–1572.

13. Ross AK. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. *Anesth Analg.* 2001;93:1393–1401. [PubMed: 11726413]

14. Morselli PL. Diazepam elimination in premature and full-term infants, and children. *J Perinat Med.* 1973;1:133–141. [PubMed: 4806567]

15. Grant IS. Ketamine disposition in children and adults. *Br J Anaesthesiology*. 1983;55:1107–1111.

16. Alonso A. Reversal of rocuronium-induced neuromuscular block by sugammadex in neonates. *Anesthesiology*. 2009;110(2):284–294. [PubMed: 19194156]

17. Oduro-Dominah L. Sugammadex for the reversal of prolonged neuromuscular blockage in a preterm neonate. Case Report. *Pediatr Anesth Crit Care J.* 2015;3(1):49–52.