Review Article

Considerations of general anesthetics in pediatric dentistry – A review

S. Shreya[1], Dhanraj Ganapathy[2]*, Visalakshi Ramanathan[2]

ABSTRACT

Pediatric patients present unique anatomic, physiologic, and pharmacologic considerations for the management of anesthesia in the presence of diseases that occur exclusively or with increased frequency in this age group. Neonates generally up to 28 days of age and infants comprise the age group, in which differences from adults are most marked. Neonates are more likely to experience adverse perioperative cardiopulmonary events. Pediatric patients deserve special considerations during administration of general anesthesia with respect to anatomic, physiologic, and pharmacologic differences from adults.

KEY WORDS: Dosage, General anesthesia, Inhalation, Pediatric patients

INTRODUCTION ON PEDIATRIC ANESTHESIA

Pediatric patients present unique anatomic, physiologic, and pharmacologic considerations for the management of anesthesia in the presence of diseases that occur exclusively or with increased frequency in this age group. Neonates generally up to 28 days of age and infants comprise the age group, in which differences from adults are most marked.[1,2] Neonates are more likely to experience adverse perioperative cardiopulmonary events. Pediatric patients deserve special considerations with respect to anatomic, physiologic, and pharmacologic differences from adults.[3]

ANATOMIC DIFFERENCES AND PHYSIOLOGIC DIFFERENCES

Anatomic and physiologic differences between children and adults are important determinants when planning management of anesthesia in pediatric patients.[4] Monitoring vital signs and organ function during the perioperative period is, especially, important, as neonates and infants have decreased physiologic reserves.

Access this article online	
Website: jprsolutions.info	ISSN: 0975-7619

Differences in the anatomy of the airway make the potential for technical airway difficulties greater in infants when compared to teenagers or adults.

The airway of infants differs in five ways:

1. The relatively large size of the infants' tongue in relation to oropharynx increases the likelihood of airway obstruction and technical difficulties during laryngoscopy.[5]
2. The larynx is located higher in the neck (at a level of C4 vs. C6 in adults), thus making straight blades more useful than curved blades.
3. Epiglottis is shaped differently, being short and stubby, and is angled over the laryngeal inlet; control with the laryngoscope blade is, therefore, more difficult.[6,7]
4. The vocal cords are angled, so a blindly passed endotracheal tube may easily lodge in the anterior commissure rather than slide into the trachea.[8]
5. The infant larynx is funnel shaped, the narrowest portion at the cricoid cartilage. In adults, an endotracheal tube that passes the vocal cords will readily pass into the trachea because the glottic opening is the narrowest portion of the larynx.[9,10] In infants or young children, an endotracheal tube that easily passes the vocal cords may be tight in

[1]Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

***Corresponding author:** Dhanraj Ganapathy, Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai - 600 077, Tamil Nadu, India. Mobile: +91-9841504523. E-mail: dhanrajmganapathy@yahoo.co.in

Received on: 09-12-2018; Revised on: 13-01-2019; Accepted on: 17-02-2019

the subglottic region due to narrowing at the cricoid cartilage. For this reason, uncuffed endotracheal tubes are usually preferred for patients younger than 6 years.[11]

These differences, i.e., the large head and tongue, mobile epiglottis and anterior position of the larynx, and characteristic of neonates make the tracheal intubation easier with neonates' head in a neutral or slightly flexed position than with the head hyperextended. Infants have often been described as obligate nasal breathers; however, 8% of premature neonates and 40% of term newborns can convert to oral breathing in the presence of nasal airway obstruction.[12,13] Most infants can convert to oral breathing if the obstruction lasts for more than 15 s.

PHARMACOLOGICAL DIFFERENCES

The response of infants and children, particularly neonates to medications, is modified by many factors including body composition, protein binding, body temperature, distribution of cardiac output, and maturation of the blood–brain barrier, liver, and kidneys. The body compartments such as fat, muscle, and water change with age. Total body water content is significantly higher in premature than term infants and in term infants than 2 years' olds. Fat and muscle content increases with age. These alterations in body composition have several clinical implications for neonates: (1) A drug that is water soluble has a large volume of distribution and usually requires a large initial dose to achieve the desired blood level (e.g., most antibiotics and succinylcholine), (2) since neonates have less fat, a drug that depends on redistribution into fat for termination of its action will have a longer clinical effect (e.g.. thiopental), and (3) a drug that redistributes into muscle may have a longer clinical effect (e.g., fentanyl).

In general, the potency of many drugs is greater in neonates and infants and less in children when compared with adults.[13,14] Similarly, most medications will have a prolonged elimination half-life in neonates and a shortened half-life in children aged over 2 years, which gradually lengthens toward adulthood. Thus, compared with adults, neonates and infants frequently require reduced drug doses, while children require increased doses in relation to their body weight.[15]

Inhaled Anesthesia

Minimum alveolar concentration (MAC) of inhaled anesthetics required in pediatric patients changes with age. Full-term neonates require lower concentrations of volatile anesthetics than do infants (1–6 months of age). For example, the MAC is about 25% less in neonates than in infants. Further, MAC in preterm neonates (<32 weeks of gestational age) is less than MAC in preterm neonates (32–37 weeks of gestational age) and MAC for both of these age groups is less than that in full-term neonates.[16] Decreased anesthetic requirements in neonates may be related to immaturity of the central nervous system and increased circulating concentrations of progesterone and beta-endorphins. MAC steadily increases until 2–3 months of age, but after 3 months, the MAC steadily declines with aging, although there are slight increases at puberty.[17,18] This fact of decreased anesthetic requirement combined with the need for deeper planes of anesthesia to achieve satisfactory conditions for endotracheal intubation places the infant in a precarious position in that the margin between anesthetic overdose (from a cardiovascular standpoint) and inadequate depth of anesthesia (for endotracheal intubation) is small.[19]

Uptake and elimination of inhaled anesthetics are more rapid in pediatric patients than in adults. The principle reasons for this appear to be increased respiratory rates and cardiac index and a greater proportional distribution of cardiac output to vessel rich organs. This rapid rise in blood anesthetic levels combined with the functional immunity of cardiac development probably explains in part why it is so easy to give an overdose to infants and toddlers. Age-related differences in blood gas partition coefficient may also facilitate a more rapid rise in alveolar concentration in infants.[20] The most important factor influencing the potential for anesthetic overdose in neonates is the number of MAC multiples that can be delivered by the vaporizer.

Types of Inhaled Anesthesia

Halothane

It has a sweet, non-pungent odor, allowing smooth induction and maintenance of anesthesia. Halothane is a potent myocardial depressant that can have profound effects on neonates and children with congenital heart disease.[21]

Approximately 20% of absorbed halothane is metabolized in the liver, mainly by oxidation. This high degree of metabolism appears to be an important factor in the etiology of halothane hepatitis, which occurs in 1 in 10000–1 in 30000 adults exposed to the drug. By contrast, halothane hepatitis is exceedingly rare in children. Another concern with halothane is sensitization of the myocardium to arrhythmias due to exogenous and endogenous catecholamines. Most arrhythmias associated with halothane anesthesia in children are caused by either hypercapnia or an inadequate level of anesthesia.[22] Up to 10 µg/kg of epinephrine may be used with minimal risk of cardiac arrhythmias in pediatric patients.

Sevoflurane

Sevoflurane is halogenated solely with fluorine. Fluorination reduces solubility in both fat and blood, thereby reducing anesthetic potency while increasing the rate of uptake and elimination. As a result of its low blood solubility, induction of anesthesia is more rapid with sevoflurane than with halothane, eyelash reflex being lost in 60–90 s. Recovery is also more rapid in case of sevoflurane than halothane. Sevoflurane is less pungent than isoflurane and desflurane. Sevoflurane and halothane are approximately equal in terms of airway complications during induction of anesthesia.[23] There is no difference in the incidence of laryngospasm or bronchospasm, but the incidence of coughing during induction with sevoflurane is slower and also sevoflurane causes less myocardial depression than halothane.[24]

Isoflurane

Isoflurane is claimed to have some advantages over halothane: Less myocardial depression, preservation of the heart rate, and a greater reduction in cerebral metabolic rate for oxygen. However, isoflurane has an irritant, ethereal odor that is associated with an increased incidence of airway problems such as coughing and laryngospasm during induction, maintenance, and recovery from anesthesia.[25]

In infants and children, equipotent concentrations of isoflurane and halothane produced similar reductions in blood pressure. Isoflurane may be associated with greater cardiovascular reserve than halothane in infants and children.

Desflurane

Like isoflurane, it has a markedly pungent ethereal odor making it unsuitable for inhalation induction of anesthesia in children due to a higher incidence of airway complications. It is also associated with emergence agitation.[26] However, by virtue of its lower solubility in blood, recovery from anesthesia maintained with desflurane is faster than that maintained with halothane or sevoflurane.[27]

Drugs used to Induce Anesthesia

Thiopental and propofol

The dose of thiopentone varies with age. Children require relatively higher doses of thiopental and propofol compared to adults due to a larger volume of distribution. The elimination half-life is shorter and the plasma clearance is greater than in adults leading to a rapid recovery in both the drugs.[28] In contrast, neonates appear to be more sensitive to barbiturates and have less protein binding, longer half-life, and impaired clearance. The thiopental induction dose for neonates is around 3–4 mg/kg and 5–6 mg/kg for infants.[29]

Ketamine

Ketamine, a phencyclidine derivative, in addition to intravenous and intramuscular routes, may be administered rectally (10 mg/kg), orally (6–10 mg/kg), or intranasally (3–6 mg/kg).[30] The combination of oral ketamine, oral midazolam (0.5 mg/kg), and oral atropine (0.02 mg/kg) provides a well-sedated patient. Intravenous administration of doses as low as 0.25–0.5 mg/kg may be used to provide sedation/analgesia for painful procedures, whereas doses of 1–2 mg/kg produce sedation sufficient for a smooth transition to general anesthesia.[31] Higher doses (up to 10 mg/kg intramuscularly) provide sufficient analgesia for insertion of invasive monitoring devices before induction of anesthesia or in patients with limited venous access.[32]

Benzodiazepines

Midazolam is the only benzodiazepine approved by the Food and Drug Administration for use in neonates. The short elimination half-life (~2 h) in comparison to diazepam (18 h) offers an advantage for use as a pre-medicament in children, the half-life being much longer (6–12 h) in neonates. Midazolam, in general, is rapidly absorbed after intramuscular (0.1–0.15 mg/kg, maximum of 7.5 mg), oral (0.25–1.0 mg/kg, maximum of 20 mg), nasal (0.2 mg/kg), or sublingual (0.2 mg/kg) administration.[33,34]

Opioids

Opioids appear to be more potent in neonates than in older children and adults. Possible explanations include easier entry across the blood–brain barrier, decreased metabolic capability, or increased sensitivity of the respiratory centers.[35]

Fentanyl

Fentanyl is the most commonly used narcotic in infants and children. Its major advantages relate to its rapid onset and brief duration of action. This narcotic is more lipophilic than meperidine; the potential effects of the blood–brain barrier are of no importance with fentanyl. Fentanyl induces a very stable cardiovascular response while providing an anesthetic state.[36,37] Oral transmucosal administration (5–15 μg/kg, maximum of 400 μg) results in reasonably rapid absorption with peak blood level achieved within 15–30 min.[38]

Morphine

Morphine remains the most commonly used opioid for the management of severe pain in children and the standard with which other potent analgesics should be compared. The newborn has lower clearance of morphine, and therefore, a lower dose will result in higher plasma values due to a longer elimination half-life. Term infants older than 10 days may clear morphine more rapidly and at a similar rate as adults.

Infants older than 6 months probably have a normal adult response to morphine.[39]

Alfentanil

Alfentanil is eliminated more rapidly than fentanyl; its pharmacokinetics is independent of dose. This property may provide a margin of safety because the greater the administered dose, the greater the elimination. Clearance of alfentanil may be increased in children in comparison to adults. There is an important patient to patient variability in pharmacokinetics and pharmacodynamics in neonates and patients with impaired hepatic blood flow.[40]

Remifentanil

Remifentanil is the most recent addition to the opioids available for the care of children. Since remifentanil is broken down by non-specific plasma and tissue cholinesterases, the importance of maturation of renal and hepatic function is minimal.[41] This also helps to explain the minimal difference in remifentanil half-life between infants and adults. This drug would appear to also have great utility in infants with hepatic or renal failure.[42]

MONITORING

Decreased cardiovascular reserve, altered anesthetic requirements, and exaggerated hypotensive responses during general anesthesia make monitoring the systemic blood pressure, especially important in neonates and infants during the perioperative period. Selecting the proper cuff size is critical, as a cuff that is too large for the patient's arm results in falsely low readings. The peripheral artery selected for taking samples for BGA is uniquely important, as blood sampled from an artery that arises distal to the ductus arteriosus (left radial artery, umbilical artery, and posterior tibial artery) may not accurately reflect the PaO being delivered to the retina or brain in a consideration, a preductal artery, such as the right radial artery or temporal artery (risk of cerebral embolism with retrograde flushing) should be cannulated.[43,44]

Monitoring body temperature is useful during the perioperative period to detect the development of hypothermia as well as the rare patient manifesting malignant hyperthermia.[45] Monitoring end-tidal carbon dioxide concentrations is reliable in children although there are some limitations in neonates and infants. For example, due to small tidal volumes and high inspired gas flows, exhaled carbon dioxide concentrations may be diluted, producing falsely low values when measuring end-tidal carbon dioxide concentrations.[30]

CONCLUSION

The review gives an idea on the dosage and proper use of the above-mentioned general anesthetic drugs. Further researches are required to study the working mechanism of each individual drug and its effect on various systems such that proper administration of the drug can be ensured in a pediatric patient and thus not only induce anesthetic drug for a sufficient time and dosage but also expand the wide array of knowledge about general anesthetics used in pediatric population.

REFERENCES

1. Rudolph AM. The changes in the circulation after birth. Their importance in congenital heart disease. Circulation 1970;41:343-59.
2. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus aeteriosus in the premature infant. N Engl J Med 1976;295:526-9.
3. Miller RD. Miller's Anesthesia. 6th ed. Philadelphia, PA: Elsevier/Churchill Livingstone; 2004. p. 2368.
4. Hoerter J, Mazet F, Vassort G. Perinatal growth of the rabbit cardiac cell: Possible implications for the mechanism of relaxation. J Mol Cell Cardiol 1981;13:725-40.
5. Murat I, Hoerter J, Ventura-Clapier R. Developmental changes in effects of halothane and isoflurane on cantractile properties of rabbit cardiac skinned fibers. Anesthesiology 1990;73:137-45.
6. Leelanukrom R, Cunliffe M. Intraoperative fluid and glucose management in children. Paediatr Anaesth 2000;10:353-9.
7. Singleton MA, Rosen JI, Fisher DM. Plasma concentrations of fentanyl in infants, children and adults. Can J Anaesth 1987;34:152-5.
8. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. Anesthesiology 1987;66:136-9.
9. Davis PJ, Lerman J, Suresh S, McGowan FX, Coté CJ, Landsman I, *et al.* A randomized multicenter study of remifentanil compared with alfentanil, isoflurane, or propofol in anesthetized pediatric patients undergoing elective strabismus surgery. Anesth Analg 1997;84:982-9.
10. Liu LM, DeCook TH, Goudsouzian NG, Ryan JF, Liu PL. Dose response to intramuscular succinylcholine in children. Anesthesiology 1981;55:599-602.
11. Mazurek AJ, Rae B, Hann S, Kim JI, Castro B, Coté CJ, *et al.* Rocuronium versus succinylcholine: Are they equally effective during rapid-sequence induction of anesthesia? Anesth Analg 1998;87:1259-62.
12. Bevan DR, Bevan JC, Donati F. Muscle Relaxants in Clinical Anesthesia. Chicago: Year Book Medical Publishers; 1988. p. 148-51.
13. Sieber FE, Smith DS, Traystman RJ, Wollman H. Glucose: A reevaluation of its intraoperative use. Anesthesiology 1987;67:72-81.
14. Leake RD, Trygstad CW. Glomerular filtration rate during the period of adaptation to extrauterine life. Pediatr Res 1977;11:959-62.
15. Jose PA, Fildes RD, Gomez RA, Chevalier RL, Robillard JE. Neonatal renal function and physiology. Curr Opin Pediatr 1994;6:172-7.
16. van den Anker JN. Pharmacokinetics and renal function in preterm infants. Acta Paediatr 1996;85:1393-9.
17. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: Part I. Clin Pharmacokinet 2002;41:959-98.
18. Furman EB, Roman DG, Lemmer LA, Hairabet J, Jasinska M, Laver MB, *et al.* Specific therapy in water, electrolyte and blood-volume replacement during pediatric surgery. Anesthesiology 1975;42:187-93.
19. Roy WL, Lerman J, McIntyre BG. Is preoperative haemoglobin testing justified in children undergoing minor elective surgery? Can J Anaesth 1991;38:700-3.
20. Himms-Hagen J. Cellular thermogenesis. Annu Rev Physiol 1976;38:315-51.
21. Bissonnette B. Temperature monitoring in pediatric anesthesia.

Int Anesthesiol Clin 1992;30:63-76.
22. Plattner O, Semsroth M, Sessler DI, Papousek A, Klasen C, Wagner O, *et al.* Lack of nonshivering thermogenesis in infants anesthetized with fentanyl and propofol. Anesthesiology 1997;86:772-7.
23. Dicker A, Ohlson KB, Johnson L, Cannon B, Lindahl SG, Nedergaard J, *et al.* Halothane selectively inhibits nonshivering thermogenesis. Possible implications for thermoregulation during anesthesia of infants. Anesthesiology 1995;82:491-501.
24. Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part II). Clin Pharmacokinet 1988;14:261-86.
25. Ehrnebo M, Agurell S, Jalling B, Boréus LO. Age differences in drug binding by plasma proteins: Studies on human foetuses, neonates and adults. Eur J Clin Pharmacol 1971;3:189-93.
26. Wood M. Plasma drug binding: Implications for anesthesiologists. Anesth Analg 1986;65:786-804.
27. Orenstein SR, Orenstein DM. Gastroesophageal reflux and respiratory disease in children. J Pediatr 1988;112:847-58.
28. de Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Glucuronidation in humans. Pharmacogenetic and developmental aspects. Clin Pharmacokinet 1999;36:439-52.
29. Ginsberg G, Hattis D, Sonawane B, Russ A, Banati P, Kozlak M, *et al.* Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicol Sci 2002;66:185-200.
30. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v. nasal and rectal administration in children. Br J Anaesth 1996;77:203-7.
31. Lerman J, Robinson S, Willis MM, Gregory GA. Anesthetic requirements for halothane in young children 0-1 month and 1-6 months of age. Anesthesiology 1983;59:421-4.
32. LeDez KM, Lerman J. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 1987;67:301-7.
33. Yakaitis RW, Blitt CD, Angiulo JP. End-tidal halothane concentration for endotracheal intubation. Anesthesiology 1977;47:386-8.
34. Friesen RH, Lichtor JL. Cardiovascular depression during halothane anesthesia in infants: Study of three induction techniques. Anesth Analg 1982;61:42-5.
35. Lerman J, Schmitt-Bantel BI, Gregory GA, Willis MM, Eger EI 2nd. Effect of age on the solubility of volatile anesthetics in human tissues. Anesthesiology 1986;65:307-11.
36. Lerman J, Gregory GA, Willis MM, Eger EI 2nd. Age and solubility of volatile anesthetics in blood. Anesthesiology 1984;61:139-43.
37. Sury MR, Black A, Hemington L, Howard R, Hatch DJ, Mackersie A, *et al.* A comparison of the recovery characteristics of sevoflurane and halothane in children. Anaesthesia 1996;51:543-6.
38. Welborn LG, Hannallah RS, Norden JM, Ruttimann UE, Callan CM. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesth Analg 1996;83:917-20.
39. Fisher DM, Robinson S, Brett CM, Perin G, Gregory GA. Comparison of enflurane, halothane, and isoflurane for diagnostic and therapeutic procedures in children with malignancies. Anesthesiology 1985;63:647-50.
40. Karl HW, Swedlow DB, Lee KW, Downes JJ. Epinephrine-halothane interactions in children. Anesthesiology 1983;58:142-5.
41. Wodey E, Pladys P, Copin C, Lucas MM, Chaumont A, Carre P, *et al.* Comparative hemodynamic depression of sevoflurane versus halothane in infants: An echocardiographic study. Anesthesiology 1997;87:795-800.
42. Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. Anesthesiology 1994;80: 814-24.
43. Klock PA, Czeslick EG, Klafta JM, Ovassapian A, Moss J. Do Sevoflurane and Desflurane Differ in Upper Airway Reactivity?. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2002;96:1275-6.
44. Murray D, Vandewalker G, Matherne GP, Mahoney LT. Pulsed doppler and two-dimensional echocardiography: Comparison of halothane and isoflurane on cardiac function in infants and small children. Anesthesiology 1987;67:211-7.
45. Davis PJ, Cohen IT, McGowan FX Jr., Latta K. Recovery characteristics of desflurane versus halothane for maintenance of anesthesia in pediatric ambulatory patients. Anesthesiology 1994;80:298-302.

Source of support: Nil; Conflict of interest: None Declared