Pharmacologic Considerations of Anesthetic Agents in Pediatric Patients: A Comprehensive Review

Alan D. Kaye, PhD, DABA, DABPM, DABIPP[a,*], Charles J. Fox, MD[b],
Ira W. Padnos, MD[a], Kenny P. Ehrhardt, MD[a],
James H. Diaz, MD DrPH[a], Elyse Cornett, PhD[a,b],
Debbie Chandler, MD[b], Sudipta Sen, MD[b], Shilpadevi Patil, MD[b]

KEYWORDS

• Pediatrics • Pain • Pharmacokinetics • Anesthetics • Analgesics

KEY POINTS

- Acute pain in the pediatric population has important differences in terms of biology, intra-population variation, and epidemiology. Aside from the many disease states that can alter physiology, children have reduced capacity for absorption, metabolism, and elimination.
- Clinical anesthesiologists often have limited clinical studies to draw from when calculating or reviewing suggested doses on anesthetic agents.
- Discussion as to the pharmacologic considerations of anesthetic agents, such as induction agents, neuromuscular blockers, opioids, local anesthetics, and adjuvant agents, is presented in this article.
- Special considerations and concerns, such as risk for propofol infusion syndrome and adverse potential side effects of anesthesia agents, are discussed.
- Anesthesiologists managing pediatric patients need to have a firm understanding of physiologic and pharmacologic differences compared with the adult population. Future studies to improve the understanding of pharmacokinetics in the pediatric population are needed.

INTRODUCTION AND PEDIATRIC CONSIDERATIONS

Although most infants and children only experience transient or brief episodes of pain, many pediatric patients are challenging in many respects, owing to physiology differences and limited clinical pharmacology data. Pediatric anesthesia is a unique

[a] Department of Anesthesiology, Louisiana State University Health Science Center, Room 659, 1542 Tulane Avenue, New Orleans, LA 70112, USA; [b] Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, PO Box 33932, Shreveport, LA 71130-3932, USA
* Corresponding author.
E-mail address: akaye@lsuhsc.edu

Anesthesiology Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.anclin.2017.01.012 anesthesiology.theclinics.com

specialty of anesthesia that covers the spectrum of life, starting with vulnerable neonates and extending to adolescence. This type of anesthetic care requires, in part, extensive knowledge of dosage and adverse reactions of anesthetics drugs, especially for the care of the youngest patients. At times a difficult specialty, pediatric anesthesia is extremely rewarding for physicians who enjoy working with children.

Physiology and pharmacology are different in children compared with adults. Understanding of pharmacokinetics in children is critical to this field. In this regard, there is a reduction in every aspect of absorption, uptake, metabolism, and elimination compared with adult pharmacokinetics. In September 2016, the US Food and Drug Administration (FDA) held a special 2-day joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee to discuss the appropriate development plans for establishing safety and efficacy of opioid analgesics; however, during this meeting, it was clearly identified that other drugs, including many anesthesia agents, lack clinical research studies as a basis for dosing and as many as half of all pediatric analgesic agents are prescribed off-label related to lack of data.

However, that surgical morbidity and mortality are inversely proportional to age, with neonates having the highest risk of an adverse outcome. Pain maturation occurs during the third trimester and, in general, there is reduced threshold and reduced localization with associated autonomic and hormonal responses. Neonates and infants have anatomic variations in the head and neck compared with older patients, which must be fully appreciated by each anesthesia provider. The larynx of a neonate is more anterior, with the glottis located at C4 compared with the C6 vertebral level of adults. The epiglottis of a child is U shaped and floppy, which can hinder the visualization of the cords, making intubation difficult. The larynx in a child is also funnel shaped, whereas the larynx in an adult is cylindrical. The head and tongue of a small baby is also larger in proportion to the rest of the neonate's body.[1] These anatomic differences must be accounted for when intubating and anesthetizing a small baby. Another crucial anatomic difference in children up to age 5 years is the cricoid cartilage being the narrowest part of the airway; in patients older than the age of 5 years, the narrowest part is the glottis.[1]

Cardiac physiology of newborns is also different than in older children. The neonatal myocardium has few contractile fibers, so young babies cannot increase their stroke volume by contractility. These contractile fibers are gained later in life once the sarcoplasmic reticulum and T tubules mature. Another important concept in pediatric anesthesia is that the cardiac output of neonates is heart rate dependent. Neonatal stroke volume is normally at a fixed rate. Thus an increase in cardiac output can only be achieved by increasing the heart rate.[2] Anesthetic overdose or hypoxia can quickly lead to bradycardia in neonates, which greatly reduces cardiac output. The neonatal heart is more sensitive to volatile anesthetics and opioids, both of which can cause profound bradycardia.[1]

Neonatal lungs have fewer alveoli and less lung surface area compared with the lungs of adults. In addition, they possess a reduced lung compliance. These two factors lead to a decrease in functional residual capacity. Neonates also lack a sufficient percentage of type 1 fibers (specific for endurance) in their diaphragm, allowing them to become hypoxic quicker than adults. This difference poses more problems during periods of apnea, such as intubation, because younger children have less oxygen reserve.[1]

Temperature regulation is different in young neonates because of an increased surface area to body weight and volume ratio compared with older children. Because they have low subcutaneous fat content and thin skin, neonates can lose heat readily. Great care must be taken to make sure that they remain normothermic while under anesthesia.[1] Instead of using shivering as a way to generate heat, neonates