Management of General Anesthesia

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INHALATION ANESTHETICS

In the United States, where "ouch-less" hospital environments are a priority, most children requiring surgery receive oral premedication with an anxiolytic agent such as midazolam, followed by an inhalational anesthetic via facemask. Sevoflurane is the induction agent of choice, although many institutions still use halothane. Once the child has lost consciousness, an intravenous catheter is inserted, and an opioid and/or neuromuscular blocker may be administered prior to endotracheal intubation. In this section, the anesthetic agents used for induction of general anesthesia in children will be reviewed.

Sevoflurane

Sevoflurane is an ether type of volatile anesthetic agent that was first described in the 1970s. It was probably not brought to market at that time because its relatively high rate of biotransformation (3–5%) led to concerns about hepatic toxicity. Many believed that the relatively high rate of biotransformation of halothane (20%) was the primary cause of its association with hepatitis. In subsequent years, the cause of "halothane hepatitis" was shown to be unrelated to the metabolism of the agent, and sevoflurane was reintroduced, first in Japan, and later in the United States. In most pediatric centers in the USA, sevoflurane has replaced halothane for inhalational induction of general anesthesia in children because of its less pungent aroma, its lower blood-gas solubility coefficient (0.65) that speeds loss of consciousness, and, perhaps most importantly, its enhanced cardiovascular safety profile.

The minimum alveolar concentration (MAC) of sevoflurane is 3.2% in neonates and infants up to 6 months of age. In school-aged children MAC is 2.5%; the concentration that prevents 95% of children from moving in response to a surgical stimulus (ED₉₅) is 2.9%.

CHAPTER

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This chapter details the differences between children and adults in induction and maintenance of, and emergence from, general anesthesia. Principles of use of general anesthetic agents in children are reviewed. These include inhalational and intravenous general anesthetic agents, opioids, and neuromuscular blockers and their antagonists.
When 60% nitrous oxide is added to sevoflurane, the MAC is lowered to 2.0%. This contribution of N₂O to sevoflurane MAC is relatively less than for halothane.

Induction of general anesthesia with sevoflurane is accomplished by initially setting the vaporizer to the maximal 8% setting. Whether or not this is combined with nitrous oxide, most children will lose consciousness within 5–10 breaths. Sevoflurane depresses ventilation by a dose-dependent reduction in tidal volume. Some studies in children suggest that sevoflurane is a more potent respiratory depressant and causes relatively more upper-airway obstruction than equipotent doses of halothane. Clinically, sevoflurane appears to cause more central apnea than halothane during induction of anesthesia.

During inhalation of sevoflurane, most children develop tachycardia. Twenty percent of children undergoing induction of anesthesia with sevoflurane will develop a nodal rhythm, and infants under 6 months of age will demonstrate lengthening of the QT interval that continues into the postoperative period. These changes, however, do not result in adverse clinical manifestations. Sevoflurane may cause a dose-dependent decrease in heart rate and blood pressure, but to a much lesser extent than halothane, which significantly decreases cardiac output during its administration.

Agitation is commonly observed during the early stages of sevoflurane induction, soon after loss of consciousness. It consists of muscular rigidity and generalized tonic-clonic or myoclonic movements, and may represent a relatively greater propensity for sevoflurane to cause central nervous system (CNS) stimulation than other inhalational agents. Case reports exist that demonstrate exacerbation of electrical seizure activity in children with and without preexisting epilepsy during sevoflurane induction. This effect is accentuated with hyperventilation. These CNS stimulatory effects do not appear to be associated with postoperative sequelae.

Fluoride Toxicity

Sevoflurane is metabolized to inorganic fluoride ion and hexafluoroisopropanol (HFIP) (Fig. 19-1). Plasma concentrations of fluoride >50 μmol/L are associated with nephrotoxicity after administration of methoxyflurane, an obsolete inhalational anesthetic. Although prolonged use of sevoflurane at high concentrations produces fluoride levels in excess of 50 μmol/L, clinical nephrotoxicity with sevoflurane has not been reported. This is most likely secondary to the absence of intrarenal metabolism of sevoflurane, as occurs with methoxyflurane. However, subtle urinary markers of occult renal damage have been demonstrated with prolonged use of sevoflurane. Therefore, prolonged use of sevoflurane is probably contraindicated in children with limited renal reserve.

![Figure 19-1](image)

**Compound A Toxicity**

Degradation of sevoflurane by carbon dioxide absorbers produces a variety of compounds (labeled A through E), of which two are produced in significant amounts: compounds A and B. Although compound A is nephrotoxic in rats, the concentration attained in the anesthesia breathing circuit in humans does not cause adverse clinical effects. Factors that increase the level of compound A within the breathing circuit include increased absorbent temperature, decreased absorbent water content, and low flows through the absorbent. Although evidence for compound A toxicity in humans is lacking, sevoflurane should probably not be used with total flows less than 2 L/min, to decrease the accumulation of compound A inside the breathing circuit.

**Halothane**

Despite halothane's long history of safe use in children, it has been largely replaced by sevoflurane because halothane is associated with slower times to loss of consciousness (blood-gas coefficient 2.3) and a greater chance of clinically significant cardiovascular depression, especially in neonates and small infants. The MAC of halothane is 0.55% in the preterm neonate, 0.87% in the full-term neonate, 1.2% in the 6-month infant, and 0.95% in the older child.

Induction of general anesthesia with halothane is usually accomplished by increasing the concentration on the vaporizer by 0.5% every two to three breaths. After placement of an intravenous catheter and institution of controlled ventilation, the concentration must be decreased to avoid bradycardia and myocardial depression. Cardiac arrests have occurred in situations where the anesthesiologist unintentionally left the halothane vaporizer at its maximal setting of 5% while continuing to increase minute ventilation with positive pressure. Bradycardia and myocardial depression can be attenuated by oral or intravenous premedication with atropine. As an alkane, halothane sensitizes the heart to catecholamines; ventricular arrhythmias are common, especially during periods of hypercapnia or stress-induced catecholamine release.
Desflurane

The most important clinical characteristics of desflurane are its low blood-gas solubility coefficient (0.42), which imparts the fastest onset and offset of all the available inhalational anesthetics, and its extremely low metabolism (0.02%). The MAC of desflurane is 9.2% for neonates, 9.4% for infants 1-6 months old, 9.9% for infants 6-12 months old, 8.7% for patients aged 1-3 years, and 8% for those aged 5-12 years.

Desflurane is extremely pungent and causes substantial airway irritation. Initial clinical pediatric trials demonstrated that the majority of children receiving desflurane for induction of general anesthesia developed respiratory complications consisting of breath-holding, laryngospasm, coughing, increased secretions, and hypoxemia. Therefore, desflurane is contraindicated for induction of general anesthesia in children, but it can be used for maintenance of general anesthesia, even when using a laryngeal mask airway (LMA) or facemask. In most procedures of indeterminate length, children will regain consciousness within several minutes of discontinuation of desflurane.

Nitrous Oxide

Although its clinical advantages are unproven, N₂O is commonly used as an adjunct to inhalational induction of general anesthesia in children because of its ability to reduce the MAC of sevoflurane and halothane, and to speed the onset of unconsciousness via the second-gas effect. It is commonly discontinued when the intravenous catheter is inserted, in preparation for airway management, which is performed after a period of breathing 100% oxygen to increase the margin of safety during the apneic phase.

Nitrous oxide may cause vomiting during induction of anesthesia, and it has been associated with myoclonic movements and even generalized seizures in some case reports. Because N₂O decreases the activity of two vitamin B₁₂ enzymes, methionine synthetase and thymidylate synthetase, its use has been implicated in the exacerbation of vitamin B₁₂ deficiency with development of neurological symptoms in susceptible patients. Therefore, N₂O should be avoided in children with vitamin B₁₂ deficiency.

Alternate Induction Techniques

The majority of children receiving a mask induction of general anesthesia begin by breathing N₂O, up to 70%, and sevoflurane 8% or halothane, incrementally up to 5%. Older children and adolescents who are cooperative may receive a single-breath induction technique, which will considerably speed the loss of consciousness. This is performed by priming the anesthesia circuit and ventilation bag with N₂O and the inhalational agent prior to the patient entering the operating room. The distal end of the breathing circuit that is normally connected to the anesthesia facemask is sealed off to prevent the leakage of anesthetic gases into the OR environment. When the child enters the OR, he or she is asked to first blow all the air out of their lungs (it is helpful to practice this technique with the child prior to entering the OR). At the very end of the child's exhalation, the facemask, which is now connected to the open anesthesia circuit, is placed over the child's mouth and nose, and the child is instructed to take "the biggest breath of their life." This technique will invariably result in loss of consciousness soon after the vital capacity breath.

When a child is sleeping prior to entering the OR, one may perform a steal induction technique. Exceptional care is taken to avoid awakening the child while he or she is transported into the OR. Once in the OR, the child is not touched or moved to the OR table and no monitors are applied. The anesthesia breathing circuit is primed with N₂O and sevoflurane or halothane, and the mask is moved progressively closer to the child's face without touching it. One must be careful not to move too close to the child's face too quickly, for the child will awaken if he or she smells the pungent anesthetic gas. Once consciousness is lost, the child is moved to the OR table and monitors are applied. Proponents of this technique favor the attraumatic nature of this type of induction, and the child's lack of knowledge of the OR environment. Opponents of this technique fear that a child could suffer psychological harm if he or she awakens from a painful procedure without realizing that it had begun.

Inhalational Agents for Maintenance of General Anesthesia

The majority of pediatric general anesthetics are maintained with an inhalational agent. There are no clear advantages or disadvantages to any agent, except perhaps the lower cost of the older agents, isoflurane and halothane. Sevoflurane and isoflurane are almost identical in their times to awakening and discharge home. Agitation is more commonly seen in the immediate postoperative period with sevoflurane than with other agents. Various theories exist to explain this phenomenon, including more rapid awakening and faster onset of perceived pain, but agitation also occurs following nonpainful procedures such as magnetic resonance imaging (MRI). Postoperative agitation is distressing to the postanesthesia care unit (PACU) staff as well as parents, but it is easily abolished with small intravenous doses of an opioid, midazolam, or clonidine. Desflurane, the least
soluble agent, has the advantage of the shortest time to awakening once it is discontinued, but is not associated with improved postoperative outcomes.

**INTRAVENOUS ANESTHETICS**

In most pediatric centers in the United States, intravenous induction of general anesthesia is reserved for children with previously established intravenous access, children with susceptibility to malignant hyperthermia, and children at risk of pulmonary aspiration of gastric contents who require a rapid sequence induction (RSI) technique. It is rarely used electively, unless the child prefers this method to inhaling gases from a facemask. For children in this latter category, pain can be minimized by using a butterfly needle to access one of the large veins in the antecubital fossa, and an intravenous catheter can then be inserted into a more accessible location (e.g., dorsum of the hand) after the child has lost consciousness. If time permits, one may apply a topical anesthetic cream to several potential intravenous sites.

The most commonly used intravenous induction agents in children are thiopental and propofol, although methohexital, ketamine, and etomidate can also be used.

**Barbiturates**

**Thiopental**

Thiopental is the most common barbiturate used for intravenous induction of general anesthesia in children. In doses of 5-7 mg/kg, it provides loss of consciousness within several seconds after administration, without hemodynamic compromise in euolemic children. Although not studied specifically in children, thiopental administration in the presence of hypovolemia may result in life-threatening hypotension secondary to venous and arterial vasodilatation. The dose of thiopental used for induction of anesthesia in neonates is less than for older children. This may be due in part to a more immature blood-brain barrier in neonates, and greater bioavailability of the drug, and/or a reduced protein binding in the plasma of neonates. In adults, it is not as effective as equipotent doses of propofol in blunting the airway response to tracheal intubation, and this is probably true for children as well.

**Methohexital**

Methohexital is shorter-acting than thiopental, but it often causes myoclonic movements immediately after administration and can exacerbate seizures in susceptible children. It is often painful at the site of administration and is associated with postoperative nausea and vomiting. For these reasons, it is used much less often than thiopental in pediatric anesthesia. The dose for induction of general anesthesia is 1-3 mg/kg.

**Nonbarbiturates**

**Propofol**

Propofol is the most common nonbarbiturate agent used for induction of general anesthesia in children. It causes immediate loss of consciousness following administration of 3-6 mg/kg. Children require larger induction doses than adults because of an apparently larger volume of distribution. Maintenance doses are also larger in children because of greater elimination clearance. Propofol is particularly well suited for use in asthmatics, as it blunts airway responses within its clinical dosing range. It has replaced ketamine as the intravenous induction agent of choice for children with asthma.

Propofol usually causes central apnea when administered as a bolus for induction of general anesthesia. If given in titrated doses, apnea can be avoided. However, the apneic dose of propofol is usually less than the dose required to prevent movement in response to a surgical stimulus. Administration of propofol may cause cardiovascular depression in hypovolemic children or those with a preexisting cardiomyopathy.

A particularly difficult problem with propofol is its propensity to cause severe pain in the limb in which it is administered. In general, injection into smaller veins (e.g., dorsum of the hand) produces more pain than injection into larger veins (e.g., antecubital). A variety of studies have attempted to determine the most reliable way to prevent this pain. Methods include concomitant or prior administration of lidocaine or an opioid but are not effective in all children. The most reliable method for preventing propofol-induced pain is to administer a small volume of 1% lidocaine while holding pressure proximal to the vein (i.e., a modified Bier block technique) as the vein distends. Pressure is held for 5-10 seconds to assure that the wall of the vein is anesthetized, after which the propofol is administered. This method effectively blunts the pain in over 90% of children.

Because of propofol’s relatively low context-sensitive half-time (see Chapter 2), lack of “hangover,” and lack of propensity to cause nausea and vomiting, it is ideally suited to be the major component of a total intravenous anesthesia (TIVA) technique. During unpainful medical procedures that require immobility (e.g., computed tomography (CT), MRI, and radiotherapy) it can be used in moderate infusion doses (150-250 µg/kg/min) that preserve spontaneous ventilation. For painful procedures (e.g., bone marrow biopsy, lumbar puncture, burn dressing changes) and surgical procedures that require a TIVA technique (e.g., rigid bronchoscopy, malignant hyperthermia-susceptible patient), much greater doses of propofol are required to ensure immobility. These larger
doses are inevitably associated with central or obstructive apnea, requiring ventilatory assistance. Alternatively, propofol can be combined with an opioid, which will decrease the total required propofol dose, but ventilatory assistance is still often required.

**Ketamine**

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that provides excellent dissociative anesthesia in children. It can be used as a sedative or as an induction agent for general anesthesia. At clinically useful doses (1–2 mg/kg), ketamine usually preserves spontaneous ventilation, upper-airway patency, and normal cardiovascular function, while providing analgesia and amnesia during painful procedures. Ketamine stimulates the sympathetic nervous system, which may cause undesirable increases in blood pressure, intracranial pressure, and intraocular pressure. In addition, ketamine is associated with psychomimetic side-effects (e.g., hallucinations, nightmares), increased airway secretions, postoperative nausea and vomiting, and delayed awakening. For these reasons, it has largely been replaced by propofol for almost all clinical uses except brief sedation for painful procedures, and intramuscularly as a sedative for uncooperative developmentally delayed adolescents. Concomitant administration of midazolam may attenuate the psychomimetic side-effects.

**Etomidate**

Etomidate is mainly used in adults with cardiovascular disease and limited cardiovascular reserve. It may be useful in the traumatized child who is hypovolemic, or in a child with a cardiomyopathy and decreased cardiovascular function. The dose range (0.2–0.3 mg/kg) and side-effects (e.g., pain on injection, myoclonus, vomiting) appear to be similar to those in adults.

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**ADJUNCTIVE ANESTHETIC AGENTS IN PEDIATRIC ANESTHESIA**

Adjunctive anesthetic agents in pediatric anesthesia include opioids and neuromuscular blockers. Their use in pediatric anesthesia will be reviewed in the following sections. More complete details on opioid use in pediatric patients for postoperative analgesia can be found in Chapter 24.

**Opioids**

Opioids are administered to pediatric surgical patients as a component of a balanced anesthesia technique, to contribute to postoperative analgesia, and to attenuate or prevent postoperative emergence delirium or agitation. The choice of opioid depends on the nature and length of the surgical procedure, and the expected duration of postoperative pain. For example, intranasal or intramuscular fentanyl (2 μg/kg) is often administered to children undergoing myringotomy and tubes because of the lack of an intravenous catheter and the short expected duration of postoperative pain. Intravenous fentanyl is often administered for neurosurgical procedures because of the intense analgesia required intraoperatively, and less analgesic requirements postoperatively. Intravenous morphine is administered for most urologic and abdominal procedures because of the requirement for a relatively longer duration of postoperative analgesia.

Opioids are commonly included as a component of a total intravenous anesthesia (TIVA) technique for painful surgical procedures. Fentanyl or one of its congeners (e.g., alfentanil, sufentanil, and remifentanil) are ideally suited for use in TIVA because of their relatively low context-sensitive half-time. Remifentanil possesses the most favorable profile, as its termination of action is directly related to its metabolism by tissue and plasma esterases. Its effects will usually dissipate within 5–10 minutes of discontinuing the infusion, regardless of the duration of the infusion.

Remifentanil bolus and infusion doses are higher in infants and young children than in adults, reflecting the larger volume of distribution and increased elimination clearance, respectively. Typically, a bolus dose of 1–2 μg/kg will be administered over several minutes, followed by an infusion dose of 0.5 μg/kg/min. This infusion dose is then titrated to achieve the desired analgesic and hemodynamic effects. There is evidence that the use of intraoperative remifentanil in former premature infants may be associated with a decreased incidence of postoperative apnea when compared to halothane for maintenance of general anesthesia. However, it has not been compared with the newer agents, sevoflurane and desflurane, which are described in an earlier section.

Well-established side-effects of opioid use in children include sedation, ventilatory depression, upper-airway obstruction in susceptible children, pruritus, and an increased incidence of postoperative nausea and vomiting. Historically, there has been concern among pediatric anesthesiologists about the increased toxicity profile of opioids when used in newborn infants. This caution relates to the possibility that opioids (especially the less lipid-soluble drug morphine) are allowed greater access through the blood–brain barrier in neonates, and may result in proportionately greater levels in the brain. Furthermore, neonates have been shown to possess increased pharmacodynamic sensitivity, decreased clearance, and a relatively greater depression of CO₂ response curves to opioids when compared with adults. These maturational changes appear to be most pronounced for morphine in comparison with fentanyl and its analogues. However, opioids, like all types of medications administered to neonates, possess substantial interindividual
variation in their pharmacokinetic and pharmacodynamic properties, so they must be titrated to effect while carefully observing cardiopulmonary side-effects.

**Neuromuscular Blockers**

Neuromuscular blockers are commonly administered to pediatric patients during induction of anesthesia to facilitate endotracheal intubation and may be continued intraoperatively to enhance optimal surgical conditions and positive-pressure ventilation. Overall, there are probably fewer airway complications in children receiving neuromuscular blockers, even in experienced hands.

There are a number of developmental physiologic differences that affect the pharmacology of neuromuscular blockers. During early childhood, an increase in muscular volume leads to an increase in the number of neuromuscular receptors; conduction velocity and myelination increase during development; and the rate of acetylcholine release progressively increases. Taken together, these developmental differences are manifested clinically as a greater pharmacodynamic sensitivity of neuromuscular blockers in infants and young children (i.e., neuromuscular blockers are more potent in younger children). In fact, during tetanic stimulation unanesthetized newborns demonstrate significant fade at 50 Hz. This fade in unparalyzed infants suggests that the supply of acetylcholine can be easily exhausted.

The difference in potency among age groups is illustrated as a comparison of the ED$_{50}$ for the neuromuscular blocking agents (Table 19-1). In practice, three (or more) times the ED$_{50}$ is usually administered to assure rapid paralysis and account for pharmacokinetic and pharmacodynamic differences between individual patients. Nondepolarizing neuromuscular blockers tend to be more potent in infants than children, and less potent in children than adults. Clinically, this manifests as a greater duration of action in infants and adults when compared with children.

Since all neuromuscular blockers are water-soluble, and younger children are known to be composed of a relatively greater volume of body water, the volume of distribution for these drugs is larger in younger children (see Chapter 2). Clinically, this translates into a higher bolus dose required to achieve a given plasma level (Table 19-2). However, since neonates and small infants demonstrate enhanced sensitivity to neuromuscular blockers, a lower plasma concentration is required, so the bolus dose is the same as for adults. Neonates and small infants will also demonstrate a prolonged duration of action because of the larger volume of distribution and the decreased liver function in the newborn period. Because of this latter characteristic, the aminosteroidal relaxants, which rely on liver metabolism for their termination of effect, become long-acting agents, often exceeding 60 minutes or more.

**Succinylcholine**

Succinylcholine, the only depolarizing neuromuscular blocker in use today, remains the fastest acting with the shortest duration of action of any available agent. Despite its many drawbacks to use in children, it retains its place as the agent of choice for rapid sequence induction and as a potential treatment for life-threatening upper-airway obstruction.

Like all other neuromuscular blockers, succinylcholine is water-soluble. Therefore, the intravenous bolus dose required in infants and young children (2 mg/kg) is larger than for older children and adults (1 mg/kg). An intramuscular dose of 4 mg/kg will provide a maximum

### Table 19-1

<table>
<thead>
<tr>
<th>ED$_{50}$ (mg/kg)</th>
<th>Infants</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>0.24</td>
<td>0.33</td>
<td>0.21</td>
</tr>
<tr>
<td>Cis-atracurium</td>
<td>&lt;0.06</td>
<td>0.06</td>
<td>0.045</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.13</td>
<td>0.34</td>
<td>0.08</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.065</td>
<td>0.095</td>
<td>0.07</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.25</td>
<td>0.40</td>
<td>0.55</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.045</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>0.61</td>
<td>0.35</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*ED$_{50}$ is the dose that produces an average block of 95% in neuromuscular function of the ulnar nerve – adductor pollicis.

*Dose-response for cis-atracurium in infants has not been adequately studied.


### Table 19-2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Multiple of ED$_{50}$</th>
<th>Minutes to Intubation</th>
<th>Minutes to T$_{25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>0.5</td>
<td>2-3</td>
<td>1.5</td>
<td>5-15</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6</td>
<td>2</td>
<td>1.0</td>
<td>10-20</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.5</td>
<td>2</td>
<td>1.5</td>
<td>45-75</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1</td>
<td>1-2</td>
<td>2.0</td>
<td>20-60</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>2.0</td>
<td>6f</td>
<td>1.0</td>
<td>3-5</td>
</tr>
</tbody>
</table>

*ED$_{50}$ is the dose that produces an average block of 95% in neuromuscular function of the ulnar nerve – adductor pollicis.

*T$_{25}$ is the time from injection of blocker to recovery of 25% of baseline neuromuscular transmission or 3 to 4 responses to a train-of-four stimulus.

onset of blockade in 3–4 minutes and will last for approximately 20 minutes. Its elimination clearance is more rapid in children, so its duration of effect is less than for adults. The major pharmacological differences for succinylcholine that exist between children and adults are not apparent in its beneficial effects, but rather in its adverse effects (Box 19-1).

Bradycardia
Succinylcholine commonly causes vagal-mediated bradycardia, junctional rhythms, or sinus arrest in children. These are commonly seen after the first dose, whereas in adults arrhythmias are usually seen after subsequent doses. For this reason, it is standard practice to administer an anticholinergic agent prior to succinylcholine in pediatric patients. Intravenous atropine (0.02 mg/kg) and glycopyrrolate (0.01 mg/kg) are equally effective in attenuating succinylcholine-induced bradycardia.

Fasciculations
Children under the age of 8 years rarely develop fasciculations or postoperative muscle pain following administration of succinylcholine. This has been attributed to the low overall muscle mass in young children. However, rhabdomyolysis and myoglobinuria can occur after succinylcholine administration despite the absence of fasciculations.

Hyperkalemia
Succinylcholine-induced paralysis results in muscle contraction by simulating the action of acetylcholine. This normally results in potassium release from the intracellular space and a transient and clinically insignificant increase in the plasma potassium level. Patients with obvious or occult muscle atrophy, or disorders associated with up-regulation of extrajunctional acetylcholine receptors (e.g., burns), will demonstrate an exaggerated potassium release after succinylcholine administration. The hyperkalemia that develops can lead to arrhythmias, cardiac arrest, and death.

In the early 1990s the anesthesiology community was alerted to a number of cases of succinylcholine-induced life-threatening hyperkalemia that occurred in young boys with undiagnosed Duchenne muscular dystrophy. As a result, the US Food and Drug Administration (FDA) recommended that succinylcholine no longer be used for routine, elective neuromuscular blockade. When using succinylcholine in an emergency situation, all anesthesiologists should be aware of this possible complication. Hyperkalemia is manifested as tall, peaked T waves on the electrocardiogram, which may develop into a wide complex tachycardia, ventricular fibrillation, and asystole. In the event this occurs, succinylcholine-induced hyperkalemia should be presumed until proven otherwise. The immediate treatment consists of intravenous calcium chloride at a dose of 5–10 mg/kg.

Succinylcholine-induced hyperkalemia can occur in any patient with muscle atrophy, especially when it is due to a progressive myopathy (e.g., Duchenne muscular dystrophy) or following an acute muscle injury or burn. However, normal potassium release after succinylcholine administration is observed in children with cerebral palsy or meningomyelocoele.

Malignant Hyperthermia
Succinylcholine is widely considered a triggering agent for malignant hyperthermia (MH). Malignant hyperthermia may manifest clinically as excessive rigidity well after fasciculations are expected to abate. In a previous era when succinylcholine was routinely used for pediatric cases, the incidence of MH was estimated to be 1 in 15,000. Many of these reported cases were likely to be rhabdomyolysis-induced hyperkalemia rather than MH per se. Nevertheless, the possibility of triggering MH is another reason that succinylcholine is no longer used in children on an elective basis.

Masseter Muscle Rigidity
Varying degrees of masseter muscle rigidity (MMR) are observed in children following succinylcholine administration. This response ranges from a mild difficulty with mouth opening to the complete inability to open the mouth ("jaws of steel"). The incidence of this response in children exceeds 1% in some studies. This phenomenon may represent a normal response to succinylcholine, especially if underdosed, or when severe, a harbinger of MH. Up to 50% of patients with a history of severe MMR test positive for malignant hyperthermia susceptibility on halothane/caffeine contracture testing.

If MMR occurs, all volatile anesthetics should be discontinued, and a nontriggering technique with TIVA should be administered. Some experts recommend awakening the patient if the procedure is not emergent and proceeding with the surgery only after a definitive evaluation of MH susceptibility. At the very least, creatine kinase levels should be obtained, along with electrolytes and a blood gas analysis. The patient should be observed
**Article To Know**


This publication constitutes an analysis of reports received by the Malignant Hyperthermia Association of the United States (MHAUS) and the North American Malignant Hyperthermia Registry from 1990 to 1993, of 25 children with a cardiac arrest within 24 hours of receiving an anesthetic. Cases were examined for causes such as inadequate ventilation, inadequate oxygenation, anesthetic overdose, hypovolemia, and hyperkalemia. Patients were diagnosed as having a myopathy after a pathologic examination of skeletal muscle was performed. Diagnosis of Duchenne muscular dystrophy was made if dystrophin was not detected by immunologic techniques.

Twenty of the cardiac arrests (80%) occurred in the operating room, and the remainder occurred in the recovery room, catheterization laboratory, or intensive care unit. Twenty of the children were previously healthy and were undergoing elective surgical procedures. Two children had an underlying disorder (sepsisemia and postcardiac surgery). A family history of myopathy was obtained in two children. No history of MH was elicited in any child.

Failure to ventilate or oxygenate was not implicated as a primary cause in any case of cardiac arrest. In addition, anesthetic overdose or hypovolemia was not judged to be present in any case. The presenting cardiac symptoms included wide complex bradycardia, ventricular tachycardia with hypotension, ventricular fibrillation, and asystole.

A potassium level during the cardiac arrest was measured in 18 of 25 patients. Thirteen of these demonstrated hyperkalemia. Mean peak serum K+ measured 7.4 ± 2.8 mmol/L (median 7.5, range 3.5–14.8). Eight of the 13 patients with hyperkalemia had received succinylcholine and potent inhalational anesthetics, while one patient had received succinylcholine alone, and four had received potent inhalational anesthetics without succinylcholine.

Cardiopulmonary resuscitation was performed for a median time of 42 minutes. In addition to standard pediatric advanced life-support measures, the following medications were given: calcium (n = 11), glucose and insulin (6), sodium bicarbonate (20), dantrolene (13), and mannitol (5). Pacemakers were used in two patients, peritoneal dialysis in one patient, and cardiopulmonary bypass was used in two patients. Fourteen patients, including a child with almost certain MH, survived with eventual return of baseline neurological function. One patient survived without meaningful neurological function.

Autopsy was performed on nine of the ten children who died. Four of these nine had a previously undiagnosed myopathy, and an additional three had an unsuspected cardiomyopathy or cardiac hypertrophy. Of the 13 patients with hyperkalemia, eight were eventually shown to have an occult myopathy.

Cases such as these emphasize the importance of preoperative screening for occult myopathies that may manifest subclinically as mild muscle weakness or failure to attain age-appropriate physical milestones. Clinical features of Duchenne muscular dystrophy include calf muscle hypertrophy, toe walking, and a waddling gait. Any suspicion of muscle weakness should warrant a preoperative creatine kinase level; if elevated it may indicate an occult myopathy.

This report highlighted the potential danger in administering succinylcholine to children who were not old enough to manifest clinical symptoms of their myopathy. Duchenne and Becker types of muscular dystrophy may not present until the child is 4 years of age or more. Because of this report, the Anesthetic and Life Support Drugs Advisory Committee of the Food and Drug Administration held hearings and eventually asked the manufacturer to place a black box warning in the package insert of succinylcholine that reads:

"It is recommended that the use of succinylcholine in children should be reserved for emergency intubation or instances where immediate securing of the airway is necessary, e.g., laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible."

This warning ultimately led to the precipitous decline of elective use of succinylcholine in children.

Nondepolarizing Neuromuscular Blockers

The nondepolarizing neuromuscular blockers are divided into two major categories based on structure and mode of elimination.

- The benzylisoquinoliniums, atracurium and cisatracurium, rely on metabolism by Hofmann degradation and ester hydrolysis by nonspecific plasma esterases for their termination of action, while mivacurium is metabolized by plasma (pseudo) cholinesterase.
- The aminosteroids (vecuronium, rocuronium, and pancuronium) are metabolized in the liver to inactive products that are eliminated by the kidney.

A major advantage of the aminosteroids is their efficacy after intramuscular administration. Rapacuronium, an ultra-short-acting aminosteroid neuromuscular blocker, was recently removed from the market because...
of concerns that it contributed to life-threatening bronchospasm.

**Atracurium**

Atracurium is an intermediate-acting (30–40 minutes) neuromuscular blocker that is usually reversible within 20 minutes after administration. Because its metabolism does not rely on hepatic function, its duration of action is predictable, even in neonates. In a dose of 0.5 mg/kg, atracurium produces reliable intubating conditions within 90 seconds after administration. Large doses of atracurium will occasionally result in histamine release that is manifested as a macular rash. Histamine-induced bronchospasm and hypotension are uncommon after atracurium administration in pediatric patients.

**Cis-atracurium**

Cis-atracurium is a cis isomer of atracurium, and possesses a similar clinical and pharmacokinetic profile as atracurium except for its increased potency and its lack of histamine release. Because of the increased potency, its onset to maximum block is slower than that of atracurium. A dose of 0.15–0.2 mg/kg will provide reliable intubating conditions within 2 minutes. Clinical studies in children indicate that administration of cis-atracurium is associated with a longer and less predictable duration of action than atracurium.

**Mivacurium**

Mivacurium is the shortest-acting neuromuscular blocker in its class (15–20 minutes), primarily due to its metabolism by pseudocholinesterase. Mivacurium was originally marketed as a replacement for succinylcholine, but initial clinical experience demonstrated a lack of satisfactory intubating conditions within 1 minute at the recommended dose (0.15 mg/kg). Therefore, most pediatric anesthesiologists have modified the dose upward to 0.25–0.3 mg/kg, which provides reliable intubating conditions within 1 minute, but is consistently accompanied by a histamine rash and occasional hypotension. These side-effects can be attenuated by increasing the duration over which the drug is administered. Because of its lack of accumulation, mivacurium is particularly suited for multiple repeated dosing or as a continuous infusion. The neuromuscular blockade of mivacurium is usually reversible within 10 minutes following administration of a bolus dose or discontinuation of a continuous infusion. This time to reversibility is relatively shorter than for adults. A disadvantage to the use of mivacurium is the possibility of prolonged duration of action in patients with qualitative or quantitative pseudocholinesterase deficiency.

**Vecuronium**

Vecuronium is an intermediate-acting neuromuscular blocker (40–75 minutes) that is usually reversible by 20 minutes following its administration. Following a dose of 0.1 mg/kg, reliable intubation conditions are usually achieved within 2 minutes. School-aged children require relatively more vecuronium to achieve a desired effect and recover faster than infants, older children, and adults. Because the termination of vecuronium depends on liver metabolism, the duration of action can be prolonged in neonates and small infants. When given in combination with thiopental, vecuronium can cause crystallization in the intravenous tubing and catheter that can be quite difficult to alleviate. Therefore, when using this combination of drugs the thiopental should be flushed through the tubing prior to injecting the vecuronium. Vecuronium administration is associated with bradycardia when given in combination with fentanyl or one of its analogues. However, vecuronium is not associated with histamine release or bronchospasm.

Vecuronium has been used for rapid sequence induction in children. At a dose of 0.4 mg/kg (four times a typical intubating dose) reliable intubation conditions can be achieved within 1 minute, but at the expense of a prolonged duration of action: reversibility may not be possible for more than 90 minutes. This large dose can be decreased with the concomitant use of an opioid.

**Rocuronium**

Rocuronium is an intermediate-acting relaxant that possesses a clinical profile similar to vecuronium and atracurium. Its main advantage is its ability to be given in relatively higher doses (1.2–1.6 mg/kg) to achieve reliable intubating conditions within 1 minute. These higher doses are not associated with the prolonged duration of action seen with vecuronium—reversibility is usually possible within 45 minutes. Therefore, rocuronium has become the neuromuscular blocker of choice for rapid sequence induction in children when succinylcholine is contraindicated. Some pediatric anesthesiologists use rocuronium for all RSI’s as an alternative to succinylcholine.

Rocuronium can be administered intramuscularly—1.0 mg/kg for infants and 1.8 mg/kg for children—to provide reliable intubating conditions within 3 minutes in most patients, at the expense of a prolonged duration of action that may exceed an hour. When administering this drug by the intramuscular route, a deltoid injection provides more reliable plasma levels than a quadriceps injection. The bioavailability of rocuronium after intramuscular administration is greater than 80%, and less than 5% of the drug remains in muscle 30 minutes after injection.

**Pancuronium**

Pancuronium is classified as a long-acting neuromuscular blocker because its duration of effect following an intubating dose is greater than 60 minutes. It is usually reversible by 40 minutes after administration.
Administration of pancuronium commonly causes tachycardia due to a combination of vagal blockade and catecholamine release, so it is ideally suited to counteract the bradycardia that results from administration of fentanyl or its analogues.

**EMERGENCE FROM GENERAL ANESTHESIA**

This section reviews the principles of emergence from general anesthesia in pediatric patients, with specific emphasis on criteria for tracheal extubation. Emergence is the process by which the patient awakens from general anesthesia and is prepared to recover from the withdrawal of ventilatory and circulatory support.

Until the latter portion of the twentieth century, halothane was routinely used for maintenance of general anesthesia. Because of its delayed excretion and prolonged duration of action, the anesthesiologist was required to predict with reasonable accuracy the time of completion of the surgical procedure. Simultaneously, the brain's concentration of halothane could be regulated with the intention of having the child awaken at or shortly after completion of the surgical procedure. In recent years, however, the majority of pediatric general anesthetics (in the USA) are maintained using isoflurane, sevoflurane, or desflurane. Because of the short duration of action of these agents, initiation down toward the completion of surgery requires less skill, especially when using desflurane, which has the shortest duration of action, similar to that of nitrous oxide.

**Tracheal Extubation**

There are three major criteria for tracheal extubation in children:

- **Sufficient muscular strength to ensure upper-airway patency after removal of the endotracheal tube**
- **The presence of a regular breathing pattern**
- **A sufficiently high level of consciousness that ensures the presence of airway protective mechanisms.**

The first two criteria may appear at any time during emergence, depending on the timing of the administration of reversal agents or discontinuation of the anesthetic agents. The third criterion is usually the last to appear. Each of these criteria will be discussed with particular regard to pediatric patients.

**Regular Breathing Pattern**

Once all general anesthetic agents have been discontinued, and neuromuscular blockers reversed (if applicable), children will begin to breathe on their own. The first spontaneous breaths may be regular, but as the child begins to regain consciousness, the breaths will become more irregular with alternating periods of breath-holding, and possibly coughing from the stimulus of the endotracheal tube. This phase is temporary and not indicative of wakefulness. During this phase of breath-holding and coughing small infants will often demonstrate profound decreases in oxygen saturation. These episodes can be extremely frightening to the entire operating room staff. During this phase, it is important that the anesthesiologist remains calm and leaves no doubts that he or she is in control of the situation, as the OR staff's emotions are often based on the anesthesiologist's reactions to critical situations. During this phase of breath-holding, coughing, and oxygen desaturation, the child's lungs should be manually ventilated at a rate (>30) and with a high enough inflation pressure to cause observable chest wall rise. Air entry is confirmed by listening with a precordial stethoscope, and by watching the capnograph. If the capnograph indicates air exchange, one can be reasonably confident that the oxygen saturation will soon begin to rise. Conversely, if air exchange does not appear on the capnograph, then the anesthesiologist knows he or she must alter the manual ventilation technique, which may often include using unusually high inspiratory pressures. It is only when the child begins to breathe regularly and maintain a normal oxygen saturation that the anesthesiologist can then begin to consider the following two criteria before removing the endotracheal tube.

**Sufficient Muscular Strength**

Muscular strength at the completion of surgery will depend on the timing of the discontinuation of the anesthetic agent and, if a neuromuscular blocker was administered, the time since the previous dose, as well as administration of an anticholinesterase agent to reverse the neuromuscular blockade (Table 19.3). Administration of anticholinesterase reversal agents should be considered after use of all nondepolarizing neuromuscular blockers, with the possible exception of mivacurium, if more than 15-20 minutes have passed since the most recent dose. Although most studies demonstrate a faster recovery from neuromuscular blockade in children when compared to adults, the acceleration of that

<table>
<thead>
<tr>
<th>Table 19.3</th>
<th>Antagonism of Neuromuscular Blockade</th>
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<tbody>
<tr>
<td>Anticholinesterase agents</td>
<td>Dose (mg/kg)</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>0.05-0.07</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Antihistaminic agents</td>
<td>Atracurium</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>0.01</td>
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recovery by administration of reversal agents is probably not age-dependent. However, as in adults, adequate reversal of a nondepolarizing neuromuscular blocker will not occur until a train-of-four (TOF) monitoring response is detected, with the possible exception of a deep mivacurium blockade. Also similar to adults, neostigmine appears to be a better antagonist of intense neuromuscular blockade than an equipotent dose of edrophonium. Much of what is known about antagonism of neuromuscular blockade is based on studies performed during maintenance of general anesthesia with halothane. Similar studies during sevoflurane or desflurane inhalation have not been performed.

An anticholinergic agent is routinely administered in combination with an anticholinesterase to prevent vagotonic bradycardia. Because of similarities in time to onset and duration of action, most anesthesiologists will choose to administer glycopyrrolate with neostigmine, and atropine with edrophonium; however, advantages of using these specific combinations have not been demonstrated experimentally or in clinical practice. Some studies indicate that use of a cholinergic-based reversal agent is associated with a greater incidence of postoperative nausea and vomiting. In contrast to glycopyrrolate, atropine crosses the blood-brain barrier and may possess a central antiemetic effect, thus lowering the incidence of postoperative nausea and vomiting when neostigmine is used.

In the absence of intense neuromuscular blockade, most children will rapidly achieve sufficient strength within several minutes after administration of a reversal agent. In adults, adequate strength is demonstrated by sustained head lift for 5 seconds or a vigorous hand squeeze on command. These criteria cannot be used in small children because of their inability to follow commands. Instead in the author's institution we use the "hip flexion" sign (Fig. 19-2), which indicates that the child has achieved sufficient strength to maintain airway patency independently after removal of the endotracheal tube. In addition, a negative inspiratory force less than \(-25 \text{ cmH}_2\text{O}\) and a vital capacity \(>15 \text{ mL/kg}\) are indicative of the strength required to sustain a patent upper airway following withdrawal of the endotracheal tube. Recovery of strength based on TOF indices is not routinely required in otherwise healthy children.

Return of Consciousness

The return of consciousness usually occurs last during emergence from general anesthesia. It is not until the child is awake that one can be assured of a regular breathing pattern and a normal airway protective response. In adults, it is relatively easy to detect wakefulness by the response to commands such as "open your eyes." The infant is obviously unable to respond in this manner. The anesthesiologist then must use other criteria such as spontaneous eye-opening, scratching of the eyebrows, or crying. One must not confuse involuntary reflexes such as reaching for the endotracheal tube as an indication of wakefulness. In general, harm is not done by leaving the endotracheal tube in too long, only by taking it out too soon. Most experienced pediatric anesthesiologists have observed children who appear to be conscious and strong just immediately prior to tracheal extubation, who then become apneic after the endotracheal tube is removed because of lack of a noxious stimulus. Removal of an endotracheal tube prior to the child regaining full consciousness may also cause laryngospasm via stimulation of laryngeal afferent nerves.

Many pediatric anesthesiologists administer an inspiratory hold, or sigh, up to 30 cmH\(_2\)O immediately prior to, and as part of, the last breath before tracheal extubation. The intent of this maneuver is to reverse any existing atelectasis that occurred during the general anesthetic, and restore the function residual capacity (FRC). However, controlled studies on the efficacy of this maneuver have not been performed.

It is not unusual, even in seemingly awake children, for breath-holding to develop immediately after tracheal extubation. This may be caused by the laryngeal stimulation that occurs from the movement of the endotracheal tube. During this phase, provided the patient does not develop hypoxemia, this author prefers to avoid positive-pressure ventilation while maintaining upper-airway patency by chin lift and jaw thrust. In the vast majority of cases, the child will resume spontaneous ventilation within 1 minute and will not develop hypoxemia. In the remainder of children who develop hypoxemia, positive-pressure ventilation is indicated, and laryngospasm should be immediately treated with a small dose of succinylcholine (0.2–0.3 mg/kg).
“Deep” Extubation

Extubation of most children occurs after they have regained consciousness, as outlined above. However, a situation occasionally arises in which it may be detrimental for the child to regain consciousness and airway reflexes with the endotracheal tube still in the trachea. This includes procedures in brittle asthmatics, and certain types of surgical procedures (e.g., ophthalmologic) where coughing may interrupt delicate suture placement. In these cases, it is feasible to remove the endotracheal tube from the trachea prior to the child regaining consciousness and before the child develops the ability to cough. This is commonly referred to as a “deep” extubation. Contraindications to deep extubation in children include suspicion of a greater than normal amount of gastric contents, difficulty with mask ventilation at the beginning of the anesthetic, or difficulty with endotracheal intubation.

A deep extubation can be performed by carrying out a series of progressive steps:

1. Establish a pattern of regular spontaneous ventilation. This can be accomplished by gradually lowering the concentration of inhaled agent and assuring adequate strength by reversing the neuromuscular blockade. During this time the stomach should be emptied with an orogastric tube. None of the inhalational anesthetics have any particular advantage during deep extubation. Desflurane has not been studied and should probably be avoided because of its pungency and tendency to increase airway irritability.

2. Once the child has established a spontaneous, regular breathing pattern, the concentration of the inhaled agent is gradually increased to approximately 2–3 MAC, within the limits of normal vital signs and continuation of spontaneous respiratory effort.

3. The oropharynx is suctioned and the endotracheal tube is removed. Some anesthesiologists prefer to further blunt laryngeal reflexes by administering lidocaine 1.5 mg/kg several minutes prior to extubation. In addition, if excess secretions are present, one may consider the administration of glycopyrrolate prior to extubation.

4. Mask ventilation is then resumed and the inhalational agent is discontinued.

A major disadvantage of performing a deep extubation is that the patient will progress through the lighter stages of anesthesia with an unprotected airway. During this phase, secretions or blood may come in contact with laryngeal structures and precipitate laryngospasm. Therefore, deep extubations should be performed only if the anesthesiologist has the ability to remain with the patient until full consciousness is regained, or if the PACU nursing staff possesses the training and experience to accommodate the emerging child.

ADDITIONAL ARTICLES TO KNOW


