Total intravenous anesthesia has been widely practiced in adult anesthesia since the introduction of propofol into routine clinical practice in 1982. Although there were reports of the use of total intravenous anesthesia in children as early as 1989, it is only in recent years that the practice in children has become more common, attributable to the publication of pediatric pharmacokinetic parameter estimates for propofol. Propofol parameter estimates for neonates and infants younger than 1 yr are less published.

These propofol pharmacokinetic parameter estimates for children were used to determine drug delivery rates given by pump that would achieve a plasma target concentration associated with anesthesia. Drug delivery rates (mass infusion rates) require frequent manual changes by the clinician to maintain the target concentration. The incorporation of parameter estimates into target-controlled infusion (or “smart”) pumps removed operator dependence. A target-controlled infusion is accomplished by a computer within the pump that performs rapid sequential calculations every 8 to 10 s to estimate the infusion rate required to produce a user-defined drug concentration in either the plasma or at the effect site of action of the drug in the brain in an open-loop system. Open-loop systems require the physician to alter the target concentration depending on the observed effect, e.g., clinical signs of depth of anesthesia and/or a processed electroencephalographic signal. When effect measures are automatically used by the device to control infusion rate (a feedback method) the system is known as closed-loop. Open-loop rather than closed-loop target-controlled infusion is the routine in pediatric anesthesia, although closed-loop systems have been described.¹²

Pharmacokinetic parameter estimates and effect measures are associated with variability,³ similar to that observed with inhalational vapors.⁴ Consequently, the anesthesiologist should use both smart pumps and mass infusion pumps as a basis for initiating a total intravenous anesthesia technique but must also use skill, knowledge, and experience to titrate the intravenous agents to effect and to avoid awareness, pain, and other adverse effects.

The aim of this article is to provide some background pharmacokinetic information essential for undertaking total intravenous anesthesia and target-controlled infusion in children of all ages and some practical advice on how this might be successfully achieved. The article concentrates on total intravenous anesthesia using propofol and remifentanil because these two drugs are commonly used in pediatric total intravenous anesthesia practice.⁵

**Reasons to Use Total Intravenous Anesthesia**

There are three main reasons for total intravenous anesthesia: necessity, benefit, and choice. Advantages and disadvantages of total intravenous anesthesia over conventional inhaled volatile anesthetic agents are outlined in table 1.
Total Intravenous Anesthesia for Children

Table 1. Advantages and Disadvantages of Total Intravenous Anesthesia in Children

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>• Less postoperative nausea and vomiting</td>
<td>• Need for venous access, pain on injection</td>
</tr>
<tr>
<td>• Less operating room pollution</td>
<td>• Risk of bacterial contamination</td>
</tr>
<tr>
<td>• Reduced emergence delirium</td>
<td>• No current ability to monitor blood concentration</td>
</tr>
<tr>
<td>• Reduced airway reactivity, laryngospasm, and bronchospasm</td>
<td>• Delivery problems may go unrecognized</td>
</tr>
<tr>
<td>• Advocated for neuromuscular disease, core myopathies, and muscular dystrophy</td>
<td>• Need specialized equipment (e.g., infusion pumps)</td>
</tr>
<tr>
<td>• Less interference with evoked potential monitoring</td>
<td>• Less training available for TIVA techniques</td>
</tr>
<tr>
<td>• Associated with overall reduced costs</td>
<td>• Drugs require metabolism for clearance</td>
</tr>
<tr>
<td>• Reliable delivery in airway procedures</td>
<td>• Risk of associated metabolic phenomena</td>
</tr>
</tbody>
</table>

TIVA, total intravenous anesthesia.

Necessity

The only absolute indication to use a total intravenous anesthesia technique in children is that there is a susceptibility to malignant hyperthermia or there is a strong family history in an untested child.

Benefit

The main benefits of using a total intravenous anesthesia technique include reduced postoperative nausea and vomiting with propofol use, quicker recovery, improved quality of recovery (including reduced emergence delirium), reduced airway reactivity and adverse events after extubation, improved neurophysiologic monitoring (e.g., during spinal instrumentation), and less operating room pollution attributable to anesthetic gases.

Choice

The occasional use of total intravenous anesthesia maintains skills for those occasions when a total intravenous anesthesia technique is required.

Contraindications

The use of propofol should perhaps be avoided in patients with mitochondrial disease because children with these disorders may be at higher risk of developing propofol-related infusion syndrome. The cause of propofol-related infusion syndrome is still not fully understood, but it is thought to be related to a metabolite of propofol inhibiting the respiratory chain within the mitochondrion, leading to reduced adenosine triphosphate production and failure of metabolic processes. Patients with mitochondrial disease already have reduced adenosine triphosphate production, so they may be more susceptible to developing propofol-related infusion syndrome. Prolonged fasting increases the risk of propofol-related infusion syndrome, and so glucose infusions may reduce that risk. A single case report of probable propofol-related infusion syndrome related to anesthesia in a patient with a possible mitochondrial disorder has been published, and this relationship between adverse events in children with mitochondrial disorders and specific anesthetic agents remains tenuous.

While propofol-related infusion syndrome is well documented in critically ill children and current guidelines suggest that propofol should not exceed 4 mg · kg$^{-1} · h^{-1}$ for periods greater than 48 h, propofol-related infusion syndrome is rarely reported in children undergoing prolonged anesthesia. It is suggested that arterial blood gases, serum lactate, creatinine kinase, electrolytes, and liver and kidney functions should be monitored during prolonged propofol infusions.

Propofol should be avoided in those with medium chain acyl-CoA dehydrogenase deficiency. These children lack the enzyme to metabolize medium chain triglycerides, which are present in propofol preparations. This can lead to the accumulation of free fatty acids that are thought to predispose patients to developing arrhythmias.

Adult and Child Pharmacokinetic and Pharmacodynamic Differences

The major differences between children and adults center on growth and development. These two processes have impact on drug pharmacokinetics and pharmacodynamics. Most enzyme systems responsible for metabolic clearance are immature at birth and mature within the first few years of life. Clearance through the renal system is also immature at birth. Consequently, drug clearance is reduced at birth, but by the age of 1 to 2 yr, it is greater than that observed in older children and adolescents (when expressed as per kilogram per unit of time). These clearance changes after maturation can be attributed to the nonlinear relationship between size and function and explained using allometric theory. Drug clearance, out of infancy, can be standardized to an adult of 70 kg using allometric scaling, where CL indicates clearance, i.e.,

$$CL_{CHILD} = CL_{ADULT} \times \left( \frac{\text{Weight}_{CHILD}}{70} \right)^{3/4}$$

This scaling theory has been used to estimate clearance in children of both propofol and remifentanil. Clearance is a major determinant of drug infusion rate at steady state.
Children, but not neonates, require higher drug infusion rates (expressed as µg · kg⁻¹ · min⁻¹) than adults to achieve the same target concentration.

However, there are some enzymes that are mature at birth, and the nonspecific blood esterases that metabolize remifentanil is one such clearance pathway. Clearance of remifentanil, when expressed as per kilogram, is highest in neonates and decreases with age to reach adult rates in adolescence.

The loading dose is dependent on volume of distribution rather than clearance. The drug volume of distribution is influenced by both body composition and drug characteristics (e.g., lipophilicity). Body composition changes are dramatic over the first few years of life. Fat, for example, contributes 3% in a 1.5-kg premature neonate and 12% in a term neonate; fat proportion doubles by 4 to 5 months of age. Protein mass increases when infants start walking (20% in a term neonate; fat proportion doubles by 4 to 5 months of age). Protein mass increases when infants start walking (20% in a term neonate; 50% in an adult), and the fat content is reduced in this cohort. This results in a larger volume of distribution for both propofol and remifentanil in children, requiring a larger loading dose (expressed as per kilogram) than healthy adults.

While size and age are major contributors to both pharmacokinetic and pharmacodynamic uncertainty, there remains known and unknown variability that requires consideration during total intravenous anesthesia delivery. Drug interactions, both pharmacokinetic and pharmacodynamic, impact on dosing. Some anticonvulsant medications, for example, can have considerable effect on intravenous anesthetic drugs, neuromuscular blocking drugs, and opioids.

Pharmacodynamic monitoring using processed electroencephalographic signals is problematic in neonates and infants younger than one year of age. Both the Bispectral Index monitor (BIS monitor, Covidien, Ireland) and Narcotrend (Monitor Technik, Germany) have shown a close relationship with the modeled effect site propofol concentration, and can serve as a measure of anesthetic drug effect in children older than 1 yr. The Narcotrend shows promise for infants older than 4 months given sevoflurane and may prove useful for propofol in that cohort. The electroencephalogram in infants is different from the electroencephalogram in older children. There are age-dependent electroencephalographic changes demonstrated with sevoflurane anesthesia that reflect the process of cerebral maturation, in particular the neuronal myelination. There is a need for specific neonatal algorithms if electroencephalographic-derived anesthesia depth monitors are to be used in neonates. Clinical signs rather than processed electroencephalograms are currently required for depth of anesthesia assessment in infants and neonates.

### Propofol

Total intravenous anesthesia techniques use propofol as the principal drug for induction and maintenance of anesthesia. The pharmacokinetics of propofol in children have been often described, but only two parameter sets (Kataria, Absalom) are currently used in commercial target-controlled infusion pumps (table 2). The Kataria parameter set has been used to determine manual infusion rates for the McFarlan manual regimen that is designed for children ages 3 to 11 yr. Other available pediatric parameter sets that can be used for propofol infusion targeting a plasma concentration are based on data from Marsh et al., Gepts et al., Short et al., Rigby-Jones et al., Schlüttler and Ihmsen, Murat et al., Saint-Maurice et al., Coppens et al., Absalom et al. (Paedfusor, Graseby Medical Ltd, United Kingdom), and Eleved et al. These parameter sets are termed “models” and named after the author who reported them (e.g., “Kataria model”). Parameter estimates (e.g., clearance, CL; intercompartment clearance, Q; central volume of distribution, V1; peripheral volume of distribution, V2) are different for each parameter set. Although parameter estimates differ for each

<table>
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<tr>
<th>Table 2. Comparison of the Marsh, Kataria, and Paedfusor PK Parameter Estimates Used in TCI Pumps</th>
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<tr>
<td><strong>Marsh:</strong></td>
</tr>
<tr>
<td>V1 (l)</td>
</tr>
<tr>
<td>V2 (l)</td>
</tr>
<tr>
<td>V3 (l)</td>
</tr>
<tr>
<td>k_{10} (min⁻¹)</td>
</tr>
<tr>
<td>k_{12} (min⁻¹)</td>
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<td>k_{13} (min⁻¹)</td>
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<tr>
<td>k_{21} (min⁻¹)</td>
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<tr>
<td>k_{31} (min⁻¹)</td>
</tr>
<tr>
<td>k_{eo} (min⁻¹)</td>
</tr>
</tbody>
</table>

Equilibration rate constants (k) between compartments are identified by subscript, e.g. k_{10} is the rate constant for equilibration between compartment 1 and 2; k_{eo} is the equilibration rate constant for the central and effect compartments, equivalent for that between the effect compartment and outside.

*Munoz estimated a keo for children age 3–11 yr. Jeleazcov has derived age-related keo values by the formula keo = 1.03 x e⁻⁰.²¹ weight. †The original estimate of 0.26 (min⁻¹) was recalculated by Struys et al. The Marsh model is identical to the Gepts et al. model in all respects except that the central compartmental volume was increased to 0.228 l/kg. Absalom is contained in the Paedfusor pump (Graseby Medical Ltd, United Kingdom).
author’s “model,” most predict similar concentrations for the same infusion regimen (fig. 1).52,53

Covariate influences that contribute variability to the parameters, such as the severity of illness are often unaccounted for; e.g., the volume of the central compartment is increased in children after cardiac surgery.54 Even weight or age, the most common sources of variability,23 may be omitted from parameter estimates. Time-concentration profiles and context-sensitive half-time will differ depending on which pharmacokinetics parameter set is used.53

Drugs Used in Combination with Propofol

The commonly used medications include the opioids remifentanil, alfentanil, and sufentanil. Ketamine is occasionally used, but it has a long context-sensitive half-time with consequent delayed awakening after prolonged exposure.54 Dexmedetomidine has also been used as an adjunct to reduce propofol requirements.55,56 Avoidance of the use of neuromuscular blocking drugs allows better titration of drug to effect, lowers the potential for awareness, and contributes to the early recognition of problems associated with drug delivery.

Remifentanil

The high potency, fast onset, and short context-sensitive half-time of 2 to 3 min means that remifentanil can be effectively used by infusion for prolonged periods of time.57 There is additivity of anesthetic effect when used with propofol described in adults58,59 and in children 1 to 11 yr,60 although effects such as apnea appear synergistic.58 A remifentanil infusion of 25 ng · kg⁻¹ · min⁻¹ reduced the concentration of propofol required for adequate anesthesia for esophagogastroduodenoscopy in children 3 to 10 yr from 3.7 to 2.8 µg/ml. Increasing the remifentanil infusion yielded minimal additional decrease in target propofol concentration.61 A pharmacodynamics model describing the propofol and remifentanil additive interaction for anesthesia in children 1 to 12 yr using Bispectral Index as an effect measure is similar to that reported in adults. The concentration in the effect compartment at half the maximum response (Ce₅₀) for remifentanil of 21 ng/ml and an Ce₅₀ for propofol of 2.99 µg/ml were reported.60 Remifentanil, delivered at clinically relevant concentration ranges in children, has little effect on Bispectral Index. This monitor provides information mainly limited to cortical brain activity that reflects the hypnotic component of anesthesia. Although during surgery, antinociception may be required to maintain hypnosis, response to painful stimulation cannot be predicted by Bispectral Index because the analgesic component of anesthesia involves subcortical autonomic responses.62

Adult remifentanil pharmacokinetics parameters (e.g., Minto model63) continue to be used in target-controlled infusion devices for all ages, despite parameter estimates having bigger values in children when expressed as per kilogram.17 There is an element of safety with this use of remifentanil adult pharmacokinetics parameter estimates because both volume of distribution21 and clearance (expressed as ml · min⁻¹ · kg⁻¹) decrease with increasing age.17 The smaller the child, the greater the clearance when expressed as ml · min⁻¹ · kg⁻¹. Owing to these higher clearances, younger children will require higher infusion rates of remifentanil than older children and adults to achieve equivalent plasma concentrations.64,65 The greater volume of distribution in children reduces the peak concentrations of remifentanil after bolus dosing; the increased clearance

![Fig. 1. Simulated time-concentration profiles for propofol using differing parameter sets. A 3 mg/kg bolus was administered, and the infusions were administered as for an adult using the 10-8-6 infusion regimen described by Roberts et al.66 From Anderson,52 with permission.](http://pubs.asahq.org/anesthesiology/article-pdf/131/1/164/455358/20190700_0-00035.pdf)
in children results in a lower plasma concentration when infused at adult rates expressed as µg · min⁻¹ · kg⁻¹.

As a rule of thumb, children less than 5 yr or 20 kg will require up to twice the dose of remifentanil (µg/kg) to produce the same clinical effect as older children and adults.⁶⁵,⁶⁶ The rapid offset, described by the equilibration half-time (t₁/₂keo) of remifentanil (t₁/₂keo 1.16 min in adults)⁶¹,⁶⁸ means that adequate postoperative analgesia needs to be established before the infusion wearing off.

Reports of a rapid development of µ-receptor tolerance with remifentanil are in conflict; activity at δ-opioid receptors may contribute.⁶⁹ It was noted that in children 1 to 5 yr undergoing laparoscopic procedures given remifentanil infusions of 0, 0.3, 0.6, or 0.9 µg · kg⁻¹ · min⁻¹, more postoperative fentanyl was given at 24 h in those who received 0.6 or 0.9 µg · kg⁻¹ · min⁻¹ than those who received 0 or 0.3 µg · kg⁻¹ · min⁻¹, suggesting that large doses of remifentanil may cause tolerance.⁷⁰ Similarly, adolescents undergoing spinal instrumentation for scoliosis also demonstrated acute tolerance.⁷¹ It has been suggested that longer acting opioids, e.g., morphine, be administered approximately 40 min before the end of surgery to allow time for it to bind to opioid receptors occupied by remifentanil.⁷² This morphine dose timing is consistent with the equilibration half-time between central and effect compartments for morphine (t₁/₂keo) of 16 min.⁷³,⁷⁴

Alfentanil

Alfentanil remains an effective analgesic component of total intravenous anesthesia. It has a relatively fast onset (t₁/₂keo 0.9 min in adults),⁷⁵ can be administered by bolus or infusion, and will usually have some residual analgesic effect at the end of surgery. It is often mixed with the propofol in ratios that range from 50:1 to 180:1 (propofol:alfentanil, µg/µg) for maintenance anesthesia.⁷⁶–⁷⁸ It has a longer context-sensitive half-time than remifentanil that increases from 10 to 45 min after a 2-h infusion.⁷⁹ Propofol/alfentanil is a useful combination, particularly if spontaneous respiration needs to be maintained. The larger context-sensitive half-time may delay recovery when compared to remifentanil, particularly in those children infused for longer than an hour.⁷⁹ Children 2 to 14 yr given alfentanil infusion 1 µg · kg⁻¹ · min⁻¹ required a longer stay (mean ± SD) in the postanesthesia recovery unit (68 ± 23 min) compared to those given remifentanil infusion 0.25 µg · kg⁻¹ · min⁻¹ (45 ± 16 min) for 1.5 h.⁸⁰ Children (2 to 12 yr) anesthetized with alfentanil also had a greater requirement for naloxone and a higher incidence of postoperative hypoxemia compared with those anesthetized with remifentanil.⁶⁷

The target concentrations for a propofol/alfentanil combination are 4.5 µg/ml and 120 ng/ml, respectively, during maintenance, reducing toward the end of surgery to 3.5 µg/ml and 90 ng/ml, although this titration depends on the nature of the surgical stimulus.⁸⁰ Alfentanil infusion can be stopped 10 to 15 min before the end of anesthesia and propofol alone used for sedation; some suggest stopping alfentanil infusion at the start of skin closure.⁸¹

Sufentanil

Sufentanil has a relatively slow equilibration half-time (t₁/₂keo of 6.2 min) compared to remifentanil and alfentanil,⁸² and a plasma concentration (Cp) 0.5 to 3 ng/ml is used for analgesia during total intravenous anesthesia (0.01 to 0.05 mcg · kg⁻¹ · min⁻¹).⁸³ The pharmacokinetic profile after cardiovascular surgery demonstrated an increased volume of distribution in infants (4.15 l/kg) compared to children (2.73 l/kg) and adolescents (2.75 l/kg). Clearance is increased in infancy (18.1 ml · kg⁻¹ · min⁻¹) with reduced values in children (16.9 ml · kg⁻¹ · min⁻¹) and adolescents (13.1 ml · kg⁻¹ · min⁻¹). There are few reports of sufentanil use when combined with propofol in children. Adult literature suggests that those given sufentanil have less analgesic requirements and delayed cognitive recovery compared to those given remifentanil in the immediate postoperative period.⁸⁴–⁸⁵ Sufentanil infusion could be ceased approximately 30 min before stopping propofol.

Ketamine

Ketamine remains popular in pediatric anesthesia due to its hypnotic and analgesic properties and its cardiorespiratory stability. The plasma concentration of racemic ketamine associated with anesthesia is approximately 3 µg/ml, and return of consciousness usually occurs at concentrations less than 0.5 µg/ml. Ketamine is very lipid soluble with rapid distribution and the onset of anesthesia after IV ketamine is approximately 30 s. The t₁/₂keo was estimated at 11 s.⁸⁵

Combined effects due to combination therapy with racemic ketamine and propofol were additive, described using a sigmoidal curve with a propofol Ce₅₀ of 3.1 µg/ml, ketamine Ce₅₀ of 0.64 µg/ml, and a slope parameter of 5.4. This means that small serum concentration changes will have dramatic effect on the degree of sedation observed. The combination of ketamine and propofol (“ketofol”) in a 1:1 ratio is being used in emergency departments with great success.⁸⁶ Less nausea and vomiting are reported when propofol is employed with ketamine for sedation. Children receiving ketamine with propofol had less vomiting than those given ketamine alone (2% vs. 12%) after orthopedic procedures.⁸⁷ Propofol has an anesthetic effect at plasma concentration with an (Cp₅₀) of 0.343 µg/ml. The time that this concentration exceeds the anesthetic threshold for ketamine (0.2 µg/ml) after return of consciousness changes with both the dose ratio and duration of infusion. An optimal ratio of racemic ketamine to propofol of 1:5 for 30 min of anesthesia and 1:6.7 for 90 min of anesthesia has been suggested. The context-sensitive half-time of ketamine increases with the duration of the infusion, resulting in delayed recovery.⁸⁸,⁸⁹

The addition of ketamine to propofol infused using a McFarlan manual infusion regimen⁹⁰ caused prolonged
postoperative sedation in a 5-yr-old, 20-kg child. The predicted 50% probability of return to consciousness after a 1.5-h infusion using a 1:5 mixture was 1.6 h; this was reduced by slowing administration infusion rates to 67% of that dictated by the McFarlan regimen. This lower rate achieved a predicted 50% probability of return to consciousness of 60 min for 1.5 h duration anesthesia.99

**Midazolam**

Midazolam continues to be used as premedication and coadministration at anesthesia induction. Coadministration reduces the propofol dose for induction and the amnestic effect. Midazolam may be desirable if lighter plains of anesthesia or sedation are used.90 The $t_{1/2}$ of midazolam is 0.9 to 1.6 min. A midazolam infusion (e.g., 0.05 mg · kg$^{-1}$ · h$^{-1}$, 0.83 µg · kg$^{-1}$ · min$^{-1}$, plasma concentration 125 ng/ml) combined with propofol reduced the clearance of one another, resulting in a 25% increase in propofol concentrations and a 27% increase in midazolam concentrations.91–93 These changes are due to cytochrome P450 inhibition by propofol and hemodynamic alterations; midazolam has an intermediate hepatic extraction ratio and clearance is reduced with a lowering of hepatic blood flow. They also both act on γ-amino butyric acid cerebral receptors contributing to pharmacodynamic interactions.94,95 The addition of midazolam to propofol infusion improves hemodynamic stability but delays recovery when compared to propofol alone.

**Dexmedetomidine**

Dexmedetomidine has ascendency over clonidine as the $\alpha_2$ -receptor agonist of choice for procedural sedation in children because it is approximately eight times more specific to the $\alpha_2$-adrenoreceptor. The sedation target concentration (0.6 µg/l) in children is similar to that described for adults. Immature clearance in the first year of life and a higher clearance (when expressed as per kilogram) in small children dictate infusion rates that change with age.96 Dexmedetomidine qualities such as maintenance of respiratory drive, conserved airway patency, opioid sparing analgesic effect, neurophysiologic evoked potential preservation, and possible neuroprotective effects make this drug an attractive option as an adjunct to propofol-based total intravenous anesthesia.97 Coadministration with other drugs such as midazolam, fentanyl, and ketamine is also reported for invasive procedures.55,56,98 An ED$_{50}$ of 0.49 µg/kg given over 5 s in children (5.4 to 9.5 yr) undergoing propofol/remifentanil total intravenous anesthesia is without hemodynamic compromise.99

There is low-grade evidence that dexmedetomidine infusion in children (0.5 to 1 µg · kg$^{-1}$ · h$^{-1}$, 8.3 to 16.7 ng · kg$^{-1}$ · min$^{-1}$) reduces propofol and opioid requirements, provides moderate hypotension, decreases blood loss, and allows monitoring of motor and somatosensory evoked potentials and reduces emergence delirium in children, but at the expense of slightly prolonged waking.55,100–103 There are no pharmacokinetic–pharmacodynamic propofol and dexmedetomidine interaction models yet described in children.

Fewer neuro-apoptotic consequences have been attributed to $\alpha_2$-agonists than most other anesthetic drugs. Consequently, dexmedetomidine is being explored as an alternative sedative in neonates requiring surgery. Dexmedetomidine 2 µg/kg over 10 min followed by 1 µg/kg over the next 10 min for sedation enabled caudal local anesthesia placement with minimal need for airway intervention during inguinal hernia repair in term neonates (mean postconception age, 39.7; interquartile range, 37.8; 45.7 weeks).104

**Manual Infusion Regimens**

Before target-controlled infusion systems were available, anesthetists wishing to administer total intravenous anesthesia relied on manual infusion regimens. These regimens comprised an intravenous propofol loading dose and then a subsequent decreasing infusion rate to maintain a target plasma concentration (e.g., plasma concentration 3 µg/ml). The first such regimen in adults was the “10–8–6 rule” from Bristol, United Kingdom.56 This comprised a loading dose of propofol 1 mg/kg followed immediately by an infusion of 10 mg · kg$^{-1}$ · h$^{-1}$ for 10 min, 8 mg · kg$^{-1}$ · h$^{-1}$ for the next 10 min, and 6 mg · kg$^{-1}$ · h$^{-1}$ thereafter.66 However, it soon became apparent that the doses of propofol delivered by this regimen were insufficient for maintenance of anesthesia in children (fig. 2). Two popular manual pediatric infusion regimens were subsequently developed: the MacFarlan regimen40 based on the Kataria pharmacokinetic parameter estimates22 for children between the ages of 3 and 11 yr, and the Steur regimen105 that was adapted from clinical
Target Concentration

The target concentration is the concentration desired in the plasma or at the effect site. The plasma and effect site concentrations are the same at steady-state. The target concentration depends on the desired effect and that effect is determined by an understanding of the effect site concentration–response relationship of the drug. This will differ with age, pathology, drug interactions, and stimulus. The target concentration will differ depending on the magnitude of the desired effect.

A propofol concentration of 2 to 3 µg/ml is an appropriate target for sedation, and 4 to 6 µg/ml is adequate for anesthesia. The estimated mean target effect-site propofol concentrations for both the loss and return of consciousness in children of 2.0 ± 0.9 µg/ml and 1.8 ± 0.7 µg/ml respectively, are similar to those reported in adults.107,108 The relation between drug concentration and effect is commonly described by the Hill equation,109

\[
\text{Effect} = \frac{E_{\text{max}} \cdot C_e^N}{(C_{50e} + C_e^N)}
\]

where E0 is the baseline level of consciousness, Emax is the maximum response, Ce is the concentration in the effect compartment, Ce 50 is the concentration at half this maximum response, and N defines the steepness of the slope.

Pharmacodynamics in children 1 to 12 yr using the Bispectral Index are similar to those described in adults, where E0 was estimated as 94; Emax, 81; Ce 50, 2.99, µg/ml; and N, 1.55.60 This relationship is very similar to that described in obese children.110 The equilibration rate constant (keo) between the plasma and effect compartment was 0.8 min⁻¹ (t ½ keo 2.38 min). Children may have a slightly lower sensitivity to propofol than adults,111 although this
difference may be due to pharmacokinetic rather than pharmacodynamic factors. Maintenance infusion requirements for propofol in neonates differ substantially from those in older infants and children. These may be attributed mostly to differences in pharmacokinetics. In terms of the kinetics, the clearance of propofol in neonates is reduced compared with older infants due to immature enzyme clearance systems. To develop a dose scheme for propofol infusion rates in neonates and infants, the adult dosage scheme was adapted to the requirements in the younger population by observing the total number and time of administration of boluses and time to awakening from propofol in infants younger than 3 yr (n = 2,271). The predicted infusion rates for the first 10 min in neonates were large (24 mg · kg⁻¹ · h⁻¹; 400 µg · kg⁻¹ · min⁻¹), values that should be used cautiously due to a danger of an overdose if the infusion continues beyond 10 min. Delayed awakening, hypotension, and an increased incidence of bradycardia have been reported in neonates and infants. Propofol can cause profound hypotension in neonates, and pharmacokinetic-pharmacodynamic relationships in this age group remain elusive.

A remifentanil target of 2 to 3 µg/l (ng/ml) is adequate for laryngoscopy and 6 to 8 ng/ml for laparotomy, and 10 to 12 ng/ml might be sought to ablate the stress response associated with cardiac surgery. The initial loading dose of remifentanil may cause hypotension and bradycardia in children, prompting some to target the plasma rather than effect-site concentration when initiating an infusion. This hypotensive response has been quantified in children undergoing cranioplasty surgery. A steady-state remifentanil concentration of 14 ng/ml would typically achieve a 30% decrease in mean arterial pressure. This concentration is twice that required for laparotomy (t₁/₂keo of 1.34 min). Even though remifentanil-induced spectral edge frequency changes described in adults (t₁/₂keo of 1.34 min) are less than remifentanil clearance, the concentration in the effect compartment describes the concentration-effect relationship. The t₁/₂keo parameter is incorporated into target-controlled infusion pumps and is used to achieve a rapid effect-site concentration. Once the concentration in the effect compartment is entered into the target-controlled infusion pump, the pump delivers drug such a way that it generates an overshoot of the blood concentration that is above the target effect-site concentration. The degree of overshoot depends on both the keo and time frame available to achieve the concentration in the effect compartment target. Effect-site concentrations cannot be directly measured, and so effect-site targeting algorithms rely on estimates of the time course of the changes in effect-site concentration based on measurements of the clinical effect (usually a processed electroencephalographic measure).

There are few estimates of the t₁/₂keo for propofol in children using simultaneous pharmacokinetic-pharmacodynamic modeling. An estimate of 1.86 min (95% CI, 1.16 to 2.31) was reported in healthy children 2 to 12 yr, another of 2.38 min (95% CI, 1.84 to 3.16) in healthy children 1 to 12 yr, and 1.2 min (95% CI, 0.85 to 2.1) in obese children. We might expect a smaller t₁/₂keo with decreasing age based on allometric theory. These smaller t₁/₂keo times in children can be accounted for by considering half-time as physiologic time that scales with an exponent of one fourth.

\[ t_{1/2}^{\text{keo,CHILD}} = t_{1/2}^{\text{keo,ADULT}} \times \left( \frac{\text{Weight}_{\text{CHILD}}}{70} \right)^{1/4} \]

where an adult has a standard weight of 70 kg. Although an increasing t₁/₂keo with age has been described for propofol in children, that for sevoflurane has been shown to correlate better with weight scaled using allometric theory. If unrecognized, this will result in excessive dose in a young child if the effect site is targeted and peak effect is anticipated to be later than it actually is because it was determined in a teenager or adult (fig. 3), e.g., a propofol bolus dose would be 37% higher in a 10-kg child if the t₁/₂keo estimated for a 70-kg patient was used.

When both pharmacokinetics and pharmacodynamics data are collected simultaneously and parameters for both models are estimated together, then the model is described as “integrated.” The Kataria parameter set and the Paedfusor (Graseby Medical Ltd., United Kingdom) were originally described as pediatric pharmacokinetics estimates only. Pharmacokinetics estimates should not be used in conjunction with pharmacodynamics estimates taken from a different data set; they are mismatched. Time to peak effect methodology is commonly used to estimate t₁/₂keo that then links separate pharmacokinetics and pharmacodynamics data sets if the original pharmacokinetics data were not integrated with pharmacodynamics data. Time to peak effect will increase with age in children. This model dependence of the t₁/₂keo results in different estimates: 1.7 min with

**Linking Pharmacokinetics with Pharmacodynamics**

A plasma concentration-effect plot can form a hysteresis loop because of a delay in effect. A single first-order parameter (t₁/₂keo) describes the equilibration half-time between plasma and effect site concentrations.

\[ t_{1/2}^{\text{keo}} = \frac{\log_e(2)}{\text{keo}} \]
the Kataria\textsuperscript{22} parameter set and 0.8 min with the Paedfusor parameter set.\textsuperscript{39} Some target-controlled infusion pumps use different estimates for $t_{\text{1/2keo}}$ for the same model; the Alaris Asena PK (Cardinal Health, Alaris Products, United Kingdom) and the Base Primea (Fresenius, France) with the Schnider model are examples.

### Smart Pumps

Open target-controlled infusion systems that are commercially available (Alaris Asena PK, Base Primea) are usually supplied with preloaded and activated pharmacokinetics parameter sets for remifentanil,\textsuperscript{63,68} sufentanil,\textsuperscript{122} and propofol. The Base Primea system uses the Gepts et al.\textsuperscript{42} and Schnider et al.\textsuperscript{123,124} propofol models. The Alaris Asena PK system uses the Marsh\textsuperscript{41} and Schnider et al.\textsuperscript{123,124} adult models and the Kataria\textsuperscript{22} and Paedfusor\textsuperscript{39} pediatric models. Both plasma and effect-site targeting are possible with these pumps, although effect-site targeting is not possible with the Marsh model implemented in the Alaris Asena PK. Unfortunately, the commercially available software packages usually limit smart pumps to ages from 1 to 3 yr or older or weight from 5 to 15 kg or greater. Commercial target-controlled infusion pumps programmed for neonates and infants younger than 1 yr are not yet available.

Commercial target-controlled infusion systems (smart pumps) programmed with pediatric pharmacokinetic-pharmacodynamic parameters are unavailable for anesthesia practices in the United States, although use is possible by employing research software in institutional review board-approved research studies.\textsuperscript{125} Originally the U.S. Food and Drug Administration expressed concerns about computer-based drug delivery and the safety of these pumps.\textsuperscript{126,127} Safety concerns and user confusion are inevitable when there is a profusion of pharmacokinetics parameter sets, each claiming reliability. Few companies have submitted applications to the Food and Drug Administration since propofol became a generic drug, suggesting that the cost of submission and licensing may outweigh subsequent profits from pump sales.\textsuperscript{129} However, there may be other, lower-cost routes to pump licensing, and it is hoped that practitioners in the United States may soon have access to smart pumps.\textsuperscript{126} This delay in availability of pumps in the United States may be advantageous. It gives the opportunity to choose one pharmacokinetic-pharmacodynamic parameter set programmed for children, rather than the profusion of current parameter sets that are available. Models that account for maturation and size using allometry in children would not be difficult to program\textsuperscript{129} and are now available for propofol\textsuperscript{130} and remifentanil.\textsuperscript{18}

### Accuracy of Propofol Pediatric Models

The Paedfusor was originally the only validated model. It was reported to have an acceptable median performance error (bias) of 4.1\% and a median absolute performance error (precision) of 9.7\% in children aged 1 to 15 yr undergoing either cardiac catheter or cardiac surgery.\textsuperscript{39} Other models have subsequently been independently reviewed. Most parameter sets except the pediatric Marsh\textsuperscript{41} model performed acceptably in children between 3 and 26 months,\textsuperscript{32} although a poor fit for the Kataria model has been described for long duration anesthesia in children 3 to 11 yr, despite it being the most widely used model.\textsuperscript{111,131} However, clearance ($\text{l} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$) decreases with age, and the median prediction error is minimized at low clearance and exaggerated at greater values. Evaluating models outside of the age range in which their parameter sets were determined will increase the bias and worsen the precision of the
The Short model for children and the Schüttler general purpose model had acceptable performance in children 3 to 11 yr when used over a longer period of up to 6 h.131 These clearance changes with age contribute to observed clinical effect. Reduced clearance (expressed as per kilogram) in older children results in a propofol effect site target concentration displayed by the smart pump that is lower than that measured in plasma when the Kataria model was used. This observation has led to the suggestion that the propofol effect-site target concentration should differ with age, e.g., $C_{e_{50}}$ 5 µg/ml in children aged 3 yr and $C_{e_{50}}$ 1.6 µg/ml at 11 yr.133,134 Age-related changes also contribute to confusion interpreting Bispectral Index values when the concentration in the effect compartment is calculated and displayed by the target-controlled infusion pump because of this link with age for the lower plasma concentration.135 Pharmacokinetics models that perform better than the Kataria22 model (e.g., pediatric Marsh,41 Short,43 or the Eleveld general purpose model16) are not currently available in commercial smart pumps.

**Clinical Anesthesia**

**Drug Delivery**

Secure intravenous access is essential, and infusion lines should be placed as close as possible to the venous cannula.136 One-way nonreturn valves prevent backflow up intravenous fluid lines.137 Combined infusions into a single vein run the risk of inadvertent bolus of a companion drug unless proximal dead space is minimized. The infusion site is not always readily accessible in small children where limbs may be covered in surgical drapes and inadvertent dislodgement, obstruction, or subcutaneous tissue infiltration may occur. Central venous access with a multilumen catheter should be considered for major surgery because it allows a dedicated port for total intravenous anesthesia and diminishes the risk of undisclosed subcutaneous infusion. Pump performance characteristics (e.g., lag time), intravenous tubing dead space, and syringe size and type all contribute to the observed response. The more dilute the solution is, the faster the syringe movement with a more matched delivery to change of prescription.136

**Processed Electroencephalogram Monitoring**

Depth of anesthesia monitors were only used in 1% of all general anesthetics in the United Kingdom in 2015. These monitors were used in 33% of children undergoing general anesthesia using a total intravenous anesthesia technique with a neuromuscular blocking drug, but not at all in infants.138 Despite limitations in infants, the Bispectral Index is useful in older children, particularly when neuromuscular blocking drugs are used in conjunction with total intravenous anesthesia; they have also been successfully used for closed-loop anesthesia.139 Feedback systems may prove superior to open-loop systems that rely on a calculated effect compartment concentration that is associated with large variability.1

The need for pharmacodynamic feedback during propofol anesthesia in children has been demonstrated.27 When propofol infusion was guided by the Bispectral Index, no major difference was found between total intravenous anesthesia and target-controlled infusion with either the Kataria22 or the Schnider model.27 Titrating intravenous anesthesia drugs to a processed electroencephalogram score has been demonstrated to reduce propofol requirement in adults,139 although others have not demonstrated this if an experienced anesthesiologist is administering anesthesia.140 Narcotrend monitoring for guidance of propofol/remifentanil anesthesia in children (1 to 11 yr) resulted in reduced propofol consumption compared to a conventional clinical practice.141

The anesthetic requirement in children with cognitive impairment may be reduced. Processed electroencephalogram use may better dictate dose. While Bispectral Index readings in children with cognitive impairment were 28 points less than unaffected peers at the same inhalational anesthetic partial pressure, minimal alveolar concentration reduction for cognitive impairment was not accounted for in that study.142 A lower minimal alveolar concentration was described in cognitively impaired children.143 Noncommunicative and nonverbal children with cerebral palsy required less propofol to obtain the same Bispectral Index values (e.g., 35 to 45) than otherwise healthy children.144 The use of the Bispectral Index may be useful in this cohort because there is a reduction in anesthetic need.

The ability of three methods (Neonatal Pain, Agitation and Sedation Scale, amplitude-integrated electroencephalogram, and Bispectral Index), and their combination, have been used to detect different level of sedation in neonates. None of the three methods alone was satisfactory to discriminate between degrees of sedation, although the combination was useful to distinguish between light and deep sedation.145 The processed electroencephalogram (spectral edge frequency, Bispectral Index, entropy) may not be reliable in infants and neonates, but some interpretation can be made from the electroencephalographic waveforms and changes in the dimensionless number that is its output.146 Changes in these cerebral effect measures with changes of dose may at least confirm that the infusion is not disconnected or subcutaneous.

**Induction**

In order to achieve an adequate effect-site concentration at induction, propofol needs to be administered as a bolus. This can be either by hand or by a variable rate infusion from the target-controlled infusion smart pump. If the preset target concentration is inadequate or the dose given too slowly, it can lead to an uncomfortable situation where the practitioner must reassure accompanying parents that their moving child...
will soon be anesthetized. An initial target concentration of 4 to 6 μg/ml is adequate to achieve anesthesia in a child and avoid unwanted adverse effects such as hypotension.

Smart pumps inject propofol at a high default rate (usually 1,200 ml/h) unless the patient weighs less than 18 kg or the duration of the pump bolus dose is increased more than the default 10 to 20 s. The pain associated with IV injection of propofol is problematic. This is especially common when given through the small veins in the hands or feet. Perhaps the best approach to reduce injection pain is to place a larger bore cannula in a proximal rather than a distal limb vein. Lidocaine 1 mg/kg placed in the IV with a proximal tourniquet (or just manual compression of the arm to stop the IV from flowing) applied for 30 to 60 s may attenuate this pain,147 but the tourniquet can cause discomfort in children. Intravenous lidocaine 2 mg/kg without a tourniquet can reduce the pain associated with propofol injection,148 and a premixed propofol/lidocaine injection may be equally effective when a medium chain triglyceride injection,148 and a premixed propofol/lidocaine injection or the duration of the pump bolus dose is increased more than the default 10 to 20 s. The pain associated with IV injection of propofol is problematic. This is especially common when given through the small veins in the hands or feet. Perhaps the best approach to reduce injection pain is to place a larger bore cannula in a proximal rather than a distal limb vein. Lidocaine 1 mg/kg placed in the IV with a proximal tourniquet (or just manual compression of the arm to stop the IV from flowing) applied for 30 to 60 s may attenuate this pain,147 but the tourniquet can cause discomfort in children. Intravenous lidocaine 2 mg/kg without a tourniquet can reduce the pain associated with propofol injection,148 and a premixed propofol/lidocaine injection may be equally effective when a medium chain triglyceride propofol emulsion is used.149 Opioid or ketamine administered IV before propofol injection is also helpful. This can be best done by beginning the remifentanil infusion first and running it at a plasma target concentration of approximately 4 ng/ml for 2 min before starting the propofol infusion or waiting for similar effect site concentrations;150; most children will continue to maintain spontaneous respirations through this short period. Alternatively, a bolus of fentanyl 1 μg/kg or remifentanil 1 μg/kg through the IV cannula is effective.

Establishing Total Intravenous Anesthesia after an Inhalational Induction

Propofol total intravenous anesthesia in children can start once gaseous induction has been performed and intravenous access obtained. The use of a fixed infusion rate of propofol after a gaseous induction is frowned upon because steady-state concentrations will not be established before three to four elimination half-lives. While end-tidal inhalational agent partial pressure decreases, it is reasonable to target a reduced propofol effect compartment concentration of 4 μg/ml for 2 to 3 min as an initial target and then titrate against clinical response. If using a manual regimen, then a reduced initial bolus after gaseous induction may be given, especially if spontaneous respiration is required; a bolus of propofol 1 mg/kg is usually satisfactory.151 These doses may not be applicable for neonates and infants younger than 1 yr where robust pharmacokinetic-pharmacodynamic information is unavailable. Hypotension due to vasodilation of peripheral vessels is described in neonates after a single bolus of propofol larger than 3 mg/kg for induction.113

Awareness has been more commonly reported after total intravenous anesthesia than after gaseous anesthesia. However, many reports of awareness occur after the switch from gaseous anesthesia to total intravenous anesthesia where a loading dose was not given.157 The future ability for point-of-care propofol assay using either breath or plasma may be useful to reduce this complication.152,153

Intubation

A target remifentanil concentration of 2 to 3 ng/ml combined with propofol 3 to 4 μg/ml modulates the sympathetic response associated with laryngoscopy using a neuromuscular blocking drug. Endotracheal intubation without the use of a neuromuscular blocking drug can be facilitated using propofol and remifentanil combinations.154 Several dose-response studies found that remifentanil 3 μg/kg combined with propofol 3 to 4 mg/kg provided the best intubating conditions similar to those with a neuromuscular blocking drug. Remifentanil 2 μg/kg did not produce satisfactory intubating conditions.155 Resumption of spontaneous respirations after a remifentanil–propofol combination was similar to that after succinylcholine.156-158

Age also has an effect on remifentanil dose. Children (0 to 3 yr) given propofol 5 mg/kg required a remifentanil ED50 for intubation of 3.1 (95% CI, 2.5 to 3.8) μg/kg at age 0 to 3 months, 3.7 (95% CI, 2.0 to 5.4) μg/kg at 4 to 12 months, and 3.0 (95% CI, 2.1 to 3.9) μg/kg at 1 to 3 yr.159

Maintenance

The maintenance target effect site concentration depends on the age of the child, the procedure, the anesthetic adjuncts used, and the depth of anesthesia required. Approximate effect site concentrations typical when propofol is used in conjunction with remifentanil (e.g., remifentanil 0.05 to 0.1 μg ⋅ kg⁻¹ ⋅ min⁻¹ for sedation and 0.1 to 0.5 μg ⋅ kg⁻¹ ⋅ min⁻¹ for anesthesia) are 0.5 to 1.5 μg/ml for light sedation (e.g., painless minor procedures), 1.5 to 2.5 μg/ml for heavy sedation (e.g., radiologic imaging), 2.5 to 3 μg/ml for light anesthesia (e.g., minor surgery) and 3 to 4 μg/ml for major surgery. It is uncommon to need a maintenance target effect site concentration of propofol higher than 4 μg/ml when propofol is used with adequate analgesia.

If an analgesic adjunct such as remifentanil (table 5) or a regional block is used in conjunction with propofol, the target concentration can be reduced by 30 to 50%.160 The same principle applies if there is an appreciable delay after induction with no surgical stimulation before the start of the procedure. This is important in children, as running a propofol plasma concentration of 4 to 5 μg/ml for any significant length of time may lead to accumulation of propofol and delayed recovery, reflected by its context-sensitive half-time. The context-sensitive half-time is greater in children 3 to 11 yr compared to young adults: 7 min after a 30-min infusion, 10 min after a 60-min infusion, but increasing to 18 min after a 4-h infusion.40

If moving from using mass rate infusion (i.e., infusion rate dictated by practitioner) to target-controlled infusion (i.e., target concentration dictated by practitioner), it is useful to know what infusion rate equates to a particular target concentration. Some of the current pumps allow predictive

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target-controlled infusion, whereby propofol can be administered by mass rate infusion while the appropriate propofol model runs in the background. This allows the pump to display an estimated plasma concentration for a given infusion rate. Supplemental Digital Content 1 (http://links.lww.com/ALN/B889) demonstrates the relationship between different propofol infusion rates and the corresponding plasma target concentrations.

When inducing anesthesia with a target-controlled infusion system that displays an estimated effect-site target concentration, it is useful to make a note of the effect compartment concentration that the child loses consciousness because most will regain consciousness at a similar effect compartment concentration. Some target-controlled infusion pumps calculate and display a “decrement time,” which is the estimated time taken for the blood concentration to fall from the current concentration to a user-defined “awakening concentration” or “decrement concentration.” As this concentration is set by the practitioner, it does not necessarily imply that the child will regain consciousness at that concentration. Rather this display gives the user an indication of the influence of infusion duration on the rate of decline in blood or effect site concentrations when the infusion is stopped. If the effect compartment concentration at which the patient loses consciousness is used as the decrement concentration, then the decrement time will provide a rough indication of how long it will take the patient to regain consciousness when the infusion is switched off. This property allows the anesthesiologist to calibrate their patient, by giving an indication of the approximate effect-site concentration they will awaken and therefore what concentration is needed to ensure they are asleep. Currently only the adult models display an estimated effect-site concentration, making this assumption difficult in children when a pediatric model is being used.

**Remifentanil Role.** Remifentanil is very useful as an adjunct. It adds a degree of “smoothing” even in those children who require sedation only (e.g., during radiologic imaging). Propofol is not an analgesic, and the addition of remifentanil reduces movement in response to surgical stimulation; there is approximately 30% more movement with propofol alone compared to an inhalational anesthetic. Remifentanil is useful to reduce pain during limb procedures where a tourniquet is used, even if regional blockade is employed. Most procedures can be covered by remifentanil effect compartment concentration of between 3 to 8 ng/ml, and it is unusual to need to go above 6 ng/ml.

**Recovery**

It remains uncertain whether propofol should be stopped before the remifentanil to improve speed of recovery or if it makes any difference. Propofol infusion can be reduced to a target effect compartment concentration of 2 μg/ml at the time of skin closure, provided a local block is being used or the remifentanil is continued at an analgesic dose (0.1 to 0.2 μg · kg⁻¹ · min⁻¹ or effect compartment concentration 1.5 to 2.5 ng/ml). Children commonly take longer to awaken than adults due to the increased context-sensitive half-time of propofol in children.

The mean time from switching off the propofol (mean rate, 14.8 mg · kg⁻¹ · h⁻¹, 246 μg · kg⁻¹ · min⁻¹, duration 30 min) and remifentanil (mean rate, 0.11 μg · kg⁻¹ · min⁻¹) infusions to purposeful spontaneous movement in children (3 months to 10 yr) was 17 min and occurred at a mean propofol effect compartment concentration of 2 (SD ± 0.5) μg/ml. Most children will awaken at an estimated plasma concentration of propofol calculated by the smart pump of 1.2 to 1.8 μg/ml. The variability associated with this plasma concentration for purposeful spontaneous movement depends on the pharmacokinetics model used in the smart pump and age of the child, adjunct drugs used, between-patient variability of pharmacokinetics and pharmacodynamics parameters, and t₁/₂ keo estimates. Opioids potentiate the sedative, hypnotic, and anesthetic effects of propofol. For example, if remifentanil is continued after cessation of propofol infusion, purposeful spontaneous movement is achieved at lower propofol concentrations. This variability dictates that clinical signs and not just the plasma concentration or effect compartment concentration predicted by the smart pump be used to assess anesthesia depth. Processed electroencephalographic signals are also useful, particularly in the presence of neuromuscular blockade.

Return of consciousness after prolonged anesthesia with propofol and remifentanil is determined primarily by the context-sensitive half-time of propofol. Context-sensitive

### Table 5. Suggested Target Concentrations or Infusion Rate for Propofol (with Remifentanil) During Maintenance Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Minor Surgery (Spontaneous Ventilation)</th>
<th>Minor Surgery (Positive Pressure Ventilation)</th>
<th>Major Surgery (Positive Pressure Ventilation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol (target-controlled infusion)</td>
<td>2.5–4 μg/ml*</td>
<td>2.5–4 μg/ml*</td>
<td>3–5 μg/ml</td>
</tr>
<tr>
<td>Remifentanil (μg · kg⁻¹ · min⁻¹)</td>
<td>0.05–0.2 μg · kg⁻¹ · min⁻¹</td>
<td>0.2–0.3 μg · kg⁻¹ · min⁻¹</td>
<td>0.3–0.5 μg · kg⁻¹ · min⁻¹</td>
</tr>
<tr>
<td>Remifentanil (target-controlled infusion)</td>
<td>1–2 ng/ml</td>
<td>2–4 ng/ml</td>
<td>3–6 ng/ml</td>
</tr>
</tbody>
</table>

*The lower limit of the target concentration is 2 μg/ml when depth of anesthesia monitoring is used.
half-time is longer in children than adults because children have proportionally greater propofol accumulation in peripheral tissues due to higher dose requirements. Opioids with a longer duration of action (e.g., sufentanil) delay recovery.164

Mixing

Fixed propofol/remifentanil combinations (mixed together in the same syringe) are frowned upon. A mixture creates a new composition drug that is unlicensed. The stability of such mixtures may alter over time. Remifentanil in such mixtures may layer out, become unstable, and have a limited lifespan in the syringe.165 The weaker the mixture, the less stable it is. This is due to a pH effect on the rate of ester hydrolysis of the remifentanil.166 The rates of infusion of the two drugs cannot be changed independently of one another, reducing delivery versatility. It may be unclear to the practitioner what rate is being administered of one or both of the drugs, depending on how the infusion is administered.

However, fixed propofol/remifentanil combinations are widely used.163,167,168 One combination is propofol 10 mg/ml with remifentanil 5 μg/ml. Clinical experience has shown that if used with a target-controlled infusion pump, then a propofol target concentration of 3 μg/ml in children 3 to 11 yr usually allows spontaneous breathing while a propofol target of 6 μg/ml requires respiratory support. Care should be exercised on induction with the higher remifentanil concentrations because high initial targets can lead to a large bolus of remifentanil being administered, causing adverse effects such as bradycardia and chest rigidity (fig. 4). The user can only target the propofol plasma concentration, and the remifentanil dose administered will be related to that (Supplemental Digital Content 2, http://links.lww.com/ALN/B890). Both manual and target-controlled infusion pumps use a decreasing infusion rate of propofol over time to maintain a constant effect compartment concentration. This means that with a mixture, the rate of the remifentanil infusion is also constantly decreasing. Supplemental Digital Content 2 (http://links.lww.com/ALN/B890) demonstrates that after 60 min, the remifentanil infusion rate will be approximately half that at the beginning of the procedure. Such mixtures are not recommended for procedures that continue beyond 1 h.

“Ketofol” is a mixture of ketamine and propofol (1:1) that is finding a niche for procedural sedation in the emergency room.88 Mixtures of propofol (1% and 2%) and ketamine at 5:1 and 6.7:1 ratios were stable in a polypropylene syringe during a 6-h period at room temperature.169 Stable hemodynamics, analgesia and good recovery are reported.170 An additive interaction for anesthesia induction in adults has been reported.171 Simulation studies in children suggest an optimal ratio of racemic ketamine to propofol of 1.5 for 30 min of anesthesia and 1.67 for 90 min of anesthesia.169 The “ideal mix” for sedation will depend on the duration of sedation and the degree of analgesia required. The context sensitive half-time of ketamine increases with the duration of the infusion, resulting in delayed recovery.172

Special Cases

There are a number of situations where it may be more challenging to use total intravenous anesthesia in children. These include neonates and young infants, obese children, and children that are big for their age.

Fig. 4. Simulations demonstrating remifentanil plasma concentration (Cp) and effect compartment (Ce) concentration predicted when mixed with propofol (5 μg/ml) and infused using the McFarlan regimen. Initial remifentanil concentrations reach a Ce ~5 μg/ml within 2.5 min, and these concentrations contribute to apnea after induction. Propofol pharmacokinetic parameter estimates are from Kataria et al.22 Remifentanil pharmacokinetic parameter estimates are from Rigby-Jones et al.17
Premature Neonates

There are few data concerning either the pharmacokinetics and pharmacodynamics of intravenous anesthetic drugs or practical conduct of intravenous anesthesia in premature neonates. The use of these drugs in premature neonates awaits further investigation.

Neonates and Young Infants

Propofol metabolism is reduced in neonates and matures over the first six months of life. Remifentanil volume of distribution and clearance are increased in neonates compared to children and adults. However, sensitivity to the both sedative effects and analgesic effects is increased. Adverse effects such as hypotension are increased in neonates given propofol. These effects can lead to delayed recovery after anesthesia.

While the Paedfusor model is capable of delivering targeted concentrations to children over the age of 1 yr, propofol infusions are not recommended in the neonatal and young infant age group, although manual dosing guidelines have been reported. There are different susceptibilities of changes in cerebral perfusion associated with blood pressure decreases in infants less than 6 months of age and those greater than 6 months of age. However, these neonates, infants and children (0 to 3 yr) given propofol and either fentanyl, alfentanil, or a regional block all had similar instances in blood pressure decreases (7 to 10%) that were readily managed with intravenous fluid 20 ml/kg. Bradycardia (greater than 15% of preinduction rate) was more common in infants aged with intravenous fluid 20 ml/kg. Bradycardia (greater than 15% of preinduction rate) was more common in infants.

There are concerns that some anesthetic drugs may cause neuronal apoptosis in the human neonatal developing brain because drugs that bind to G-aminobutyric acid type A receptors cause neuronal apoptosis and other neurodegenerative changes in animal models ranging from rodents to primates. Dexmedetomidine and remifentanil may be alternative options because their action is not mediated through G-aminobutyric acid type A receptors, and they do not cause neuronal apoptosis or other neurodegenerative effects in rodents and primates. Dexmedetomidine also attenuates isoflurane-induced neurocognitive impairment in neonatal rats.

Dexmedetomidine infusion combined with remifentanil infusion is also being used in infants (younger than 1 yr) undergoing lower limb/low abdominal surgery expected to last longer than 2 h in another pilot study. A loading dose of dexmedetomidine 0.6 µg/kg and 1 µg/kg remifentanil was followed by an infusion rate of dexmedetomidine 1 to 1.5 µg · kg⁻¹ · h⁻¹ and remifentanil infusion starting at 0.1 µg · kg⁻¹ · min⁻¹. Airway management required an endotracheal tube or supraglottic device and ventilation assistance to maintain normocapnia in some infants.

Obese Children

Investigation of propofol pharmacokinetics in obese children suggests that using actual body weight scaled as per kilogram in the models will lead to a relative overdose of propofol. Scaling using total body weight and allometry was a better option.

Remifentanil infusions scale better using lean body mass. There are problems implementing lean body mass into anesthesia practice because the formula programmed into many common infusion pumps in adults for intravenous anesthesia is inconsistent at extremes of size, particularly in those adults of short stature where a reduction of lean body mass is predicted as total body weight increases.

Methods used to circumvent this problem in pumps used for adults include calculation of a fictitious height, creating a new metric, or placing limits on maximum programmable weight allowed. The addition of 40% of the excess weight to the ideal body weight for propofol infusion calculation has been suggested.

An approach to circumvent this dosing difficulty in children is to use actual body weight, deliver generous amounts of remifentanil, and adjust the propofol effect-site target concentration according either Bispectral Index monitoring or clinical response. A similar clinical result can be achieved by reducing the prescribed target concentration (e.g., propofol 4 µg/ml rather than 6 µg/ml) and then titrating to effect, while ideally avoiding neuromuscular blockade.

Children Big for Their Age

It is increasingly common to encounter adult-sized children in pediatric anesthetic practice. The Paedfusor model uses age as a covariate between 12 and 16 yr, such that by 16 yr of age, the pharmacokinetics parameters are the same as the adult Marsh model. Both the Paedfusor and Kataria models have a maximum weight of 61 kg. The concern is that larger children below the age of 16 may be relatively overdosed if an adult model is used. Clinical options include using a pediatric model and entering a fictitious weight or using an adult model and entering a fictitious age into the target-controlled infusion pump. The authors suggest that for adolescents who have adult physiology (e.g., Tanner stage 5), an adult model can be used, with the patient’s actual weight entered and the dose (or effect compartment concentration) altered to clinical effect.

Spontaneously Breathing with Total Intravenous Anesthesia

If it is desirable to keep a child breathing during anesthesia (e.g., during bronchoscopy), then some changes to technique are usually required. Avoidance of remifentanil as the opioid is perhaps the easiest way to keep the child breathing spontaneously, and dexmedetomidine infusion can be substituted. Remifentanil causes apnea after bolus doses or
high infusion rates and consequent high effect compartment concentration. Substituting fentanyl or alfentanil for remifentanil often allows the patient to continue to breathe spontaneously, although neither provides such a profound degree of analgesia, and therefore patient movement is more likely, unless coupled with a local anesthetic agent to supplement analgesia. Remifentanil infusion of up to 0.15 µg · kg⁻¹ · min⁻¹ used with propofol in patients older than 3 yr or up to 0.3 µg · kg⁻¹ · min⁻¹ in those younger than 3 yr may allow spontaneous breathing to continue.64 These infusion rates reflect changing clearance with age and achieve similar target concentrations of 1 to 1.5 mcg/l.130 Monitoring the child’s respiratory rate may give an indication of impending apnea, with a rate less than 10 breaths per minute often indicating apnea is imminent.194 A tail to the end-tidal carbon dioxide trace, suggesting prolonged expiration, often precedes apnea, as does an observed tidal volume reduction.

The Future

The field of total intravenous anesthesia continues to develop and evolve. Perhaps the major obstacle to it becoming more widely adopted in routine clinical practice is the absence of a reliable feedback to indicate that the patient is receiving an appropriate quantity of drug. The introduction of processed electroencephalogram as a surrogate measure has gone some way to achieving this, but lack of validation in infants means it is yet to become the routine standard of care.195 An accurate closed-loop system based on depth of anesthesia monitoring, proportional correction, or exhaled propofol concentration will be developed in the future, and this will allow us to titrate our intravenous agents more accurately.1

Increasing the accuracy of models will also allow more predictable drug delivery to our patients. Refinement, validation, and implementation of models that encompass broader age ranges (e.g., propofol196) in pediatric patients may go some way to achieving this. It is also probable that similar universal models for remifentanil will be available in the future.18

Conclusions

Total intravenous anesthesia and target-controlled infusion is an increasingly popular choice for anesthesia in children in a number of situations, due to the availability of valid pharmacokinetics models for propofol administration and the interaction propofol displays with remifentanil. However, a number of challenges remain, including teaching total intravenous anesthesia administration to our trainees, improving the accuracy of current pharmacokinetics models, and our ability to monitor propofol blood concentrations in near real-time, thus avoiding concerns regarding pharmacokinetics and pharmacodynamics variability.


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