Review article

Overview of total intravenous anesthesia in children

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Summary

Total intravenous anesthesia (TIVA) can be defined as a technique, in which general anesthesia is induced and maintained using purely i.v. agents. TIVA has become more popular and possible in recent times because of the pharmacokinetic (PK) and pharmacodynamic properties of propofol and the availability of short-acting synthetic opioids. Also, new concepts in PK modeling and advances in computer technology have allowed the development of sophisticated delivery systems, which make control of anesthesia given by the i.v. route as straightforward and user friendly as conventional, inhalational techniques. Monitoring of depth of anesthesia is being validated for these techniques, and in the future, measurements of expired propofol may be possible to guide administration. TIVA is being used increasingly in children.

Keywords: propofol; TIVA; paediatrics

Inhalational anesthesia has been the mainstay in pediatric anesthesia till recent times. But with the advances in understanding of pharmacology and availability of new fast-acting drugs and the modern infusion pumps, total intravenous anesthesia (TIVA) has become an attractive option in the administration of general anesthesia in children.

Indications/uses for TIVA in children are (1–5):
1. Children undergoing frequent, repeated anesthesia (e.g., radiation therapy).
2. Brief radiologic or painful procedures where rapid recovery is needed (e.g., MRI, bone marrow aspiration, gastrointestinal endoscopy).
3. During major surgery to control the stress response.
4. During neurosurgical procedures to assist with control of intracranial pressure and for cerebral metabolic protection.
5. During spinal instrumentation surgery to provide controlled hypotension and when there is a need for evoked motor and auditory brain potentials or intraoperative wake-up test.
6. During airway procedures (e.g., bronchoscopy).
7. Children at risk of malignant hyperthermia.
8. Children with an increased risk of postoperative nausea and vomiting.

Advantages and disadvantages of TIVA

The arguments for and against TIVA when compared with volatile anesthesia were recently debated.
The main advantages of TIVA are summarized in Table 1.

**Basic principles**

The most commonly used drugs for TIVA include propofol, remifentanil, alfentanil, sufentanil, ketamine, midazolam, and recently, dexmedetomidine. These drugs can be delivered either by using a manual infusion scheme or by using a method called target controlled infusion (TCI). TCI uses a real-time pharmacokinetic (PK) model to calculate the bolus dose and infusion rates, to achieve a user-defined target plasma or effect site concentration. This is achieved by an infusion pump controlled by a microprocessor, which incorporates PK models with age-appropriate parameters. TCI with propofol is limited to the age group 3 years or more for most models, but 1 year or more, or weight of 5 kg for the Paedfusor system (Glasgow, UK), although it is not well validated below the age of 3 years at present. Also, there are considerable gaps in PK models for some drugs for ill children and for young children, infants, and neonates, so caution is needed when applying such programs to these populations. Future models will incorporate more sophisticated pharmacokinetic–pharmacodynamic (PK–PD) algorithms. Hence, when using the TCI technique at present, the anesthesiologist must still use knowledge and experience to titrate the i.v. agents to effect to avoid awareness, pain, and adverse effects. Concerns about lipid load can be ameliorated by the use of a 2% propofol solution, which contains half the relative dose of lipid but causes more severe injection pain. Propofol-sparing techniques are also highly recommended such as regional blockade and/or concurrent use of systemic opioids.

Automated delivery systems can be classified as open-loop control or closed-loop control. Open-loop control is one where the input to the system is independent of the output, i.e., there is no measurable feedback signal. This is the commonest delivery system used. Closed-loop system is where at any given moment the input to the system is a function

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Advantages and disadvantages of TIVA (6–8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td>Induction is very rapid in onset</td>
<td>Pain during injection of propofol</td>
</tr>
<tr>
<td>Large $k_{e0}$ in children results in very quick induction and rapid equilibration between plasma and effect site</td>
<td>Needs sophisticated infusion pumps with algorithms for the TCI software</td>
</tr>
<tr>
<td>Rapid onset of action independent from alveolar ventilation</td>
<td>Greater pharmacokinetic and pharmacodynamic interindividual variability</td>
</tr>
<tr>
<td>Improved quality of emergence from anesthesia</td>
<td>Depth of anesthesia monitoring using BIS/AEP has interindividual variability</td>
</tr>
<tr>
<td>Very smooth and peaceful recovery</td>
<td>Difficult to estimate blood concentration of propofol in real time at the moment</td>
</tr>
<tr>
<td>No risk of environmental pollution</td>
<td>Difficult to monitor continuous administration of i.v. agents into the patient</td>
</tr>
<tr>
<td>Reduction in the incidence of postoperative nausea and vomiting</td>
<td>Slightly prolonged context-sensitive half-time in children when compared to adults in view of the requirement of higher doses of propofol</td>
</tr>
<tr>
<td>Increased patient comfort, parental satisfaction in the postoperative period</td>
<td>Propofol infusion syndrome (7,8)</td>
</tr>
<tr>
<td>Propofol reduces brain metabolism and cerebral blood flow, hence used in reduction of intracranial pressure</td>
<td></td>
</tr>
<tr>
<td>Method of choice in patients at risk of malignant hyperthermia</td>
<td></td>
</tr>
<tr>
<td>Method of choice in some patients with congenital myopathies</td>
<td></td>
</tr>
<tr>
<td>Propofol does not suppress somatosensory evoked potential during spinal surgery; hence, SSEP can be reliably monitored. TIVA is the method of choice in these patients</td>
<td></td>
</tr>
<tr>
<td>Can be reliably administered to maintain anesthesia in patients undergoing airway procedures</td>
<td></td>
</tr>
</tbody>
</table>

TIVA, total intravenous anesthesia; TCI, target controlled infusion; BIS, bispectral index; AEP, auditory evoked potentials; SSEP, somatosensory evoked potentials.
of the previous output (e.g. bispectral index (BIS), blood pressure, heart rate, etc.), and here there is a measurable feedback signal that completes the loop.

**PK concepts related to TIVA/TCI in children** (1)

Healthy children need a relatively high dose of i.v. agent per unit of body weight, and maintenance infusion rates need to be higher than the weight corrected dose for adult. This is because there are changes in regional blood flow, body composition, and body proportions in children when compared to adults. At steady state, the rate of infusion is determined by clearance, and clearance is very high in children (and low in neonates), hence they need a higher maintenance infusion rate at steady state. A three-compartmental model can be used to mathematically describe the behavior of most anesthetic drugs with reasonable accuracy (Figure 1).

The drug is delivered and eliminated from a central compartment V₁, which is also referred to as the initial volume of distribution. The drug also distributes to and redistributes from two peripheral compartments, one of them V₂ representing well-perfused organs and tissues also called fast redistribution compartment (because there is rapid drug distribution between V₁ and V₂), and the other V₃ referred to as the vessel-poor or slow compartment (because there is rather slow drug distribution between V₁ and V₃). The sum of V₁, V₂, and V₃ gives the volume of distribution at steady state (Vdss). It is a common misconception that V₁ equates to blood volume. It should be stressed that V₁ is an artificial volume, which includes blood volume, but may be far larger than blood volume for drugs, which are highly lipid soluble or which have high protein binding.

The rate of transfer between compartments and elimination can be described using rate constants. By convention, \( k_{10} \) means rate constant for elimination, whereas \( k_{12} \), \( k_{21} \), \( k_{13} \), and \( k_{31} \) are used to denote the rate constants for drug transfer between V₁ and V₂, V₂ and V₁, V₁ and V₃, and between V₃ and V₁, respectively.

A drug that is highly lipid soluble and/or highly protein bound will have a large volume of distribution. Clearance is the volume of blood from which the drug is eliminated per unit of time. With propofol, children have a large volume of distribution and also higher clearance when compared with adults. The time required for the drug concentration in blood to decrease by 50% is known as the elimination half-life (\( t_{1/2} \)). Prolongation of the elimination of a drug reflects either an increase in the volume of distribution or a reduction in clearance or both. When a drug is administered intravenously at a fixed infusion rate, it takes five half-lives to reach a steady-state concentration in the blood (Figure 2). To rapidly achieve steady-state conditions, a bolus dose or loading infusion may be administered. This rapidly fills the volume of distribution after which a new rate of infusion is calculated to maintain the blood concentration.

**Target-controlled infusions**

The problem with infusion targeting based upon the blood concentration is that when the target concentration is changed, there is a long temporal delay before the concentration at the effect site equilibrates with the plasma concentration (Figure 3). As the clinical effect of a drug depends on the concentration at the effect site, there is usually a hysteresis in clinical effect when the target blood concentration of the agent is increased as well as when it is decreased (Table 2). The rate of equilibration between plasma and effect site depends on several factors. These include the factors that influence the rate of delivery of the drug to the effect site (such as cardiac output and cerebral blood flow) and the pharmacologic properties of the drug that determine the rate of transfer of the drug across the blood–brain barrier (lipid solubility and degree of ionization). The time
course of plasma–effect site equilibration can be mathematically described by a rate constant typically referred to as the $k_{e0}$. This term $k_{e0}$ should be strictly used to describe the rate of removal of drug from the effect site, but the effect site is usually regarded as a volume-less additional compartment, so that there is no need for separate constants describing the rate constants for movement into and out of the effect compartment. It is not possible for us to directly measure the concentration of the drug at the effect site. However, the time course of the changes in the effect site concentration can be estimated from measures of clinical effect [pharmacodynamic (PD) effect] such as evoked EEG parameters, BIS, and auditory evoked potentials. So, when the blood concentration in a group of subjects is
known, then PD measurements can be used to estimate the $k_{e0}$. This is the basis of PK–PD modeling (9), in which PK and PD parameters from a study population is used to derive the $k_{e0}$ for that particular population and thus applicable to a similar population. The other parameter $t_{1/2}k_{e0}$, which is $0.693/k_{e0}$, is sometimes used to express this rate constant. In situations where the PD and PK data are not available from the same or similar subject group, then a model independent parameter called ‘time to peak effect’ (TTPE) can be used to estimate the $k_{e0}$ for a PK model and hence for that patient group (9). TTPE is defined as the time delay between the bolus injection and the peak clinical effect (which when derived graphically, is the time when the plasma site concentration and the effect site concentration curves intersect each other). It is important to understand that this TTPE is independent of the size of the bolus dose at submaximal dose (9). With effect site targeting, the TCI system manipulates the blood concentration to bring about the user-defined effect site concentration as rapidly as possible. When the effect site target concentration is increased, the TCI system calculates the optimal peak blood concentration that will cause sufficient blood-to-effect site concentration gradient to produce the most rapid increase in effect site concentration (analogous to the overpressure effect with volatile agents), but without an overshoot of the targeted effect site concentration. This results in a relatively large loading infusion or bolus dose with a high peak blood concentration (Figure 4). While healthy children may be able to tolerate this higher peak blood concentration, in children who are ill, this could cause cardiovascular instability with hypotension and bradycardia. The concept of context-sensitive half-time (CSHT) is worth mentioning at this point. When a drug is administered by infusion, it distributes from the central compartment to all the peripheral compartments. Once the infusion is stopped, the drug has to distribute back from the peripheral compartment into the central compartment and is then eliminated. The half-time of the decrease in drug concentration therefore is related to the duration of the infusion for most drugs (except remifentanil). This is termed the CSHT, where the context is the duration of the infusion. For an

<table>
<thead>
<tr>
<th>Blood concentration targeting</th>
<th>Effect site concentration targeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>1.7 mg·kg⁻¹</td>
</tr>
<tr>
<td>Maximum blood target reached</td>
<td>5 mcg·kg⁻¹</td>
</tr>
<tr>
<td>Total propofol infused after 60 min</td>
<td>23.2 mg·kg⁻¹</td>
</tr>
<tr>
<td>Time to achieve effect site target of 5 mcg·ml⁻¹</td>
<td>17.5 min</td>
</tr>
</tbody>
</table>

Table 2
Example of Target-controlled infusion (5 μg·ml⁻¹) based on calculated blood concentration targeting compared with calculated effect site concentration targeting for a healthy 1-year-old, weighing 10 kg, using the ‘Paedfusor’ pharmacokinetic dataset.
individual drug in an individual patient, CSHT can be determined from graphing the elimination half-lives against the duration of the infusion. The CSHT graph will eventually become parallel to the time (x) axis. At that time, the infusion has become context insensitive. This pattern is observed for nearly all i.v. anesthetics. The exception is remifentanil whose half-time becomes context insensitive almost immediately after the initiation of the infusion because its elimination is rapid and complete. The capacity of the tissue esterase enzyme system is enormous suggesting that the elimination occurs at a constant rate, regardless of the duration of the infusion (Table 3). Fentanyl has a short CSHT when given by infusion for a short time, but this dramatically increases as the duration of the infusion increases. Alfentanil’s CSHT becomes constant after approximately 90 min of infusion (Figure 5). Clearances of fentanyl, alfentanil, and sufentanil are reduced in neonates and young infants because of the immaturity or a limited capacity of hepatic enzyme systems, whereas clearance of remifentanil is relatively age independent because tissue esterases are ubiquitous throughout the body and fully mature even in early life. Transitioning is somewhat smoother after sufentanil than after alfentanil or remifentanil in children. The problem of acute tolerance to ultra-short-acting opioids has been noted after the use of remifentanil in pediatric scoliosis surgery (10). An understanding of the CSHT rather than the elimination half-life provides a guide for choice of drug and an indication of when to terminate the infusion.

## Drugs used for TIVA

### Propofol

**Manual infusion scheme.** The simple scheme of 10-8-6 regimen devised by Roberts et al. (11) is very effective in adults to maintain a plasma concentration of 3 μg·ml⁻¹ (Figure 6). This involves a loading dose of around 1 mg·kg⁻¹ of propofol followed by an infusion of 10 mg·kg⁻¹·h⁻¹ for 10 min, then 8 mg·kg⁻¹·h⁻¹ for 10 min, and 6 mg·kg⁻¹·h⁻¹ thereafter. When this regimen is used in children, a subtherapeutic plasma concentration of propofol is achieved (Figure 7). This low concentration is because of the larger V₁ and increased clearance of propofol in children when compared to adults (Table 4). Using the Paedfusor data (12), it has been found that to achieve a plasma concentration of 3 μg·ml⁻¹ in children, the dosing of propofol infusion in children is approximately twice than that in adults (approximates to a 19-15-12 regimen) (Table 5; Figure 8).

The other simple manual infusion scheme was devised by Macfarlan et al. (13) and validated by Engelhardt et al. (14) to obtain a propofol plasma target concentration of 3 μg·ml⁻¹, using the Kataria dataset (15) in children aged 1–6 years. In the Macfarlan model, anesthesia is induced with a bolus dose of 2.5 mg·kg⁻¹ and then maintained with a propofol infusion regimen (commenced within 1 min of the propofol bolus) of 15 mg·kg⁻¹·h⁻¹ for the first 15 min, 13 mg·kg⁻¹·h⁻¹ for the next 15 min, 11 mg·kg⁻¹·h⁻¹ from 30 to 60 min, 10 mg·kg⁻¹·h⁻¹ from 1 to 2 h, and 9 mg·kg⁻¹·h⁻¹ from 2 to 4 h. This resulted in a pseudo steady-state concentration of 3 μg·ml⁻¹.

**TCI with propofol.** There is limited availability of TCI systems for use in children. Plasma concentration targeting can be achieved using the ‘Paedfusor’ dataset (12), which incorporates the ‘Marsh model’ or the Kataria dataset (15) (Table 6).

The accuracy of the ‘Paedfusor’ model is validated (16), and it performs well clinically (4). The lower age limit for the use of ‘Paedfusor’ is 1 year, and the lower weight limit is 5 kg. The Kataria model is also well validated in children. The lower age limit for the use of the Kataria model is 3 years, and the lower weight limit is 15 kg.

For effect site targeting (Table 7), the adult k-e₀ value of 0.26 min⁻¹ could be used, but extrapolations using adult microconstants do not seem logical. Recently, Munoz et al. (17), in a study of children aged 3–11 years, derived k-e₀ values for the Paedfusor model of 0.91 min⁻¹ (t₁/₂k-e₀ 0.8 min) and for the Kataria models of 0.41 min⁻¹ (t₁/₂k-e₀ 1.7 min). Jelazcov et al. (18), in a study of PD modeling using

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**Table 3**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Infusion duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Remifentanil CSHT</td>
<td>3–6</td>
</tr>
<tr>
<td>Alfentanil CSHT</td>
<td>10</td>
</tr>
<tr>
<td>Sufentanil CSHT</td>
<td>20</td>
</tr>
<tr>
<td>Fentanyl CSHT</td>
<td>12</td>
</tr>
</tbody>
</table>

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BIS in children during propofol-based TIVA, found that $k_{e0}$ is age dependent, varying from 0.91 min$^{-1}$ at 1 year of age to 0.15 min$^{-1}$ at 16 years. They also found that the median plasma propofol concentration to produce a 50% propofol-induced BIS decrease was 4.8 µg·ml$^{-1}$ in children. This concentration (EC50) was higher than that reported by Munoz et al. (19), and they thought that EC50, along with the difference in the $k_{e0}$, was because of the difference in the PK model used (Jeleazcov et al. 2009).

Figure 5
(a) Context-sensitive half-times (CSHT) after short duration infusions. (b) CSHT after longer duration infusions. For very lipid soluble drugs like fentanyl and propofol, $V_3$ is very large compared with $V_1$. Intercompartmental clearance between $V_1$ and $V_3$ is given by the equation $V_1k_{13} = V_3k_{31}$, which implies that if $V_1$ is much smaller than $V_3$, rapid distribution from $V_1$ to $V_3$ is associated with very slow redistribution from $V_3$ to $V_1$. This is indeed seen with propofol and fentanyl, which have slow offset of effects after prolonged infusion. Propofol has a CSHT, which varies between around 3 min for a short duration infusion to 18 min after a 12-h infusion. This is because elimination is quite rapid compared with the rate of redistribution from $V_3$. For alfentanil, the concentration of the unionised form is 100 times greater than that of fentanyl (pKa alfentanil 6.4, fentanyl 8.5). Alfentanil therefore has a more rapid onset time and shorter $t_{1/2}$ at $k_{e0}$, a smaller $V_1$, lower volume of distribution at steady state, and lower clearance than fentanyl. Fentanyl does, however, have a shorter CSHT than alfentanil after a short duration infusion lasting <2 h, but for longer duration infusions, alfentanil reaches a maximum CSHT after about 90 min, whereas for fentanyl the CSHT is still increasing after 12 h. This is because fentanyl has a huge $V_3$ and redistribution back to $V_1$ maintains the blood concentration when the infusion stops.
used the Schuttler model and Munoz et al. used the Kataria model. They also reported that BIS can be used to monitor anesthetic effect produced by propofol in children above 1 year (19). In contrast to adults, children need a higher target plasma and effect site concentration to induce anesthesia and also take longer to reach the peak effect, which probably is because they have a larger volume of distribution (18).

**Opioids**

Short-acting opioids used for TIVA are remifentanil, alfentanil, sufentanil, and fentanyl. Appropriate postoperative analgesia must be planned for especially when ultrashort-acting opioids like remifentanil are used. Some suggested doses for opioids to be used for TIVA are summarized in Table 5.

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**Table 4**

Differences between adult and pediatric pharmacokinetic parameters for propofol

<table>
<thead>
<tr>
<th>Age</th>
<th>( V_1 ) (ml·kg(^{-1}))</th>
<th>Elimination ( t_{1/2} ) (min)</th>
<th>Clearance (ml·min(^{-1})·kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 years</td>
<td>9500</td>
<td>188</td>
<td>53</td>
</tr>
<tr>
<td>3–11 years</td>
<td>9700</td>
<td>398</td>
<td>34</td>
</tr>
<tr>
<td>Adults</td>
<td>4700</td>
<td>312</td>
<td>28</td>
</tr>
</tbody>
</table>

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**Dexmedetomidine**

It is a highly selective alpha2 agonist, which has sedative anxiolytic and analgesic properties. It does not produce respiratory depression and provides stable hemodynamics when given as a continuous infusion, except in children who are hypovolemic or have heart block. Some of its PK parameters are \( V_1 = 1 \text{ kg}^{-1} \); protein binding, 93%; clearance, 13 \text{ ml kg}^{-1} \text{ h}^{-1}; \) terminal \( t_{1/2} = 1.8 \text{ h} (20). \)

**Uses (21).**

1. Sedation during mechanical ventilation and for spontaneous breathing patients in PICU.

2. Procedural sedation:
   a. Sedation for noninvasive radiologic procedures.
   b. Sedation and anesthesia for invasive radiologic procedures.
   c. Endoscopy.
   d. Cardiac catheterization.

3. Perioperative uses:
   a. Intraoperative sedation/analgesia in cardiac surgery.
   b. Providing controlled hypotension during orthopedic spine surgery.
   c. Treatment of emergence delirium.
   d. Treatment of postoperative shivering.
   e. Prefuente.

4. Treatment of substance abuse withdrawal.

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**Table 5**

<table>
<thead>
<tr>
<th>Drug (Ref)</th>
<th>Loading dose</th>
<th>Maintenance infusion</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol (11)</td>
<td>1 mg kg(^{-1})</td>
<td>13 mg kg(^{-1}) h(^{-1}) for 10 min, then 11 mg kg(^{-1}) h(^{-1}) for 10 min, then 9 mg kg(^{-1}) h(^{-1})</td>
<td>Concurrently with alfentanil infusion</td>
</tr>
<tr>
<td>Propofol (13)</td>
<td>2.5 mg kg(^{-1})</td>
<td>15 mg kg(^{-1}) h(^{-1}) for the first 15 min, 13 mg kg(^{-1}) h(^{-1}) for the next 15 min, 11 mg kg(^{-1}) h(^{-1}) from 30–60 min, 10 mg kg(^{-1}) h(^{-1}) from 1 to 2 h, 9 mg kg(^{-1}) h(^{-1}) from 2 to 4 h</td>
<td>Achieves plasma concentration of around 3 µg ml(^{-1})</td>
</tr>
<tr>
<td>Alfentanil (30)</td>
<td>10–50 µg kg(^{-1})</td>
<td>1–5 µg kg(^{-1}) min(^{-1})</td>
<td>Results in blood concentration of 50–200 ng ml(^{-1})</td>
</tr>
<tr>
<td>Remifentanil (1)</td>
<td>0.5 µg kg(^{-1}) min(^{-1}) for 3 min</td>
<td>0.25 µg kg(^{-1}) min(^{-1})</td>
<td>Produces blood concentrations of 6–9 ng ml(^{-1})</td>
</tr>
<tr>
<td>Remifentanil (1)</td>
<td>0.5–1.0 µg kg(^{-1})</td>
<td>0.1–0.5 µg kg(^{-1}) min(^{-1})</td>
<td>Produces blood concentrations of 5–10 ng ml(^{-1})</td>
</tr>
<tr>
<td>Sufentanil (for sedation and analgesia) (31)</td>
<td>0.1–0.5 µg kg(^{-1})</td>
<td>0.005–0.01 µg kg(^{-1}) min(^{-1})</td>
<td>Results in blood concentration of 0.2 ng ml(^{-1})</td>
</tr>
<tr>
<td>Sufentanil (31)</td>
<td>1–5 µg kg(^{-1})</td>
<td>0.01–0.05 µg kg(^{-1}) min(^{-1})</td>
<td>Results in blood concentration of 0.6–3.0 ng ml(^{-1})</td>
</tr>
<tr>
<td>Fentanyl (30)</td>
<td>1–10 µg kg(^{-1})</td>
<td>0.1–0.2 µg kg(^{-1}) min(^{-1})</td>
<td>Produces blood concentration of 3 mg l(^{-1})</td>
</tr>
<tr>
<td>Ketamine (22)</td>
<td>2 mg kg(^{-1})</td>
<td>11 mg kg(^{-1}) h(^{-1}) for first 20 min, then 7 mg kg(^{-1}) h(^{-1}) for next 20 min, 5 mg kg(^{-1}) h(^{-1}) for the next 20 min, 4 mg kg(^{-1}) h(^{-1}) for the next hour and then on at 3.5 mg kg(^{-1}) h(^{-1})</td>
<td>Produces blood concentration of 3 mg l(^{-1})</td>
</tr>
<tr>
<td>Ketamine (22) (Anesthetic dose when administered with N(_2)O or midazolam)</td>
<td>2 mg kg(^{-1})</td>
<td>7 mg kg(^{-1}) h(^{-1}) for first 20 min, then 5 mg kg(^{-1}) h(^{-1}) for next 20 min, 4 mg kg(^{-1}) h(^{-1}) for the next 20 min and then 3 mg kg(^{-1}) h(^{-1}) from then on</td>
<td>Produces blood concentration of 2–2.2 mg l(^{-1})</td>
</tr>
<tr>
<td>Midazolam (30)</td>
<td>0.05–0.1 mg kg(^{-1})</td>
<td>0.1–0.3 mg kg(^{-1}) h(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Dexametomidine (sedation for noninvasive procedures) (21)</td>
<td>0.5–1 µg kg(^{-1}) over 10 min</td>
<td>0.5–1 µg kg(^{-1}) h(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Dexametomidine (sedation for invasive procedures) (21)</td>
<td>1–2 µg kg(^{-1}) over 10 min</td>
<td>1–2 µg kg(^{-1}) h(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Dexametomidine (treatment of withdrawal) (21)</td>
<td>0.5 µg kg(^{-1}) over 10 min</td>
<td>0.25 µg kg(^{-1}) h(^{-1}) and weaned over 2–3 days</td>
<td></td>
</tr>
<tr>
<td>Dexametomidine (sedation in ICU) (21)</td>
<td>0.25 µg kg(^{-1}) h(^{-1})</td>
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</tr>
</tbody>
</table>

TIVA, total intravenous anesthesia.
Ketamine

Ketamine can be used in a simple basic manual regimen as a loading dose of 1 mg·kg$^{-1}$ and a maintenance infusion of 0.1 mg·kg$^{-1}$·h$^{-1}$ with additional boluses of 1–2 mg·kg$^{-1}$ and increase in maintenance rate to 0.2 mg·kg$^{-1}$·h$^{-1}$ (Table 5). Although there are TCI PK models for adults, there is no described PK model for children.

Dallimore et al. (22), in their simulator study using PK parameters from the published studies, suggested an infusion regimen aimed to attain a plasma concentration of 3 mg·l$^{-1}$. They suggested that a lower rate of infusion could be employed when ketamine is used along with nitrous oxide and⁄ or midazolam (22).

Large clearance and hence short CSHT for infusions under 2 h of racemic ketamine infusion in children make ketamine a good choice sedative or anesthetic agent for shorter duration procedures. Dallimore et al. (23), in their study on sedation in the emergency department using racemic ketamine, found that smaller bolus doses and repeated top ups resulted in faster recovery. They suggested a dosing regimen of 0.275, 0.3, and 0.35 mg·kg$^{-1}$ followed by infusion of 2.5 and 2.75, 3, and 3.5 mg·kg$^{-1}$·h$^{-1}$ (12-, 6-, and 2-year olds, respectively) for 15 min gives a more even sedation level and rapid recovery (20 min to being awake).

Midazolam

Slow bolus dosing of up to 0.1 mg·kg$^{-1}$ followed by an infusion rate of 0.1 mg·kg$^{-1}$·h$^{-1}$ provides baseline...
Drug interactions

PK interactions with i.v. agents

Most commonly described interactions for i.v. agents are that between propofol and various opioid agents. Both fentanyl and alfentanil increase the volume of $V_1$ and clearance of propofol, while propofol and midazolam inhibit the metabolism of alfentanil by competing for the same cytochrome P450 enzyme isoform CYP$_{3AA}$ (24). Also, the higher concentration of propofol alters its own metabolism by causing changes in cardiac output and hepatic blood flow. Alfentanil concentrations were also significantly higher when it was infused with propofol than when it was infused alone (25). Mertens et al. (26) found significant reductions in elimination clearance of alfentanil in the presence of propofol. Bouillon et al. (27) found that propofol caused a 15% decrease in the elimination clearance of remifentanil, whereas remifentanil did not appear to alter the PK of propofol.

Although all these PK interactions should be borne in mind, it is seldom necessary to alter the target concentrations. It is the synergism arising from PD interactions among anesthetic agents that requires a decrease in target concentration.

PD interactions

In practice, the effect site concentration of propofol required to produce and maintain unconsciousness is lower than recommended, when used along with remifentanil infusion. In the study by Struys et al. (28), remifentanil concentration of 4 ng·ml$^{-1}$ was found to reduce the Cp50 for loss of response to verbal command from 2.9 to 2.2 μg·ml$^{-1}$. It has been found from various studies, when a combination of a hypnotic agent and opioid is used, the dose of the hypnotic could be reduced to enhance cardiovascular stability. Vuyk et al. (29) also found that even at concentration not known to produce loss of consciousness, combination of propofol and remifentanil completely eliminated the respiratory drive.

Conclusions

Experience with TIVA techniques is increasing, and the next quantum leap will be in making TCI equipment and pediatric software more widely available. The World SIVA Pediatric Committee met recently for the first time in Berlin in April 2009 and has a new site Web forum to discuss pediatric TIVA and TCI techniques. Multicenter research is needed to improve upon the currently available techniques and software. Research on PK–PD links and depth of anesthesia monitoring in children is needed to optimize the delivery of TIVA to minimize its adverse effects and to maximize its safety.

References


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