

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.

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Advantages and disadvantages of TIVA

The arguments for and against TIVA when compared with volatile anesthesia were recently debated

(6). The main advantages of TIVA are summarized in Table 1.

Basic principles

The most commonly used drugs for TIVA include propofol, remifentanyl, 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 1
Advantages and disadvantages of TIVA (6–8)

<i>Advantages</i>	<i>Disadvantages</i>
Induction is very rapid in onset	Pain during injection of propofol
Large k_{e0} in children results in very quick induction and rapid equilibration between plasma and effect site	Needs sophisticated infusion pumps with algorithms for the TCI software
Rapid onset of action independent from alveolar ventilation	Greater pharmacokinetic and pharmacodynamic interindividual variability
Improved quality of emergence from anesthesia	Depth of anesthesia monitoring using BIS/AEP has interindividual variability
Very smooth and peaceful recovery	Difficult to estimate blood concentration of propofol in real time at the moment
No risk of environmental pollution	Difficult to monitor continuous administration of i.v. agents into the patient
Reduction in the incidence of postoperative nausea and vomiting	Slightly prolonged context-sensitive half-time in children when compared to adults in view of the requirement of higher doses of propofol
Increased patient comfort, parental satisfaction in the postoperative period	Propofol infusion syndrome (7,8)
Propofol reduces brain metabolism and cerebral blood flow, hence used in reduction of intracranial pressure	
Method of choice in patients at risk of malignant hyperthermia	
Method of choice in some patients with congenital myopathies	
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	
Can be reliably administered to maintain anesthesia in patients undergoing airway procedures	

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 V_1 , 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 V_2 representing well-perfused organs and tissues also called fast redistribution compartment (because there is rapid drug distribution between V_1 and V_2), and the other V_3 referred to as the vessel-poor or slow compartment (because there is rather slow drug distribution between V_1 and V_3). The sum of V_1 , V_2 , and V_3 gives the volume of distribution at steady state ($V_{d_{ss}}$). It is a common misconception that V_1 equates to blood volume. It should be stressed that V_1 is an artificial volume, which includes blood volume, but

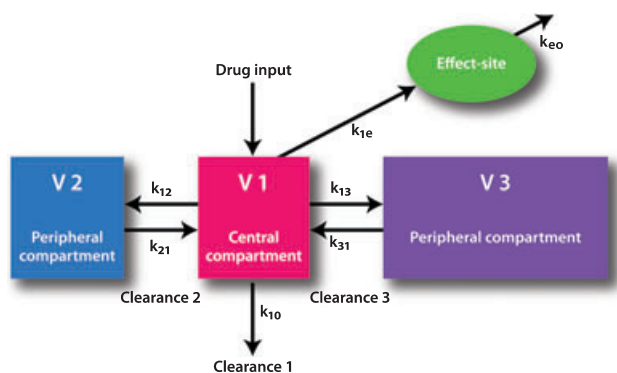


Figure 1
Three-compartment pharmacokinetic model.

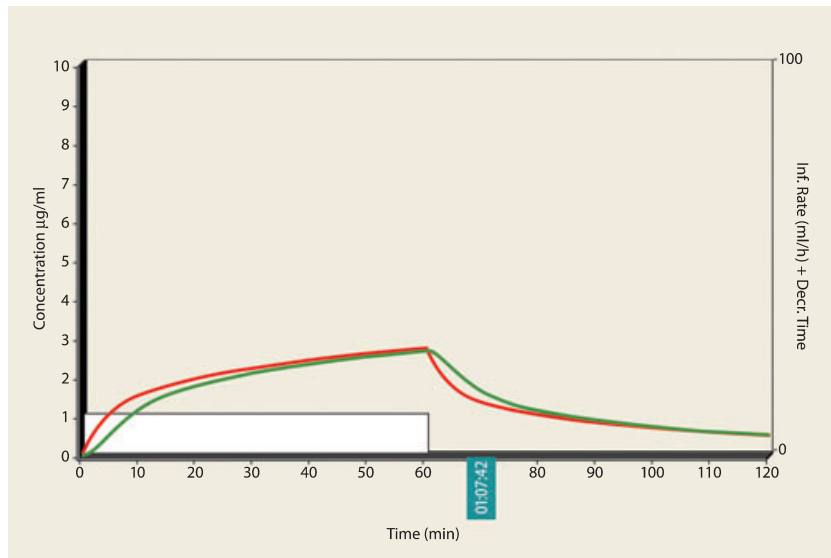
may be far larger than blood volume for drugs, which are highly lipid soluble or which have high protein binding.

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 V_1 and V_2 , V_2 and V_1 , V_1 and V_3 , and between V_3 and V_1 , respectively.

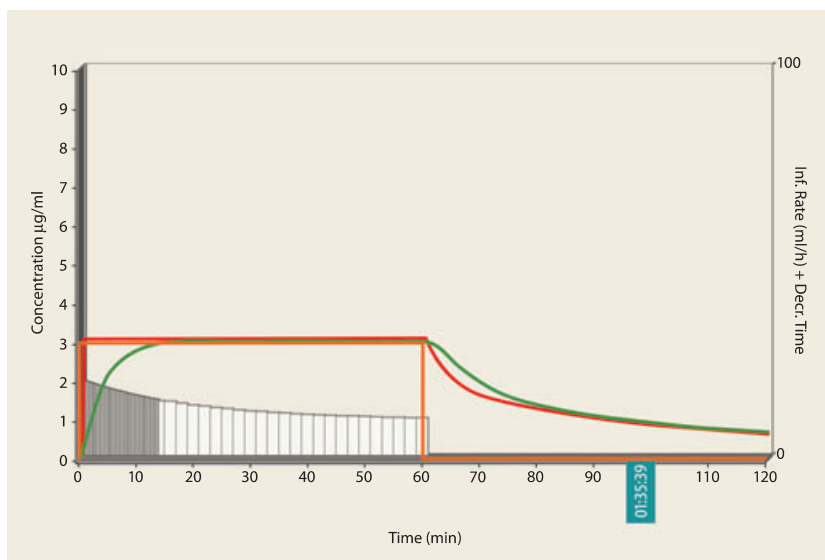
A drug that is highly lipid soluble and/or highly protein bound will have a large volume of distribution. Clearance is the volume of blood from which the drug is eliminated per unit of time. With propofol, children have a large volume of distribution and also higher clearance when compared with adults. 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

**Figure 2**

Fixed rate infusion of propofol at $10\text{-mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ with no bolus dose in a healthy 10-kg, 1-year-old infant. Steady state is still not reached after 1 h. Effect site concentration lags behind blood concentration both during infusion and after stopping infusion. C_e reaches C_p at about 1 h. Neither blood nor effect site concentration reaches $3\ \mu\text{g}\cdot\text{ml}^{-1}$. Context-sensitive half-time = 9 min. Graph color key: red line, blood concentration; green line, effect site concentration; white box, infusion rate in $\text{ml}\cdot\text{h}^{-1}$.

**Figure 3**

Blood-targeted infusion of propofol in healthy 1-year-old child of 10-kg body weight using the Paedfusor PK dataset. Blood target = $3\ \mu\text{g}\cdot\text{ml}^{-1}$ infusion stopped at 60 min i.e. Blood target = $0\ \mu\text{g}\cdot\text{ml}^{-1}$. The pump delivers bolus dose of $1.4\text{-mg}\cdot\text{kg}^{-1}$, then stepwise-reducing infusion of from 19.1- to $9.5\text{-mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ at 1 h. The effect site concentration does not reach $3\ \mu\text{g}\cdot\text{ml}^{-1}$ until 15 min 44 s. Total dose of propofol = $13.6\ \text{mg}\cdot\text{kg}^{-1}$. Context-sensitive half-time = 10 min. Graph color key: red line, blood concentration; green line, effect site concentration; orange line, target concentration; white boxes, infusion rate in $\text{ml}\cdot\text{h}^{-1}$.

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

Table 2

Example of Target-controlled infusion ($5 \mu\text{g}\cdot\text{ml}^{-1}$) 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

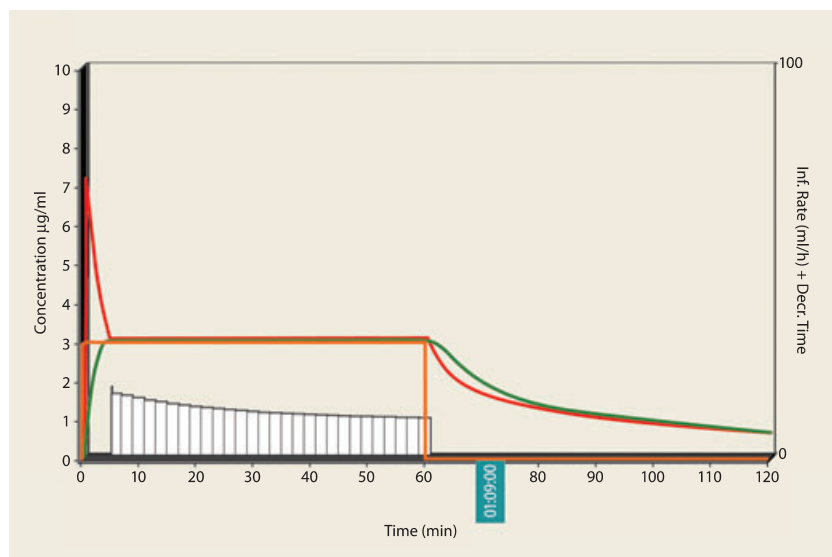
	Blood concentration targeting	Effect site concentration targeting
Loading dose	$1.7 \text{ mg}\cdot\text{kg}^{-1}$	$5.7 \text{ mg}\cdot\text{kg}^{-1}$
Maximum blood target reached	$5 \text{ mcg}\cdot\text{kg}^{-1}$	$12 \text{ mcg}\cdot\text{kg}^{-1}$
Total propofol infused after 60 min	$23.2 \text{ mg}\cdot\text{kg}^{-1}$	$23.3 \text{ mg}\cdot\text{kg}^{-1}$
Time to achieve effect site target of $5 \text{ mcg}\cdot\text{ml}^{-1}$	17.5 min	4.5 min

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 remifentanyl). This is termed the CSHT where the context is the duration of the infusion. For an

Figure 4

Effect site-targeted infusion of propofol in healthy 1-year-old child of 10-kg body weight using the Paedfusor PK dataset. Effect site target = $3 \mu\text{g}\cdot\text{ml}^{-1}$ infusion stopped at 60 min i.e. Effect site target = $0 \mu\text{g}\cdot\text{ml}^{-1}$. Delivers bolus dose of $3.4 \text{ mg}\cdot\text{kg}^{-1}$ at $45.5 \text{ ml}\cdot\text{h}^{-1}$ to accentuate the gradient from blood to effect site. Then, infusion switches off for 4 min. Peak blood concentration after bolus dose = $7.1 \mu\text{g}\cdot\text{ml}^{-1}$. Stepwise-reducing infusion of from 15.7 to $9.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ at 1 h. Effect site concentration reaches $3 \mu\text{g}\cdot\text{ml}^{-1}$ at 3 min 39 s. Total dose of propofol = $14 \text{ mg}\cdot\text{kg}^{-1}$. Context-sensitive half-time = 10 min 37 s.



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 remifentanyl 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 remifentanyl 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 remifentanyl in children. The problem of acute tolerance to ultra-short-acting opioids has been noted after the use of remifentanyl 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 concentra-

tion of $3 \mu\text{g}\cdot\text{ml}^{-1}$ (Figure 6). This involves a loading dose of around $1 \text{ mg}\cdot\text{kg}^{-1}$ of propofol followed by an infusion of $10 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for 10 min, then $8 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for 10 min, and $6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 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 V_1 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 $3 \mu\text{g}\cdot\text{ml}^{-1}$ in children, the dosing of propofol infusion in children is approximately twice 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 $3 \mu\text{g}\cdot\text{ml}^{-1}$, using the Kataria dataset (15) in children aged 1–6 years. In the Macfarlan model, anesthesia is induced with a bolus dose of $2.5 \text{ mg}\cdot\text{kg}^{-1}$ and then maintained with a propofol infusion regimen (commenced within 1 min of the propofol bolus) of $15 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for the first 15 min, $13 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for the next 15 min, $11 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ from 30 to 60 min, $10 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ from 1 to 2 h, and $9 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ from 2 to 4 h. This resulted in a pseudo steady-state concentration of $3 \mu\text{g}\cdot\text{ml}^{-1}$.

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} ($t_{1/2}k_{e0}$ 0.8 min) and for the Kataria models of 0.41 min^{-1} ($t_{1/2}k_{e0}$ 1.7 min). Jel-eazcov *et al.* (18), in a study of PD modeling using

Table 3
Context-sensitive half-times (CSHT) of opioids in children

Drugs	Infusion duration (min)				
	10	100	200	300	600
Remifentanyl CSHT	3–6	3–6	3–6	3–6	3–6
Alfentanil CSHT	10	45	55	58	60
Sufentanil CSHT		20	25	35	60
Fentanyl CSHT	12	30	100	200	

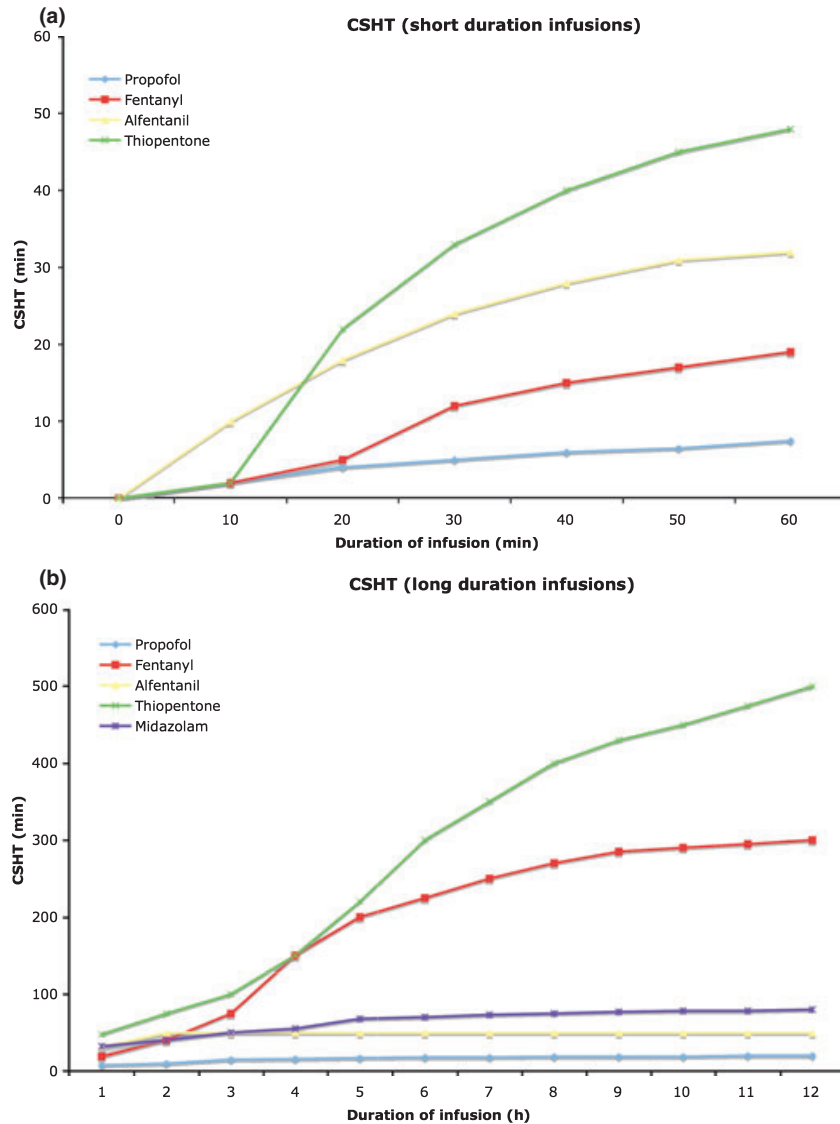
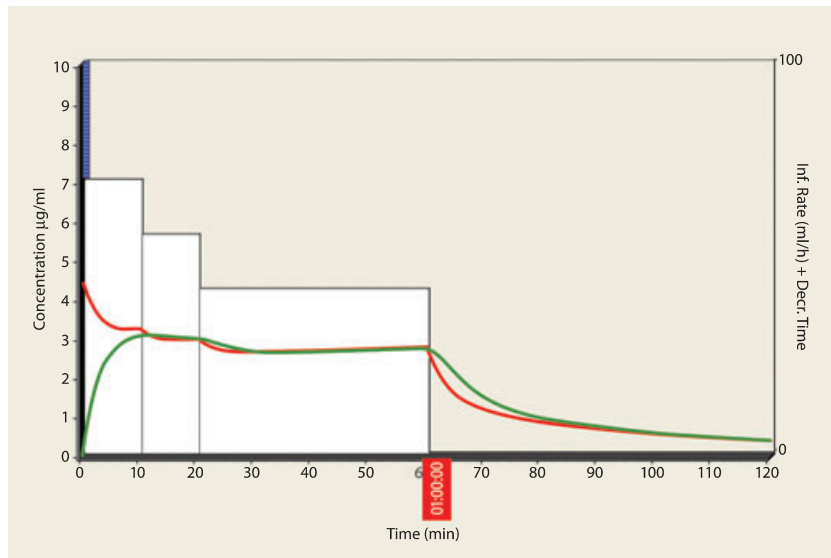


Figure 5

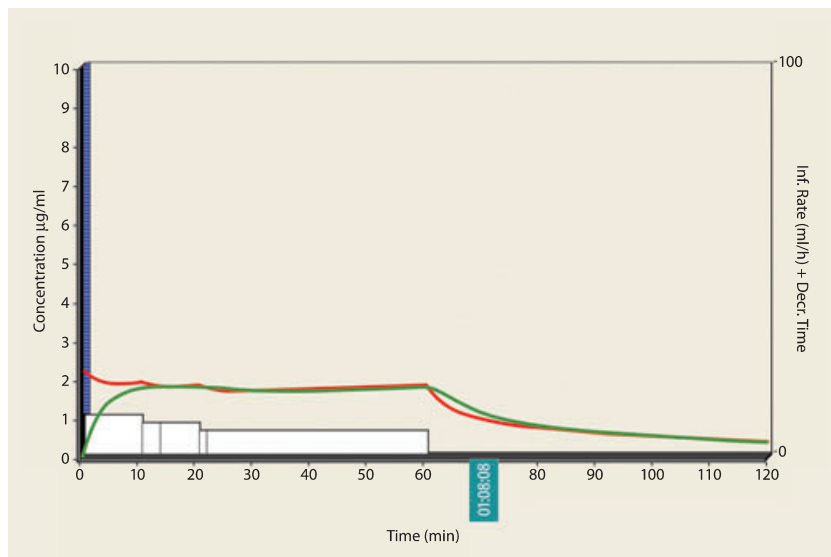
(a) Context-sensitive half-times (CSHT) after short duration infusions. (b) CSHT after longer duration infusions. For very lipid soluble drugs like fentanyl and propofol, V_3 is very large compared with V_1 . Intercompartmental clearance between V_1 and V_3 is given by the equation $V_1 \cdot k_{13} = V_3 \cdot k_{31}$, 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 $t_{1/2k_{e0}}$, 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.

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 $4.8 \mu\text{g}\cdot\text{ml}^{-1}$ 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.*

**Figure 6**

Manual infusion in a healthy adult age 40 years, 70 kg. Diprifusor pharmacokinetic dataset. Bolus dose $1 \text{ mg}\cdot\text{kg}^{-1}$, then $10 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for 10 min, $8 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for 10 min, then $6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ until 60 min when infusion is discontinued. Maximum blood concentration is $4.5 \text{ }\mu\text{g}\cdot\text{ml}^{-1}$. Effect site concentration reaches $3 \text{ }\mu\text{g}\cdot\text{ml}^{-1}$ after around 10 min, but drifts down to around $2.6 \text{ }\mu\text{g}\cdot\text{ml}^{-1}$, then very gradually rises. Context-sensitive half-time after 1 h = 7 min.

**Figure 7**

Manual infusion of propofol in 1-year-old child of 10-kg body weight. Bolus dose of $1 \text{ mg}\cdot\text{kg}^{-1}$, then $10 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for 10 min, then $8 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for 10 min, then $6 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. Infusion stopped at 60 min. Paedfusor PK dataset. Effect site concentration does not equilibrate until 11 min. Blood and effect site concentrations stabilize around $1.8 \text{ }\mu\text{g}\cdot\text{ml}^{-1}$. This is unlikely to represent a sufficient depth of anesthesia for surgery. Context-sensitive half-time after 1 h = 9 min.

Table 4

Differences between adult and pediatric pharmacokinetic parameters for propofol

Age	$V_1 \text{ (ml}\cdot\text{kg}^{-1}\text{)}$	Elimination $t_{1/2} \text{ (min)}$	Clearance $\text{(ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}\text{)}$
1–3 years	9500	188	53
3–11 years	9700	398	34
Adults	4700	312	28

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

Table 5
Commonly used doses for TIVA in children

Drug (Ref)	Loading dose	Maintenance infusion	Notes
Propofol (11)	1 mg·kg ⁻¹	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	Concurrently with alfentanil infusion
Propofol (13)	2.5 mg·kg ⁻¹	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	Achieves plasma concentration of around 3 µg·ml ⁻¹
Alfentanil (30)	10–50 µg·kg ⁻¹	1–5 µg·kg ⁻¹ ·min ⁻¹	Results in blood concentration of 50–200 ng·ml ⁻¹
Remifentanil (1)	0.5 µg·kg ⁻¹ ·min ⁻¹ for 3 min	0.25 µg·kg ⁻¹ ·min ⁻¹	Produces blood concentrations of 6–9 ng·ml ⁻¹
Remifentanil (1)	0.5–1.0 µg·kg ⁻¹ over 1 min	0.1–0.5 µg·kg ⁻¹ ·min ⁻¹	Produces blood concentrations of 5–10 ng·ml ⁻¹
Sufentanil (for sedation and analgesia) (31)	0.1–0.5 µg·kg ⁻¹	0.005–0.01 µg·kg ⁻¹ ·min ⁻¹	Results in blood concentration of 0.2 ng·ml ⁻¹
Sufentanil (31)	1–5 µg·kg ⁻¹	0.01–0.05 µg·kg ⁻¹ ·min ⁻¹	Results in blood concentration of 0.6–3.0 ng·ml ⁻¹
Fentanyl (30)	1–10 µg·kg ⁻¹	0.1–0.2 µg·kg ⁻¹ ·min ⁻¹	
Ketamine (22)	2 mg·kg ⁻¹	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	Produces blood concentration of 3 mg·l ⁻¹
Ketamine (22) (Anesthetic dose when administered with N ₂ O or midazolam)	2 mg·kg ⁻¹	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	Produces blood concentration of 2–2.2 mg·l ⁻¹
Midazolam (30)	0.05–0.1 mg·kg ⁻¹	0.1–0.3 mg·kg ⁻¹ ·h ⁻¹	
Dexmedetomidine (sedation for noninvasive procedures) (21)	0.5–1 µg·kg ⁻¹ over 10 min	0.5–1 µg·kg ⁻¹ ·h ⁻¹	
Dexmedetomidine (sedation for invasive procedures) (21)	1–2 µg·kg ⁻¹ over 10 min	1–2 µg·kg ⁻¹ ·h ⁻¹	
Dexmedetomidine (treatment of withdrawal) (21)	0.5 µg·kg ⁻¹ over 10 min	0.25 µg·kg ⁻¹ ·h ⁻¹ and weaned over 2–3 days	
Dexmedetomidine (sedation in ICU) (21)		0.25 µg·kg ⁻¹ ·h ⁻¹	

TIVA, total intravenous anesthesia.

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 V₁, 1 l·kg⁻¹; protein binding, 93%; clearance, 13 ml·kg⁻¹·min⁻¹; terminal t_{1/2}, 1.8 h (20).

Uses (21).

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

2. Procedural sedation:

- Sedation for noninvasive radiologic procedures.
- Sedation and anesthesia for invasive radiologic procedures.
- Endoscopy.
- Cardiac catheterization.

3. Perioperative uses:

- Intraoperative sedation/analgesic in cardiac surgery.
- Providing controlled hypotension during orthopedic spine surgery.
- Treatment of emergence delirium.
- Treatment of postoperative shivering.
- Premedicant.

4. Treatment of substance abuse withdrawal.

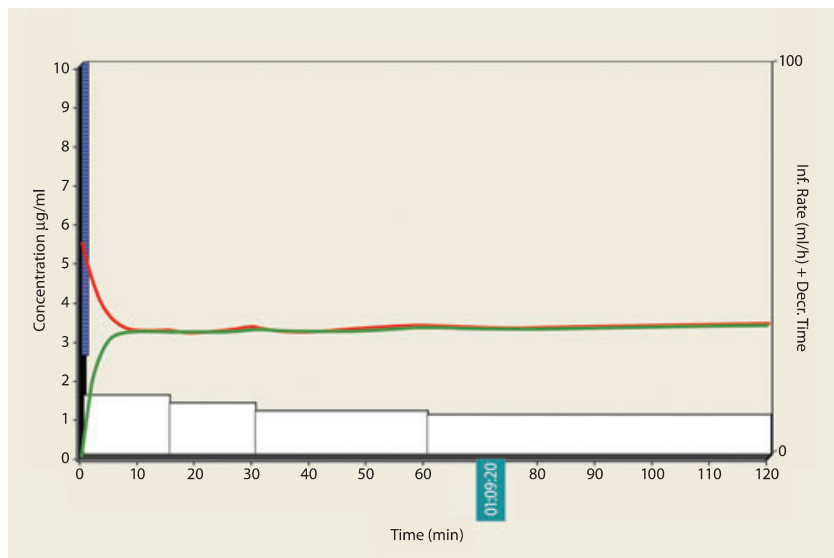


Figure 8
McFarlan model (13) for manual infusion of propofol in 1-year old child of 10 kg body weight. Bolus dose 2.5 mg·kg⁻¹, then 15 mg·kg⁻¹·h⁻¹ for 15 min, 13 mg·kg⁻¹·h⁻¹ for 15 min, 11 mg·kg⁻¹·h⁻¹ for 30 min, 10 mg·kg⁻¹·h⁻¹ for 1 h. Achieves and maintains blood and effect site concentrations around 3 µg·ml⁻¹.

Table 6
Comparison between 'Paedfusor' (12) and Kataria (15) models for propofol in children

	'Paedfusor'	Kataria
V ₁	0.458 × weight	0.41 × weight
V ₂	0.95 × weight	0.78 × weight + 3.1 × age
V ₃	5.82 × weight	6.9 × weight
k ₁₀	0.1527 × weight ^{-0.3}	0.085
k ₁₂	0.114	0.188
k ₂₁	0.055	0.102
k ₁₃	0.0419	0.063
k ₃₁	0.0033	0.0038
k _{e0}	0.26	n/a

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

Table 7
Required effect site target concentrations for commonly used TIVA drugs (1)

Drug	Effect	Required effect site concentration
Propofol	Sedation	2–3 µg·ml ⁻¹
	Anesthesia	4–6 µg·ml ⁻¹
Remifentanyl	Laryngoscopy	2–3 ng·ml ⁻¹
	Analgesia for superficial surgery	3–4 ng·ml ⁻¹
	Analgesia for laparotomy	6–8 ng·ml ⁻¹
Alfentanil	Analgesia for cardiac surgery	10–12 ng·ml ⁻¹
	Analgesia for major surgery	75–100 ng·ml ⁻¹
Sufentanyl	Analgesia for cardiac surgery	150–220 ng·ml ⁻¹
	Analgesia for major surgery	0.1–0.4 ng·ml ⁻¹
	Analgesia for cardiac surgery	0.6–1.0 ng·ml ⁻¹

TIVA, total intravenous anesthesia.

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

sedation with adjustments and additional bolus doses often needed. Caution is required with bolus dosing in neonates and infants and in the critically ill as hypotension may occur and the depth of sedation achieved with midazolam is tremendously variable (Table 5).

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 P_{450} enzyme isoform CYP_{3A4} (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 remifentanyl, whereas remifentanyl 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 remifentanyl infusion. In the study by Struys *et al.* (28), remifentanyl concentration of $4 \text{ ng}\cdot\text{ml}^{-1}$ was found to reduce the Cp_{50} for loss of response to verbal command from 2.9 to $2.2 \text{ }\mu\text{g}\cdot\text{ml}^{-1}$. 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 con-

sciousness, combination of propofol and remifentanyl 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 Web site 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

- 1 Absalom ASM. *An Overview of TCI and TIVA*. Gent, Belgium: Academic Press, 2005.
- 2 Marsh B, White M, Morton N *et al.* Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth* 1991; **67**(1): 41–48.
- 3 Marsh BJ, Morton NS, White M *et al.* A computer controlled infusion of propofol for induction and maintenance of anaesthesia in children. *Can J Anaesth* 1990; **2**(4 Pt 2): S97.
- 4 Varveris DA, Morton NS. Target controlled infusion of propofol for induction and maintenance of anaesthesia using the paedfusor: an open pilot study. *Pediatr Anesth* 2002; **12**(7): 589–593.
- 5 Eyres R. Update on TIVA. *Pediatr Anesth* 2004; **14**(5): 374–379.
- 6 Lerman J, Johr M. Inhalational anesthesia vs total intravenous anesthesia (TIVA) for pediatric anesthesia. *Pediatr Anesth* 2009; **19**(5): 521–534.
- 7 Kam PC, Cardone D. Propofol infusion syndrome. *Anaesthesia* 2007; **62**(7): 690–701.
- 8 Bray RJ. Propofol infusion syndrome in children. *Pediatr Anesth* 1998; **8**(6): 491–499.
- 9 Minto CF, Schnider TW, Gregg KM *et al.* Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *Anesthesiology* 2003; **99**(2): 324–333.
- 10 Crawford MW, Hickey C, Zaarour C *et al.* Development of acute opioid tolerance during infusion of remifentanyl for pediatric scoliosis surgery. *Anesth Analg* 2006; **102**(6): 1662–1667.
- 11 Roberts FL, Dixon J, Lewis GT *et al.* Induction and maintenance of propofol anaesthesia. A manual infusion scheme. *Anaesthesia* 1988; **43**(Suppl.): 14–17.
- 12 Absalom A, Kenny G. 'Paedfusor' pharmacokinetic data set. *Br J Anaesth* 2005; **95**(1): 110.
- 13 McFarlan CS, Anderson BJ, Short TG. The use of propofol infusions in paediatric anaesthesia: a practical guide. *Pediatr Anesth* 1999; **9**(3): 209–216.
- 14 Engelhardt T, McCheyne AJ, Morton N *et al.* Clinical adaptation of a pharmacokinetic model of Propofol plasma concentrations in children. *Pediatr Anesth* 2008; **18**(3): 235–239.

- 15 Kataria BK, Ved SA, Nicodemus HF *et al.* The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology* 1994; **80**(1): 104–122.
- 16 Absalom A, Amutike D, Lal A *et al.* Accuracy of the 'Paedfusor' in children undergoing cardiac surgery or catheterization. *Br J Anaesth* 2003; **91**(4): 507–513.
- 17 Munoz HR, Cortinez LI, Ibacache ME *et al.* Estimation of the plasma effect site equilibration rate constant (k_{e0}) of propofol in children using the time to peak effect: comparison with adults. *Anesthesiology* 2004; **101**(6): 1269–1274.
- 18 Jeleazcov C, Ihmsen H, Schmidt J *et al.* Pharmacodynamic modelling of the bispectral index response to propofol-based anaesthesia during general surgery in children. *Br J Anaesth* 2008; **100**(4): 509–516.
- 19 Munoz HR, Cortinez LI, Ibacache ME *et al.* Effect site concentrations of propofol producing hypnosis in children and adults: comparison using the bispectral index. *Acta Anaesthesiol Scand* 2006; **50**(7): 882–887.
- 20 Potts AL, Warman GR, Anderson BJ. Dexmedetomidine disposition in children: a population analysis. *Pediatr Anesth* 2008; **18**(8): 722–730.
- 21 Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. *Pediatr Crit Care Med* 2007; **8**(2): 115–131.
- 22 Dallimore D, Anderson BJ, Short TG *et al.* Ketamine anesthesia in children – exploring infusion regimens. *Pediatr Anesth* 2008; **18**(8): 708–714.
- 23 Dallimore D, Herd DW, Short T *et al.* Dosing ketamine for pediatric procedural sedation in the emergency department. *Pediatr Emerg Care* 2008; **24**(8): 529–533.
- 24 Vuyk J. Pharmacokinetic and pharmacodynamic interactions between opioids and propofol. *J Clin Anesth* 1997; **9**(Suppl. 6): 23S–26S.
- 25 Pavlin DJ, Coda B, Shen DD *et al.* Effects of combining propofol and alfentanil on ventilation, analgesia, sedation, and emesis in human volunteers. *Anesthesiology* 1996; **84**(1): 23–37.
- 26 Mertens MJ, Vuyk J, Olofsen E *et al.* Propofol alters the pharmacokinetics of alfentanil in healthy male volunteers. *Anesthesiology* 2001; **94**(6): 949–957.
- 27 Bouillon TW, Bruhn J, Radulescu L *et al.* Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. *Anesthesiology* 2004; **100**(6): 1353–1372.
- 28 Struys MM, Vereecke H, Moerman A *et al.* Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. *Anesthesiology* 2003; **99**(4): 802–812.
- 29 Nieuwenhuijs DJ, Olofsen E, Romberg RR *et al.* Response surface modeling of remifentanil-propofol interaction on cardiorespiratory control and bispectral index. *Anesthesiology* 2003; **98**(2): 312–322.
- 30 Shann F. *Drug Dosing*, 13th edn. Melbourne: Royal Children's hospital, 2005.
- 31 Glass PSS, Reves J. *Intravenous Drug Delivery Systems, Anesthesia*, 5th edn. New York: Churchill-Livingstone, 2000.

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