Chapter 14

Total Intravenous Anaesthesia in Children

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Introduction

Anaesthesia in children has traditionally been achieved using volatile agents. Total intravenous anaesthesia (TIVA) has recently gained popularity in children due to:

- Availability of newer anaesthetic and analgesic drugs with favourable pharmacokinetic (PK) and pharmacodynamics (PD) properties
- Better understanding of the pharmacokinetics of these drugs in children, resulting in the availability of newer PK and PK-PD models to achieve the desired clinical effect
- Widely available and user-friendly infusion devices with these pharmacokinetic models suitable for use in children

In addition, there are specific advantages of TIVA over volatile agents, which include:

- Reduced emergence delirium
- Reduced incidence of airway complications
- Reduced incidence of postoperative nausea and vomiting
- Reduced pollution
- Minimal interference with neurophysiological monitoring under anaesthesia
- Reliable delivery of anaesthesia in children undergoing airway procedures using bronchoscopes/suspension laryngoscopes

TIVA can be used for all procedures but is particularly useful for:

- Children undergoing microlaryngoscopy, bronchoscopy and other airway procedures
- Frequent and brief radiological or painful procedures where rapid recovery is needed (e.g. MRI, CT scans, endoscopy, paediatric oncology procedures and radiotherapy)
- During neurosurgical procedures to assist with control of intra-cranial pressure and for cerebral protection and smooth emergence from anaesthesia
- During transfer of anaesthetised children including transfer for remote site procedures (e.g. scans)
- Children at very high risk of postoperative nausea and vomiting

TIVA is absolutely indicated now for the following:

- Any neurosurgical procedure where evoked potential monitoring is required
- Spinal instrumentation surgery where evoked potential monitoring is used
- Children at risk of malignant hyperthermia
- Children at risk of rhabdomyolysis due to volatile agent exposure (e.g. Duchenne muscular dystrophy)

The most used drugs for TIVA include propofol, remifentanil and dexmedetomidine. Drugs such as alfentanil, ketamine and midazolam are occasionally used. These can be given by simple manual infusion schemes or by a target-controlled infusion (TCI) method, currently only available for propofol in children.

Basic Science of TIVA and TCI

We will briefly describe the important concepts needed to understand TIVA and TCI.

Pharmacokinetics (PK)

Sometimes described as 'what the body does to the drug', PK is more accurately defined as the movement of a drug within the body, including its elimination. A PK model can be used to predict the plasma or effect-site concentration profile of a drug after a bolus dose or an infusion. The behaviour of most drugs used for TIVA can be described

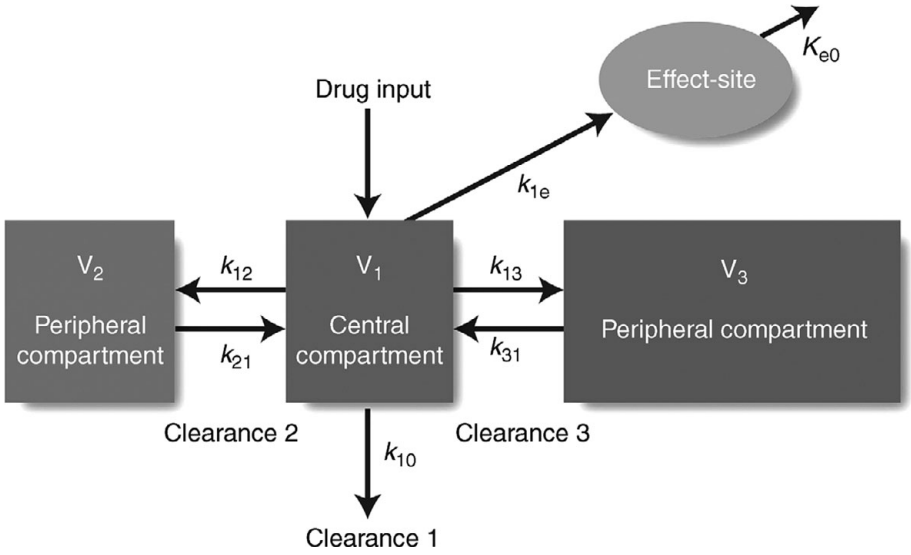

Figure 14.1 Three-compartment pharmacokinetic model (see text for details).

by models using either two or three theoretical compartments. Each model is described by:

- The compartments and their volumes
- The rate of transfer between compartments
- The rate of drug elimination

The drug is delivered and eliminated from a central compartment (V1) and distributes to and redistributes from two peripheral compartments (V2 and V3, Figure 14.1). V2 (the 'fast' compartment) represents well-perfused organs and tissues, whilst V3 (the 'slow' compartment) represents the less perfused tissue, mainly fat. A drug that is highly lipid soluble or highly protein bound will have a large volume of distribution. It should be noted that V1 includes blood volume but may be far larger than blood volume for these drugs. 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 V3 and V1 respectively.

Elimination by metabolism in the liver and excretion via the kidneys is assessed by the clearance (Cl), which is the volume of blood from which the drug is eliminated per unit time. The time required for the blood concentration of a drug to decrease by 50% is its elimination half-life ($_{1/2}$). The context-sensitive half-time (CSHT) is another helpful concept. 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 must distribute back from the peripheral compartment into the central compartment before it is eliminated. The half-time of the decrease in drug concentration is therefore related to the *duration* of the infusion for most drugs (except remifentanil). For an individual drug in an individual patient, CSHTs can be determined by graphing the elimination half-lives against the duration of the infusion. This CSHT graph will eventually become parallel to the time (*x*) axis. At that time, the infusion has become context *in*sensitive. This pattern is observed for nearly all intravenous anaesthetics. The exception is remifentanil, for which the half-time becomes context insensitive almost immediately after starting the infusion because its elimination is rapid and complete. Alfentanil's CSHT becomes constant after approximately 90 minutes' infusion.

Prolongation of the elimination of a drug reflects either an increase in the volume of distribution or a reduction in clearance, or both, and is evident in neonates and infants (due to both increased volume of distribution and reduced clearance) and patients with liver or renal dysfunction (reduced clearance). Propofol has a larger volume of distribution and higher clearance in children than in adults. In neonates, the variety of enzymatic phenotypes responsible for glucuronidation further complicates the picture by leading

to variations in the speed of metabolism and subsequent elimination of the drugs. This is especially noticeable in the metabolism of propofol, which rather than following the glucuronidation pathway of older children and adults, will be hydroxylated slowing drug clearance and elimination. This concept is further complicated by the speed at which these enzyme systems begin to mature and explains the covariates of propofol elimination and the impact of postconceptual age versus postnatal age.

Concept of Effect-Site

The clinical effect of a drug depends on the concentration at the effect-site. After intravenous administration, there is usually a delay in clinical effect as the drug must reach the effect-site from V1. 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 pharmacological properties of the drug, such as those that determine the rate of transfer across the blood–brain barrier (lipid solubility and degree of ionisation).

The time course of plasma/effect-site equilibration can be mathematically described by a rate constant typically referred to as *k*e0. This term should strictly be used to describe the rate of removal of drug from the effect-site, but the effect-site is usually regarded as a volumeless additional compartment, and so there is no need for separate rate constants describing movement into and out of the effect-site compartment.

Pharmacokinetic-Pharmacodynamic (PK-PD) Modelling

Pharmacodynamics can be thought of as 'what the drug does to the body', or its biological effect. It is not possible to directly measure the concentration of the drug at the effect-site in vivo, but the time course of the changes in the effect-site concentration can be estimated from measures of clinical effect (PD effect) such as evoked EEG parameters and bispectral index (BIS). When the blood concentration in a group of subjects is known, then PD measurements can be used to estimate the *k*e0 for that drug. This is the basis of PK-PD modelling. The $_{1/2}$ *k*e0 (which is 0.693/*k*e0) is sometimes used to express this rate constant. As *k*e0 increases, $t_{1/2}$ *k*e0 decreases, and equilibration between blood and effect-site is quicker. Recently, age-related *k*e0 values have been derived for children. Neonates, critically ill children or those with major organ failure need significantly smaller doses of intravenous anaesthetic agents, and particular care is needed in children receiving vasodilator medication and in those with some types of congenital heart disease, as hypotension is a significant risk.

Target-Controlled Infusion (TCI)

TCI is administered using a microprocessor-controlled infusion pump incorporating a PK-PD model. The user enters the patient parameters and chooses the appropriate paediatric TCI model. The pump then calculates the bolus dose and infusion rate needed to achieve a user-defined plasma or effect-site drug concentration.

Plasma Target TCI

When plasma target TCI is used, one selects the desired PK model and inputs the selected drug, its concentration and the patient's age and weight. The microprocessor then calculates the bolus required to fill the central compartment rapidly. Once the target plasma concentration is reached, the system stops the rapid bolus and commences a stepwise-reducing infusion rate to replace drug that is lost by elimination and intercompartmental transfer (Figure 14.2). To increase depth of anaesthesia, a bolus is given and the infusion rate recalculated to maintain a higher target blood concentration. To reduce depth of anaesthesia, the system stops the infusion until the calculated new lower target concentration is reached. The rate at which the plasma concentration falls depends on the rate of elimination and the intercompartmental drug concentration gradients.

Effect-Site-Targeted TCI

When plasma TCI is used, there is a delay before the effect-site and plasma concentrations equilibrate. With effect-site targeting, the TCI system calculates the plasma concentration to bring about the user-defined effect-site concentration as rapidly as possible (Figure 14.3)

This results in a relatively larger loading bolus dose with a higher peak plasma concentration. Whilst healthy children may be able to tolerate

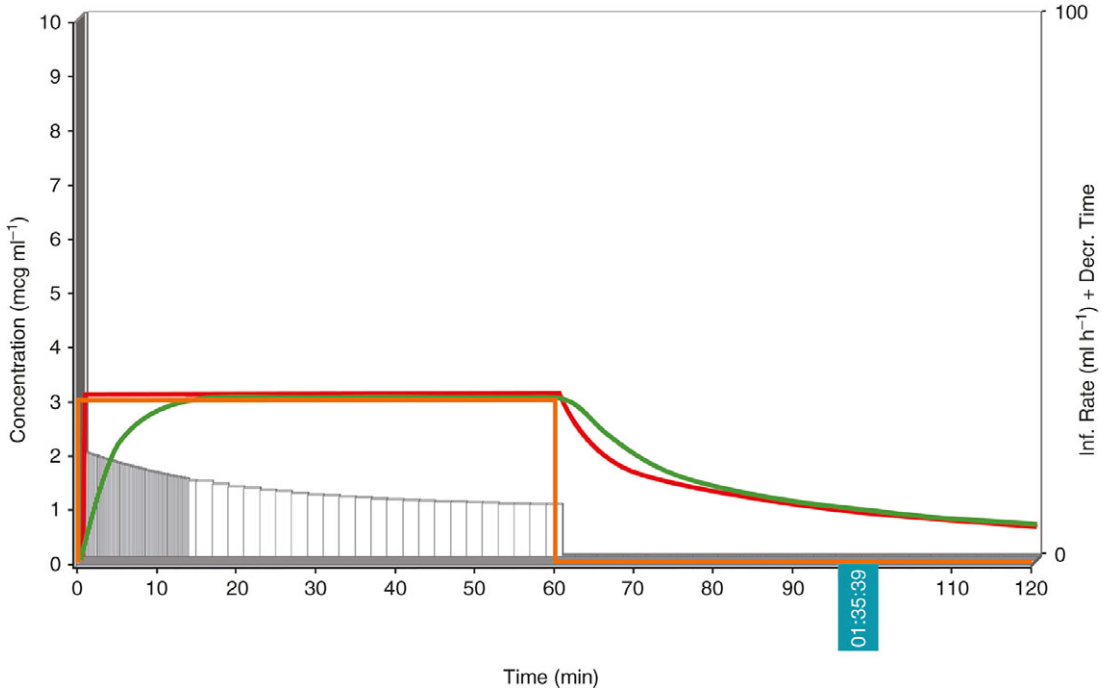

Figure 14.2 Blood-targeted infusion of propofol in a child using the Paedfusor PK model. This diagram represents a 60-minute infusion of propofol where the blood-target concentration (the orange line) has been set at 3 mcg ml^{-1}, and then the infusion is switched off (blood target 0). The red line represents the predicted blood concentration, whilst the green line represents the effect-site concentration, which correlates with depth of sedation or anaesthesia. The effect-site concentration lags behind the blood concentration, and it takes around 10 minutes to reach an effect-site concentration equal to the target. The context-sensitive half-time is represented by the time it takes for the blood concentration to drop from 2 mcg ml^{-1} to 1.5 mcg ml^{-1}, which is in this case after 60 minutes of infusion approximately 20 minutes. Inf = infusion.

this higher peak blood concentration, it may cause cardiovascular instability with hypotension and bradycardia in those who are ill.

The commercially available plasma target models for propofol are Paedfusor and Kataria. Paedfusor uses age and weight as covariates; it can be used between 5–61 kg and 1–16 years of age. Kataria can be used from 3 to 16 years of age and works with a minimum weight of 15 kg.

The newer Eleveld TCI model for a wide patient age group is now commercially available. This second-generation model was developed by combining the PK-PD data of different studies from diverse populations, including neonates, children, adults and the elderly. This model incorporates the variables of weight, age, post-menstrual age (PMA), height, sex and BMI. The predictive performance, which was measured across children, adults, elderly and high-BMI individuals, performed within acceptable limits. The PD target in this model is Ce50 (corresponding with a predicted BIS of 47), which is an age-specific effect-site concentration corresponding with 50% of maximal effect for the induction of anaesthesia. It can be seen in Figure 14.4 that with increasing age, the Ce50 required is less. This model can also be used in obese children, where it calculates the propofol infusion rates using allometric scales, with maximum body weight to be 40% above the ideal body weight for patient age, height and sex.

Drugs Used for TIVA

Propofol

Manual Propofol Infusion

The simple '10–8–6' scheme devised by Roberts for propofol infusion in adults is very effective in maintaining a propofol blood concentration of 3 mcg ml^{-1}, which in most adults produces a state of anaesthesia. This scheme involves a loading dose of around 1 mg kg^{-1} of propofol followed by an infusion of 10 mg kg^{-1} hr^{-1} for 10 minutes, then 8 mg kg^{-1} hr^{-1} for 10 minutes and 6 mg kg^{-1} hr^{-1} thereafter. When this regimen is used in

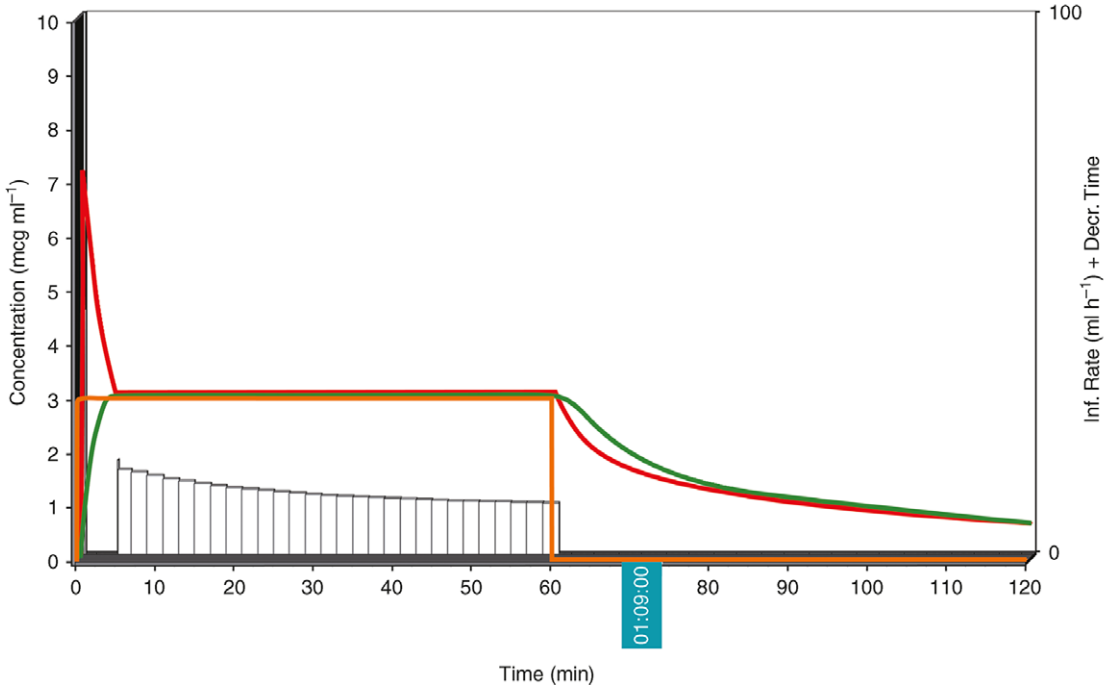

Figure 14.3 Effect-site targeted infusion of propofol in a child using the Paedfusor PK model. This diagram represents a 60-minute infusion of propofol where the effect-site target concentration (the orange line) has been set at 3 mcg ml^{-1}, and then the infusion is switched off (blood target 0). As in Figure 14.2, the red line represents the predicted blood concentration, whilst the green line represents the effect-site concentration, which correlates with depth of sedation or anaesthesia. Although the effect-site concentration still lags behind the blood concentration, it takes only around three minutes to reach an effect-site concentration equal to the target. This is because a larger bolus is given to increase the blood concentration quickly to a higher peak, which drives the propofol along a concentration gradient into the effect-site much more quickly. Thus induction of anaesthesia will be quicker but at the expense of potential adverse effects related to the higher peak blood concentration, such as hypotension and bradycardia.

children, however, a subtherapeutic blood concentration of propofol is achieved. This low concentration is because of the larger V1 and increased clearance of propofol in children.

Using the Paedfusor data, it has been found that to achieve a plasma concentration of 3 mcg ml^{-1}, the dosing of propofol infusion in children must be approximately twice that in adults (a '19–15–12' regimen). Recent studies have shown that the target concentrations to produce anaesthesia in children above one year old are slightly higher than in adults (Figure 14.4).

The other simple manual infusion scheme to obtain a propofol blood concentration of 3 mcg ml^{-1} was devised by McFarlan and validated by Engelhardt, using the Kataria dataset in children aged one to six years. In the McFarlan model, anaesthesia is induced with a bolus dose of 2.5 mg kg^{-1} and then maintained with a propofol infusion regimen (commenced within one minute of the propofol bolus) of: 15 mg kg^{-1} hr^{-1} for the first 15 minutes, 13 mg kg^{-1} hr^{-1} for the next 15 minutes, 11 mg kg^{-1} hr^{-1} from 30 to 60 minutes, 10 mg kg^{-1} hr^{-1} from 1 to 2 hours and 9 mg kg^{-1} hr^{-1} from 2 to 4 hours. This results in a near steady-state blood concentration of 3 mcg ml^{-1}.

For children under three years, Steur et al. suggested a dosing regimen which has been used in neonates (see Table 14.1).

Propofol TCI

Currently the Paedfusor and Kataria models are the most popular for achieving plasma-targeted propofol TCI. Effect-site targeting is now possible in paediatrics using the Eleveld model as discussed earlier in this chapter.

Depth of Anaesthesia Monitoring

The popular modalities available for monitoring depth of anaesthesia (DOA) are BIS and entropy. These were used in only 1% of the paediatric anaesthesia cases reported in NAP5 in 2015. Both the

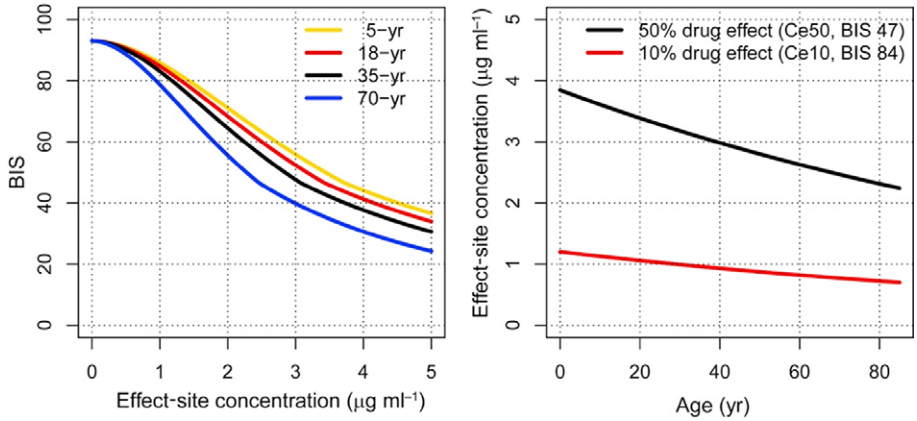

Figure 14.4 The relationship between target concentration and age for the Eleveld PK-PD model showing the expected drug effect and suppression of BIS values.

Table 14.1 The Steur regimen for propofol TIVA in children under three years, which has been used in neonates (all doses in mg kg^{-1} hr^{-1})

Time (mins)	0–3 months	3–6 months	6–12 months	1–3 years
0–10	25	20	15	12
10–20	20	15	10	9
20–30	15	10	10	9
30–40	10	10	10	9
40–50	5	5	5	9
50–60	5	5	5	9
60–120	5	5	5	9
120–240	2.5	2.5	2.5	6

Bispectral Index™ monitor (BIS monitor, Covidien, Ireland) and Narcotrend™ (Monitor Technik, Germany) have shown a close relationship to effect-site target concentration and can serve as a measure of anaesthetic drug effect in children older than one year. Clinical signs are currently required for depth of anaesthesia assessment in infants and neonates, as processed electroencephalograms (EEGs) are unreliable. BIS has only been validated in children above three years of age and therefore should only be used to titrate propofol dosing in this cohort. DOA monitoring is especially useful when TIVA is used with neuromuscular blockade. The National Institute for Health and Care Excellence (NICE) recommends using DOA to reduce awareness, even in cases where it has not been validated. Awareness has been reported when using TIVA. These case reports suggest that awareness possibly happens at the time of transition from inhalational induction to TIVA, when a maintenance infusion of propofol is started without administering a bolus first.

Propofol-Related Infusion Syndrome (PRIS)

TIVA with propofol is a safe anaesthetic technique, but it is important to be aware of PRIS when infusing propofol in children. This was originally reported following its use for sedation in paediatric intensive care and is defined as the occurrence of bradycardia associated with lipaemia, fatty liver enlargement, metabolic acidosis with a negative base excess of more than 10 mmol l^{-1}, rhabdomyolysis or myoglobinuria.

Risk factors for developing PRIS are:

- Respiratory tract infection
- A dosage of propofol $>$ 5 mg kg^{-1} hr^{-1} for $>$ 48 hours
- Severe head injury
- Concomitant use of corticosteroids with increased catecholamine and glucocorticoid serum levels
- Low carbohydrate levels

The pathophysiology seen in PRIS is due to an increase in malonyl carnitine, which inhibits carnitine palmitoyl transferase 1 (CPT1), leading to a failure of long-chain fatty acid transport mechanisms via impairment of co-enzyme Q. This results in the accumulation of free fatty acids in mitochondria and cytolysis of cardiac and skeletal muscle. Caution is required in children

with disorders of fat or carbohydrate metabolism, but it must be remembered that PRIS is rare in children undergoing anaesthesia. If children with these disorders present for anaesthesia in which propofol is absolutely indicated, then this can be mitigated by infusing a constant source of carbohydrate (dextrose infusion).

Treatment for PRIS is to stop propofol and institute the necessary supportive measures dependent on the clinical features present. These may include cardiac pacing, inotropic support, carbohydrate substitution and haemofiltration. Extracorporeal membrane oxygenation (ECMO) support may be required.

Propofol and Lipid-Sparing Techniques

Adjuncts may be used to reduce propofol requirement. Opioids, particularly remifentanil, have been studied extensively and found to reduce the dose of propofol needed to produce unconsciousness when used in TCI. In one study, a plasma remifentanil concentration of 4 ng ml^{-1} was found to reduce the propofol target concentration for loss of response to verbal command from 2.9 mcg ml^{-1} to 2.2 mcg ml^{-1}.

Mixtures of propofol with short-acting opioids have also been used for many years to achieve a maximum effect with minimum doses, utilising their synergistic effects on sedation. Propofol (10 mg ml^{-1}) mixed with alfentanil (20 mcg ml^{-1}) or propofol (10 mg ml^{-1}) with remifentanil (5 mcg ml^{-1}) have been used successfully to provide anaesthesia, with the latter shown to be non-inferior to volatile agents. The lower propofol dose improves haemodynamic stability. Alpha-2 agonists, such as clonidine and dexmedetomidine, also have a propofol-sparing effect, as does regional anaesthesia.

Propofol 1% is a solution of 10 mg ml^{-1} propofol in an emulsion containing 0.1 g ml^{-1} lipid. Propofol 2% solution contains 20 mg ml^{-1} propofol but the same lipid content and is therefore preferred for longer-duration anaesthesia, as this halves the lipid load to the child. The disadvantage of propofol 2% is severe pain on injection. This can be reduced by techniques described later in this chapter.

Opioids for TIVA

Short-acting opioids used for TIVA include remifentanil, alfentanil, sufentanil and fentanyl. Appropriate postoperative analgesia must be considered, especially when ultra-short-acting opioids such as remifentanil are used. Suggested doses for opioids when used for TIVA are summarised in Table 14.2. Recent evidence suggests that infants and younger children outside the neonatal period are more resistant to the effects of remifentanil, even when combined with propofol. This is possibly due to the clearance of remifentanil being highest in neonates, decreasing with age to reach adult rates in adolescence. Spontaneous breathing can be maintained at doses that are adequate to suppress somatic responses to painful procedures, but large interindividual variation of respiratory depressant effects mandates individualised dose titration. The drug dose is more linearly related to variation in the respiratory rhythm and respiratory rate than to minute volume or end-tidal carbon dioxide. Apnoeic episodes are less likely when respiratory depressant drugs are administered slowly.

The maximum dose of remifentanil tolerated by children breathing spontaneously under anaesthesia varies widely (between 0.05 and 0.3 mcg kg^{-1} min^{-1}). A dose of 0.05 mcg kg^{-1} min^{-1} will allow spontaneous breathing in more than 90% of children; a dose of 0.3 mcg kg^{-1} min^{-1} will produce apnoea in 90% of children. Younger children, especially those <3 years old, maintain spontaneous breathing at higher doses of remifentanil, up to 0.35 mcg kg^{-1} min^{-1}; this is in contrast to the lower dose ranges tolerated in adults. The dose required to produce significant respiratory depression in children of the same age and weight is highly variable, despite the predictable plasma half-life of remifentanil. This variation may be due to an intrinsic difference in receptor sensitivity.

Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 agonist with sedative, anxiolytic and analgesic properties. It does not produce respiratory depression and provides stable haemodynamics when given as a continuous infusion, except in children who are hypovolaemic or have heart block (Table 14.2).

Ketamine

Ketamine can produce dissociative sedation and analgesia when given as an intravenous loading

Table 14.2 Commonly used doses for TIVA in children

Drug	Loading dose	Maintenance infusion	Notes
Propofol (Roberts)	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} thereafter	Concurrently with alfentanil infusion
Propofol (McFarlan)	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 to 60 min, 10 mg kg^{-1} h^{-1} from 1 to 2 hours, 9 mg kg^{-1} h^{-1} from 2 to 4 hours	Achieves blood concentration of around 3 mcg ml^{-1}
Alfentanil	10–50 mcg kg^{-1}	1–5 mcg kg^{-1} min^{-1}	Results in blood concentration of 50–200 ng ml^{-1}
Remifentanil	0.5 mcg kg^{-1} min^{-1} for 3 minutes	0.25 mcg kg^{-1} min^{-1}	Produces blood concentrations of 6–9 ng ml^{-1}
Remifentanil	0.5–1.0 mcg kg^{-1} over 1 minute	0.1–0.5 mcg kg^{-1} min^{-1}	Produces blood concentrations of 5–10 ng ml^{-1}
Sufentanil	0.1–0.5 mcg kg^{-1}	0.005–0.01 mcg kg^{-1} min^{-1}	Results in blood concentration of 0.2 ng ml^{-1}
Sufentanil	1–5 mcg kg^{-1}	0.01–0.05 mcg kg^{-1} min^{-1}	Results in blood concentration of 0.6–3.0 ng ml^{-1}
Fentanyl	1–10 mcg kg^{-1}	0.1–0.2 mcg kg^{-1} min^{-1}	
Ketamine	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, then at 3.5 mg kg^{-1} h^{-1}	Produces blood concentration of 3 mg l^{-1}
Ketamine (anaesthetic dose when administered with N_2O 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, 3 mg kg^{-1} h^{-1} from then on	Produces blood concentration of 2–2.2 mg l^{-1}
Midazolam	0.05–0.1 mg kg^{-1}	0.1–0.3 mg kg^{-1} h^{-1}	
Dexmedetomidine (sedation for non-invasive procedures)	0.5–1 mcg kg^{-1} over 10 min	0.5–1 mcg kg^{-1} h^{-1}	
Dexmedetomidine (sedation for invasive procedures)	1–2 mcg kg^{-1} over 10 min	1–2 mcg kg^{-1} h^{-1}	

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 increases in maintenance rate to 0.2 mg kg^{-1} h^{-1} if required. To achieve anaesthetic target blood concentrations, a higher loading dose and infusion rates are needed (see Table 14.2).

TCI PK models for ketamine are described for adults; there are no PK models for children. In their simulator study using PK parameters from published studies, Dallimore suggested an infusion regimen aiming 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 alongside nitrous oxide and/or midazolam. The large clearance and hence short context-sensitive half-time for infusions under

two hours of racemic ketamine in children make it a good choice as a sedative or anaesthetic agent for shorter procedures. In a study on sedation in the emergency department using racemic ketamine, Dallimore found that smaller bolus doses and repeated top-ups resulted in faster recovery. In children aged 12, 6 and 2 years, the study suggested that a dosing regimen of 0.275, 0.3 and 0.35 mg kg^{-1} respectively, followed by an infusion of 2.75, 3 and 3.5 mg kg^{-1} h^{-1} for 15 minutes, gives stable sedation with rapid recovery (20 minutes to being awake).

Table 14.3 Morse regimen for manual infusion scheme for propofol

Duration (min)	Dosing in neonates	Dosing in 1–2 year olds
Loading dose	2 mg kg^{-1}	2.5 mg kg^{-1}
0–15	9 mg/kg/hr	13 mg/kg/hr
15–30	7 mg/kg/hr	12 mg/kg/hr
30–60	6 mg/kg/hr	11 mg/kg/hr
60–120	5 mg kg^{-1} hr^{-1}	10 mg kg^{-1} hr^{-1}

Special Circumstances

Neonates

There is concern about the use of TIVA in neonates, due to immaturity of the enzymes responsible for glucuronidation leading to slower drug clearance. This is further complicated by the speed at which these enzyme systems begin to mature and explains the variability of propofol elimination in neonates with respect to postmenstrual age as compared to postnatal age. This implies that preterm neonates and neonates in the first week of postnatal life are at an increased risk of propofol accumulation during either intermittent bolus or continuous administration. Adverse effects to propofol, such as hypotension, are also more common in neonates. These can lead to delayed recovery after anesthesia.

The Eleveld model could be used for TCI in neonates and infants even though it has not been validated in a neonatal population. Commercial TCI pumps for neonates and infants younger than one year are not yet available.

There are two manual infusion regimens which can be used in cases when there is an indication for TIVA: the Steur regimen is shown in Table 14.1 and the Morse regimen in Table 14.3.

Morse and colleagues used pooled clinical data to determine a manual infusion regimen to achieve steady plasma concentrations in neonates and infants. Their work highlights the difficulties experienced by all anaesthetists in dealing with such diverse populations, and the use of these techniques is only recommended for experienced users of TIVA in neonates. Propofol and remifentanil infusions are useful in this patient group for examinations of the airway, and remifentanil can be used for intubation without muscle relaxant.

Adolescents and Children Large for Their Age

Children vary significantly with regards to height and weight for a given age; this is particularly so around puberty, when children may be significantly larger than predicted by their age model. There is therefore a risk that these children are underdosed using paediatric TCI models. Whilst some clinicians advocate using paediatric TCI models in adolescents and entering higher target values to compensate for the underdosing, we believe it may be better in bigger adolescents to use an adult TCI model and input actual patient weight, but with age entered as 16 years (which is the lowest that Schneider/Marsh models allow). Alternatively, the newly validated Eleveld model can be used, as this has been proposed to have high precision across these cohorts.

Obese Children

Obesity creates difficulties in estimating drug doses. None of the current paediatric TCI models can be reliably used in obese children; however, the Eleveld model has been reported to deliver TCI with some precision in these patients. Regardless of what model is used, we suggest using BIS or entropy to titrate the propofol target in these children where interindividual variability may be high.

Practical Aspects

Equipment

Most departments have access to programmable TCI pumps. These must be programmed with appropriate paediatric infusion models, and the practitioner must be familiar with their setup. It is best practice to use luer lock syringes for TIVA to avoid disconnection at the syringe end

and potential underdosing. Some pumps are programmed to accept a variety of sizes and manufacturers of syringes, others are not. It is essential to know which syringes work with your pump when using TIVA techniques.

IV access is obviously required for TIVA. Local anaesthetic creams and distraction techniques have made this more tolerable for awake children, but this may not be possible in all cases, and a cannula may need to be placed under inhalational anaesthesia for some children. If this is the case, a bolus dose of propofol is required before starting the manual infusion, or plasma levels of propofol will not reach adequate anaesthetic levels soon enough. When using TCI after gas induction, it may be better to start with a slightly lower target, such as 3 mcg ml^{-1} and then to titrate further according to BIS, entropy or clinical markers. Return of consciousness after prolonged anaesthesia with propofol and remifentanil is determined primarily by the context-sensitive half-time of propofol. Context-sensitive half-time is longer in children than adults because children have proportionally greater propofol accumulation in peripheral tissues due to their higher dose requirements.

The output from TIVA infusion lines should be placed as close as possible to the venous cannula (rather than on IV extensions) with one-way non-return valves to prevent backflow up intravenous fluid lines. It is important to have access to the IV cannula. The infusion site is not always easily accessible in small children where limbs may be covered by surgical drapes and inadvertent dislodgement, obstruction or extravasation may occur. If central venous access is available, then it should be used where possible as it provides a dedicated port for TIVA and reduces the risks posed by peripheral IV access malfunction. When using a PICC line for TIVA, it is common for the pump's high-pressure alarm to sound due to the small radius and long tubing. It also is important to consider the dead space of the tubing used and the syringe size and type, as they can have an impact on the initial clinical response time. The dead space of all TIVA lines needs to be primed with the anaesthetic agents, including small extension sets, CVCs, PICCs and IV giving sets. The bolus dose programmed by the TCI pump will not compensate for the dead space, and so underdosing and miscalculation of plasma and effect site concentrations may occur if this is neglected.

We suggest opioids are diluted to an appropriate concentration (around 1–2 mcg kg^{-1} ml^{-1} for remifentanil) so that when a change of target or infusion rate is made, an adequate volume is delivered to ensure a quicker drug effect.

Target Concentrations

All anaesthetists are familiar with the use of expired anaesthetic gas concentration as an estimate of effect-site concentration when providing inhalational anaesthesia. This differs from TIVA users, who instead use predicted plasma concentration targets (and effect-site concentrations if using the Marsh adult TCI model or the Eleveld universal model) as programmed into and displayed by the TCI pump.

The plasma concentration will take time to equilibrate with the effect-site concentration, approximately four minutes, as a rule of thumb. The use of adjuvant drugs such as opioids must be taken into account, especially if the patient has received neuromuscular blocking drugs, and depth of anaesthesia monitoring is strongly recommended to avoid accidental awareness. If the patient is not paralysed, movement in response to stimulation gives a good indication of inadequacy of anaesthesia or analgesia, which can be adjusted accordingly.

The authors' practice is to use a mixture of propofol 1% and remifentanil 5 mcg ml^{-1} in the same syringe using the Paedfusor TCI program; a target of 3 mcg ml^{-1} is suitable for less stimulating procedures (e.g. endoscopy or MRI), whilst 4 mcg ml^{-1} is suitable for surgery requiring anaesthesia with spontaneous ventilation and a supraglottic airway device (SAD). If intubation without muscle relaxants is required (mastoid surgery), then a concentration target of 6 mcg ml^{-1} is usually adequate.

It must be remembered that these are only guides; experience with TCI TIVA is essential, and as with all anaesthetic agents there is individual variation of pharmacodynamics and pharmacokinetics requiring titration to effect.

Disadvantages of TIVA

- Injection pain with propofol, minimised by using:
  - Lidocaine 1 mg kg^{-1}
  - An appropriate dose of opioids before starting TIVA

  - Using a large bore vein
  - Using propofol 1% instead of 2% propofol for induction and then switching to 2% propofol for maintenance
- Potential for disconnection from cannula
- Drug extravasation due to high pressures from the infusion pump
- Need for infusion pumps capable of delivering TIVA/TCI
- Need for training and knowledge to use TIVA/TCI
- Risk of awareness, minimised by:
  - Avoiding muscle relaxants if possible
  - Using depth of anaesthesia monitoring
- Lipid load

Key Points

- TIVA is becoming more popular in paediatric anaesthesia, and TCI pumps with appropriate open-source paediatric software are now available.
- TCI propofol is possible for those at least one year of age.
- Blood-targeted propofol infusions may be replaced by effect-site targeted infusions as age-appropriate software is introduced.
- Techniques should be used to limit the propofol and lipid dose, and 2% propofol solutions are recommended.
- Injection pain can and should be minimised using a range of techniques.

Further Reading

Absalom A, Struys M. *An Overview of TCI and TIVA*. Academic Press. 2005.

Anderson BJ, Holford NHG. What is the best size predictor for dose in the obese child? *Pediatric Anesthesia* 2017; 27: 1176–84.

Elevel DJ et al. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. *British Journal of Anaesthesia* 2018; 120(5):942–59.

Jeleazcov C, Ihmsen H, Schmidt J et al. Pharmacodynamic modelling of the bispectral index response to propofol-based anaesthesia during general surgery in children. *British Journal of Anaesthetics* 2008; 100(4):509–16.

Kam PC, Cardone D. Propofol infusion syndrome. *Anaesthesia* 2007; 62(7):690–701.

Lerman J, Johr M. Inhalational anesthesia vs total intravenous anesthesia (TIVA) for pediatric anesthesia. *Paediatric Anaesthesia* 2009; 19(5): 521–34.

Mani V, Morton NS. Overview of total intravenous anesthesia in children. *Paediatric Anaesthesia* 2009; 20(3):211–22.

Munoz HR, Cortinez LI, Ibacache ME, Leon PJ. Effect site concentrations of propofol producing hypnosis in children and adults: comparison using the Bispectral Index. *Acta Anaesthesiologica Scandinavica* 2006; 50(7):882–7.

Tirel O, Wodey E, Harris R, Bansard JY, Ecoffey C, Senhadji L. Variation of Bispectral Index under TIVA with propofol in a paediatric population. *British Journal of Anaesthesia* 2008; 100(1):82–7.