Chapter 14

Ankle Biters

How to Use TIVA in Children

Brian Anderson and James Houghton

Introduction

Indications for TIVA in children are essentially the same as adults with the additional benefit of reducing emergence delirium and possibly cognitive dysfunction.[1,2] Fears that children may develop propofol infusion syndrome during routine anaesthesia have not eventuated.[3]

Why Are Kids Different?

Size, Age and Body Composition

Three major features separate children from adults: size, age and body composition. Size has a major impact on drug clearance (CL), the parameter that determines infusion rate at steady state.

infusion rate = CL x target concentration

Larger infusion rates are required in children to achieve the same target concentration as in adults. This is typical of maintenance dosing of almost all drugs in children and can be explained by allometric theory and its implications for clearance.[4,5] The increased clearance in children can be attributed to size factors.

$$CL_{CHILD} = \left({}^{WT}CHILD/_{70}\right)^{3/4} CL_{ADULT}$$

A standard adult weight (WT) is 70 kg. Figure 14.1 demonstrates the apparent increased clearance in children when clearance is expressed as $ml.min^{-1}.kg^{-1}$.

Age, particularly below the age of two years, also contributes to dosing estimation. Clearance pathways generally mature in the first few years of life. Decreased requirements in neonates are due to immature enzyme clearance pathways for propofol. Contrarily, remifentanil is cleared by plasma esterases and these are mature at birth.[6] Remifentanil clearance is determined by size alone and clearance, expressed as $l.kg^{-1}.h^{-1}$ (Figure 14.2), is increased in neonates compared to children.[7]

Body composition impacts on the volume of distribution. Total body water and extracellular fluid (ECF)[8] are increased in neonates and reduction tends to follow post-natal age (PNA). The percentage of body weight contributed by fat is 3% in a 1.5 kg premature neonate and 12% in a term neonate; this proportion doubles by 4 to 5 months of age. 'Baby fat' is lost when infants start walking and protein mass increases (20% in a term neonate, 50% in an adult). These body component changes affect volumes of distribution of drugs. Volume of distribution influences initial dose estimates.

loading dose =
volume of distribution x target concentration

Further, regional blood flow, body composition and body proportions vary during development, rendering PK and PD relationships more complex in children than in adults.

Organ Dysfunction

Organ dysfunction will also result in reduced requirements. The critically ill child, or one with major organ failure, needs a smaller dose of IV anaesthetic; care is particularly needed in children receiving vasoactive medication and those with congenital heart disease.[9] Titration is essential to allow for between-subject variability of PK and PD parameters.

Distribution to the Effect Site

There is usually a delay while plasma and effect sites equilibrate as the drug needs to cross the blood–brain barrier. A single first-order parameter ($T_{1/2}$keo) describes the equilibration half-time. Adult $T_{1/2}$keo values are well described and are incorporated into target-controlled infusion (TCI) pumps in order to reflect and achieve a rapid effect site concentration. $T_{1/2}$keo estimates for propofol in children are shorter

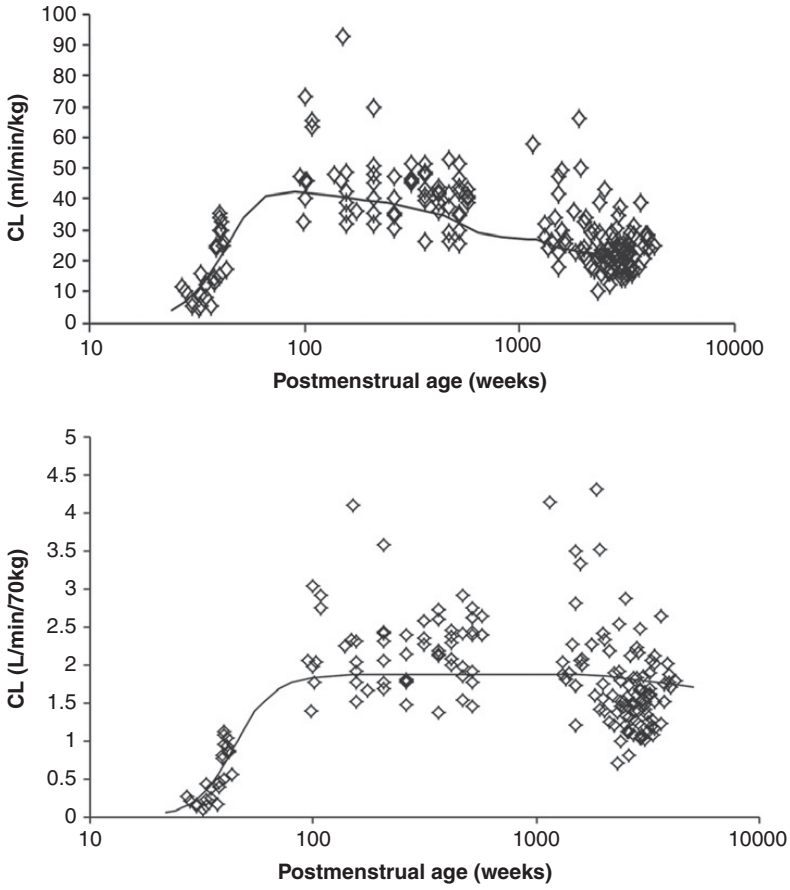

Figure 14.1 Maturation of propofol clearance using the per kilogram model (upper panel) and an allometric ¾ size model and a sigmoid Emax maturation model (lower panel). The reduced clearance in neonates is obvious in both panels. The upper panel demonstrates an increased clearance in children compared to adults when expressed as per kilogram. There is a slight decrease in clearance at old age evident in the lower panel. (Modified from Anderson, BJ. Paediatric models for adult target-controlled infusion pumps. *Paediatr Anaesth* 2010; 20: 223–32, with permission.)

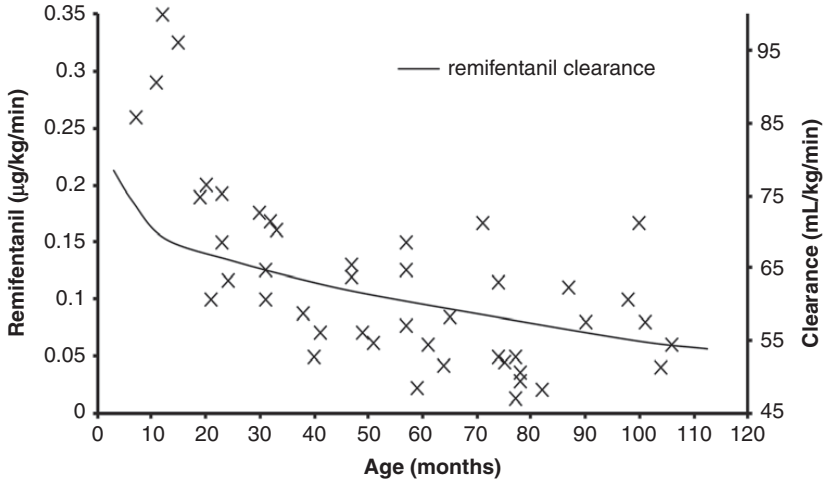

Figure 14.2 The effect of age on the dose of remifentanil tolerated during spontaneous ventilation under anaesthesia in children undergoing strabismus surgery. Superimposed on this plot is estimated remifentanil clearance determined using an allometric model. There is a mismatch between clearance and infusion rate for those individuals still in infancy. The higher infusion rates recorded in those infants can be attributed to greater suppression of respiratory drive in this age group than the older children during the study; a respiratory rate of ten breaths per minute in an infant is disproportionately slow compared to the same rate in a seven-year-old child, suggesting excessive dose. (From Anderson, BJ. *Paediatr Anaesth* 2010; 20: 223–32, with permission.)

than those reported in adults. An estimate of 1.9 minutes was reported in 2- to 12-year-old children[10] while an estimate of 1.2 minutes (95%CI 0.85–2.1) has been reported in obese children.[11]

A decreasing $T_{1/2}$keo with age (linked to weight) has been described for propofol in children.[12] If no allowance is made for this with TCI then it will result in an excessive dose in a young child if effect-site targeting is used. This will happen because an adult TCI model will 'under-read' the true value of the peak effect (T_{peak}).

See Chapter 20 for more details.

The Usual Suspects

Propofol

Pharmacokinetics

Propofol clearance matures rapidly in the first six months of life (Figure 14.1). Induction and maintenance doses of propofol are higher in children than in adults because the volume of the central compartment is 50% larger and the plasma clearance (per kg) is 25% faster in children.[13] Consequently, a higher infusion rate is required to achieve the same target concentration as adults (Figure 14.3). Clearance is limited by the hepatic blood flow and is, consequently, reduced in children in low cardiac output states. The use of allometric scaling has simplified interpretation of changing clearance values with age[14,15] and may improve programming for TCI pump delivery.[16]

Pharmacodynamics

Propofol concentrations producing sedation and anaesthesia should be similar to adults and, as with adults, can vary thereby requiring careful titration. Both the loss and return of consciousness occur at similar target effect-site propofol concentrations (2.0 +/– 0.9 $mg.L^{-1}$ vs 1.8 +/– 0.7 $mg.L^{-1}$) as in adults[17] and a 'wake-up' concentration of 1.8 $mg.L^{-1}$ is described in children.[18] The relation between drug concentration and effect may be described by the Hill equation[19] and this has been used to describe propofol[10–12] (see Chapter 20 for more details).

Pharmacodynamic estimates in both non-obese children[20] and obese children[11] are similar to those described for adults. The equilibration half-time ($T_{1/2}$keo) described for the effect compartment was 1.15 minutes,[12] but ranged from 0.21 to 2.1 minutes.[20] Children possibly have a slightly lower sensitivity to propofol than adults (Figure 14.4), although this difference may be due to PK rather than PD factors.[21] (See the discussion of the Kataria parameter set below.) Propofol can cause profound hypotension in neonates and PK–PD relationships in this age group have not been defined.[22]

Adverse Effects

Pain on injection of propofol has been markedly reduced by the advent of mixed medium-chain triglyceride (MCT)–long-chain triglyceride (LCT) propofol formulations and can be virtually abolished by the addition of 10 mg of lidocaine.[23] Paediatric studies have consistently demonstrated a reduction in systolic

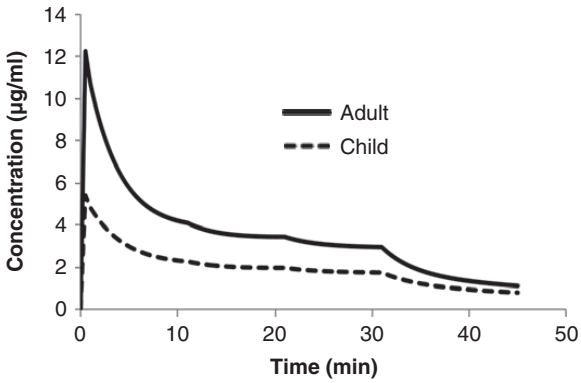

Figure 14.3 Simulated time-concentration profiles for propofol using a paediatric parameter set and an adult set. A 3 $mg.kg^{-1}$ bolus was administered and the infusions were administered as for an adult (10–8–6 regimen). Peak concentrations in the child are lower because of an increased volume of distribution. Increased clearance (expressed per kilogram) in children means subsequent concentrations also remain lower.

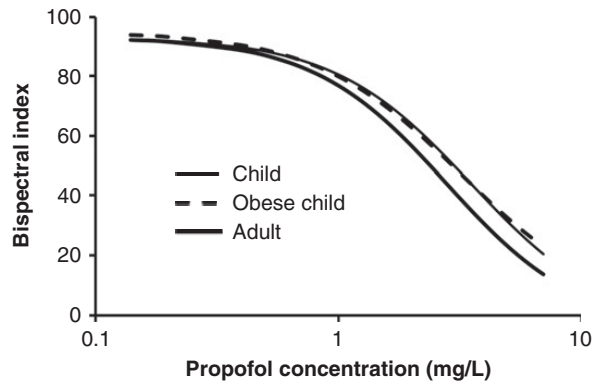

Figure 14.4 Propofol concentration and its relationship with bispectral index in children and adults. (Data from Coppens et al. *Anesthesiology* 2011; 115: 83–93 and Chidambaram et al. *Pediatr Anesth* 2015; 25: 911–23.)

and mean arterial pressures ranging from 5 to 30% occurring in the first five minutes following injection of propofol.[24–26]

The use of propofol for prolonged sedation in paediatric intensive care is associated with a rare syndrome comprising metabolic acidosis, heart failure, lipaemia, rhabdomyolysis and death. It is associated with high doses and long-term use of propofol (>4 $mg.kg^{-1}.h^{-1}$ for more than 24 hours) so is very unlikely during anaesthesia. Critically ill patients receiving catecholamines and glucocorticoids are at high risk. Treatment is supportive. Early recognition of the syndrome and discontinuation of the propofol infusion reduces morbidity and mortality. Impairment of fatty-acid oxidation by propofol is a possible cause.[3,27] The fact that this syndrome is more common in children than adults may be a reflection of the relatively higher dose requirements and consequent lipid load in children.

Remifentanil

Remifentanil has similar effects as in adults, although children may be more prone to bradycardia.

Pharmacokinetics

Remifentanil clearance can be described in all age groups by simple application of an allometric model.[7,28] The smaller the child, the greater the clearance when expressed as $ml.min^{-1}.kg^{-1}$ (Figure 14.2). Clearance decreases with increasing age, with rates of 90 $ml.kg^{-1}.h^{-1}$ in infants <2 years of age, 60 $ml.kg^{-1}.h^{-1}$ in children 2 to 12 years of age, and 40 $ml.kg^{-1}.h^{-1}$ in adults. The steady-state volume of distribution is greatest in infants <2 months of age (452 $ml.kg^{-1}$) and decreases to 308 $ml.kg^{-1}$ in children 2 months to 2 years, and to 240 $ml.kg^{-1}$ in children >2 years of age.[29]

Although co-variate effects, such as cardiac surgery, appear to have a muted effect on PK, cardiopulmonary bypass (CPB) does have an impact. Remifentanil dose adjustments are required during and after CPB due to marked changes in its volume of distribution.[30] Remifentanil plasma concentration decreases with the volume change accompanying institution of bypass and may require a bolus dose. Other PK changes during CPB are consistent with adult data in which a decreased metabolism occurred with a reduced temperature[31] and with reports of greater clearance after CPB (increased metabolism) compared with during CPB.[32] Drug infusion rates dictate clearance and should be adjusted accordingly.

Pharmacodynamics

Target concentrations vary depending on the magnitude of the desired effect and are broadly similar to adult requirements (3–5 $ng.ml^{-1}$ during surgery, up to 12 $ng.ml^{-1}$ for short periods of intense stimulation). Onset is rapid with a $T_{1/2}keo$ estimated range from 0.64 to 1.16 minutes.[28,33] Respiratory depression is concentration dependent. Muscle rigidity can also occur at high doses. The initial loading dose of remifentanil may cause bradycardia and hypotension as young children are more heart-rate dependent for cardiac output and more susceptible to this effect. An anti-cholinergic drug can prevent or treat this. This hypotensive response has been quantified in children undergoing cranioplasty surgery.[34] The steady-state remifentanil concentration that would typically cause a 30% decrease in mean arterial blood

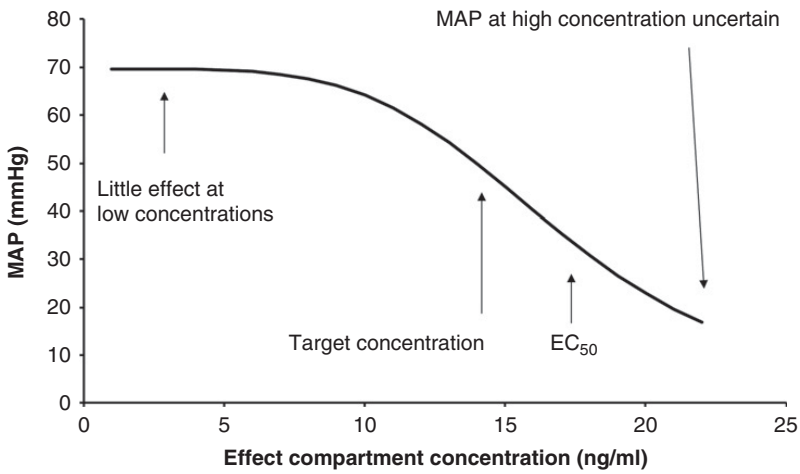

Figure 14.5 The relationship between remifentanil concentration and mean arterial blood pressure (MAP) for a typical individual. A steady-state remifentanil concentration of 14 $\mu g.L^{-1}$ would typically achieve a 30% decrease in mean arterial blood pressure. (From Anderson, BJ. *Pediatr Anesth* 2010; 20: 1–6, with permission.)

pressure was 14 ng.ml^{-1} (Figure 14.5), a concentration higher than that common in adults (4–6 ng.ml^{-1}). This concentration is, however, more than twice that required for laparotomy, but is easily achieved with a bolus injection, reinforcing the importance of using either TCI or careful manual titration.

Adverse Effects

The usual manual infusion dose of remifentanil is 0.1 to 0.5 μg.kg^{-1}.min^{-1}, as in adults. The short elimination half-time often makes a loading dose unnecessary, although boluses of 0.5 to 1 μg.kg^{-1} can be used for particularly painful events. In a multi-centre trial in full-term infants aged less than two months, remifentanil provided stable haemodynamic conditions with no new onset of post-operative apnoea.[35] Analgesic alternatives should be available for when the short-duration effect from remifentanil has dissipated. Reports of a rapid development of mu-receptor tolerance with remifentanil use are conflicting.[36] Respiratory depression is concentration dependent.[37,38] Muscle rigidity may occur when very high bolus doses above 3 μg.kg^{-1} are used in neonates.[39]

Parameter Sets (Models)

Propofol

Popular paediatric models used for propofol infusion targeting plasma concentration are based on data from Marsh,[40] Gepts,[41] Kataria,[42] or Absalom[43] (Paedfusor). Parameter estimates (e.g. CL, Q, V_1, and V_2) are different for each parameter set (see Chapter 20 for more details). Validation studies for differing models are few. The Paedfusor[43] is reported to have a median performance error (MDPE) bias of 4.1% and a median absolute performance error (MDAPE) precision of 9.7% over the age range investigated (1–15 years). A later study suggested that all except Marsh performed acceptably in children of 3 to 26 months.[44] Others have described a poor fit for Kataria, the most widely used model.[45] However, clearance (L.h^{-1}.kg^{-1}) decreases with age and MDPE is minimised at low CL and exaggerated at higher values. Evaluating models outside of the age range that they were determined from will increase bias and worsen precision.

Remifentanil

Adult remifentanil PK parameters[33] continue to be used in TCI devices for all ages, despite an increasing knowledge about this drug in children.[46] There is an element of safety with this approach because both volume of distribution[29] and clearance (expressed as ml.min^{-1}.kg^{-1})[7] decrease with age from adulthood and because the elimination half-life is small with a constant context sensitive half-time. The larger volume of distribution results in lower peak concentrations after a bolus; the higher clearance in children results in lower plasma concentration when infused at adult rates expressed as mg.min^{-1}.kg^{-1}. The smaller the child, the greater the clearance when expressed as ml.min^{-1}.kg^{-1}. Owing to these enhanced clearance rates, smaller (younger) children will require higher remifentanil infusion rates than larger (older) children and adults to achieve equivalent blood concentrations.

Monitoring in Kids

A common effect measure used to assess depth of anaesthesia is the EEG or a modification of detected EEG signals (spectral edge frequency, Bispectral Index, entropy). Physiological studies in adults and children indicate that EEG-derived anaesthesia depth monitors can provide an imprecise and drug-dependent measure of arousal. Although the numeric values from these monitors do not closely represent any true physiological entity and exhibit inter-individual variability, they can be used as guides for anaesthesia. In older children the physiology, anatomy and clinical observations indicate that the performance of the monitors may be similar to that in adults. The BIS™ showed a close relationship with the modelled effect-site propofol concentration, and serves as a measure of anaesthetic drug effect in children older than one year.[12] In infants their use cannot yet be supported in theory or in practice.[47,48] During anaesthesia, the EEG in infants is fundamentally different from that in older children; there remains a need for specific neonate-derived algorithms if processed EEG monitors are to be used in neonates.[49,50] Despite limitations in infants, BIS™ is useful in older children particularly when neuromuscular blocking drugs are used.

A Practical Approach in Children

Mastery of TIVA requires familiarity with the technique. Such familiarity can be gained by practice with healthy adults and older children before progressing to those younger. Familiarisation using children on

elective, non-urgent surgery, preferably without muscle relaxants, where a known stimulus will be supplied is best. Surgical colleagues may be more co-operative if you explain the advantages of TIVA.

Drug Delivery

Secure IV access is essential. A dedicated line is not necessarily required as long as there is access to the IV cannula being used. Luer lock syringes reduce the risk of poor or leaky connection. Infusion lines should be placed as close as possible to the venous cannula to minimise dead space. The set-up should not allow retrograde infusion of propofol up a fluid-giving set, so one-way, non-return valves are essential if connected to a fluid infusion line. Percutaneous intravenous central catheters (PICC) may be unsatisfactory because high infusion rates are not possible. Combined infusions into a single vein run the risk of inadvertent bolus of a companion drug but this shouldn't be a problem if the lines are close to the cannula. Anaesthesia for major surgery may be best served using central venous access, diminishing the risk of undisclosed subcutaneous infusion.

TCI parameter sets (models) available for use in children generate different plasma propofol concentrations. It is important to be aware of these differences, especially with regard to initial loading dose, and it is best to get familiar with one parameter set and then use it routinely. Consequently, it is important to be aware of the performance of the infusion pump you are using, the particular parameter set installed and its appropriateness for a given clinical scenario, and make sure pumps are serviced regularly. Unrecognised pump failures can occur with subsequent patient awareness and so vigilance is required. If problems with anaesthesia occur, then the prudent thing to do may be to convert to an inhalational anaesthetic technique if clinically appropriate.

Infusion Regimes

In general TCI pumps deliver propofol more accurately than manual regimes, result in better haemodynamic stability, use a lower induction dose and facilitate improved recovery time. If a dedicated TCI pump is available, then it should be preferred over a manual regime. Loss of consciousness requires careful titration and propofol effect-site concentrations are around 2 to 3 $\mu g.ml^{-1}$. In contrast with adults, paediatric anaesthetists tend to start with a higher target concentration (4–6 $\mu g.ml^{-1}$) in infants and titrate down rather than up. This is to stop small children moving and struggling during induction (faster onset) but there is merit in titrating up if possible.

Most TCI models are inaccurate for some ages within their specified age ranges[20,43,44] or in scenarios where parameter estimates have not been tested (e.g. children in intensive care or with neuromuscular disease undergoing scoliosis surgery).[51] Clearance (per kg) is increased as age decreases in children (allometric theory). The Kataria parameter set is known to under-predict concentration as age increases. When this parameter set is used to estimate PD parameters, it appears that the older children require a lower concentration to maintain anaesthesia;[21] this is because of the pharmacokinetics and is not a PD effect.[52]

The adult models may be more accurate than either the paediatric Kataria,[42] paediatric Marsh[40,41] or Schuttler[53] models in children weighing more than 35 kg.[45] The Kataria TCI model is plasma targeted and is valid for children from 3 to 15 years, weighing 15 to 65 kg. For children under three years of age Steur et al.[54] have produced a manual regime. Neonates are susceptible to hypotension with propofol[22] and it is advisable to gradually increase the infusion rate until anaesthesia is achieved rather than starting at a high rate.[55] Manual regimes have also been produced to mimic Kataria plasma targeted infusion for 3 to 6 $\mu g.ml^{-1}$.[56,57] One approach to the use of propofol regimes in children for TIVA is shown in Table 14.1.

Table 14.1 Possible weight-based propofol regimes in children.

Weight	Infusion scheme
>50 kg	Adult TCI pump Roberts manual plasma concentration '10–8–6' regimen
>35 kg	Schnider effect-site concentration model Paedfusor with parameter modification (13–16 years)
15–35 kg	Kataria plasma concentration model or McFarlan manual plasma concentration regimen (3–11 years) Paedfusor (1–12 years)
<15 kg	Steur manual infusion regimen (0–3 years)

The Obese Child

The problems with drug dosing in obese adults also apply to children. The size metric varies with both drug and infusion type. The initial bolus may be dependent on ideal body mass while the infusion is dependent on another size metric;[58,59] propofol infusion for example relates best to total body weight scaled using allometry[11,14,15,60] while ideal body weight is a better metric for remifentanil infusion, as there is less redistribution of drug to other compartments. Skeletal muscle mass tends to increase as body fat increases and this may not be accounted for in some estimates of lean or ideal body weight. A further complication is that the calculator program (James formula) used in the Schnider model to estimate lean body mass fails in short people.[61] Solutions to this problem include putting limits on maximum weight or inventing a fictitious height, but use of a better metric such as fat free mass might be the best solution.[28,61,62] Investigations using normal fat mass[63] as a size metric suggest that the appropriate 'size' may differ for each drug. These dose calculation problems can be circumvented by setting the target concentration lower (e.g. propofol 4 $\mu g.ml^{-1}$ rather than 6 $\mu g.ml^{-1}$) and then titrating to effect. The use of a processed EEG monitor such as BIS can be helpful.

Remifentanil as an Adjunct

Remifentanil adds a degree of 'smoothing' even in those children who require sedation only (e.g. for radiological imaging). Propofol is not an analgesic and the addition of remifentanil is very important to attenuate surgical stimulation.[64] It also modestly reduces the propofol target concentration for loss of consciousness.

Figure 14.2 demonstrates the remifentanil infusion rates that will maintain spontaneous respiration rate of around ten breaths per minute. Use of the adult Minto parameter set for remifentanil infusion in children confers a degree of safety because concentrations measured will be lower than those predicted, due to the higher clearance (expressed as per kilogram) in children. Occasionally some respiratory support may be required and that is easily done using pressure support ventilation. Controlled ventilation is required when high target concentrations of remifentanil are used. Very high effect-site remifentanil concentrations (>10 $ng.ml^{-1}$) are associated with hypotension (Figure 14.5) and this property can be used advantageously during some neurosurgical procedures.[34]

Injection Pain with Propofol

Propofol injection pain can be a problem in small children with small-gauge IV lines in the small veins of the hands or feet. Perhaps the best approach to reduce injection pain is to place a larger bore cannula in a large vein. Lidocaine 1 $mg.kg^{-1}$ placed in the IV line with a proximal tourniquet left on for 30 to 60 seconds is useful in reducing injection pain. Opioid administration before propofol injection is also helpful. This can be best done by beginning the remifentanil infusion first and running it at a plasma target concentration (C_p) of approximately 2 to 3 $ng.ml^{-1}$ for two minutes (using the Minto model) before starting propofol infusion; most children and adults will continue to maintain spontaneous respiration through this short period. Alternatively, a bolus of fentanyl 1 $\mu g.kg^{-1}$ or remifentanil 1 $\mu g.kg^{-1}$ through the IV cannula is effective. MCT–LCT propofol formulations are associated with much less pain and should be used where possible.

Establishing TIVA after an Inhalational Induction

Propofol TIVA can start once gaseous induction has been performed and IV access obtained. The use of a fixed infusion rate only is frowned upon because steady-state concentrations will not be established before three to four elimination half-lives. While end-tidal inhalational agent partial pressure decreases it is reasonable to target a reduced propofol concentration of 3 $\mu g.ml^{-1}$ as an initial target and then titrate against clinical response. If using a manual regime, it is sensible to reduce the initial bolus, especially if spontaneous respiration is required; a bolus of propofol 1 $mg.kg^{-1}$ is reasonable.[65]

Manipulating Adult TCI Pumps for Paediatric Use

TCI pumps may only be programmed with adult models, especially in those institutions where children contribute the minority of patient load. These adult model parameters are programmed as per kilogram and because clearance, the main determinant of infusion rate at steady state, increases as age decreases, these TCI pumps under-estimate the infusion rate

required to maintain a target concentration. One trick to compensate for this under-estimation is to increase the target concentration sought. Clearance scales to weight in a non-linear function and can be estimated in children from adult estimates using allometry. Consequently, the target C_e can be scaled using the same logic. For example, if the target concentration is 3 $\mu g.ml^{-1}$ in an adult, the target in a 10 kg child might be 5.3 $\mu g.ml^{-1}$, a 20 kg child 4.8 $\mu g.ml^{-1}$, a 30 kg child 4.4 $\mu g.ml^{-1}$ and a 40 kg child 4.0 $\mu g.ml^{-1}$. These target C_e estimates are guides only and must be adjusted to clinical need.

A weight below 35 kg cannot be entered as a variable in some adult TCI pumps. In this situation, clearance will be reduced in those children weighing less than 35 kg but the infusion rate is too large for that reduced clearance. The entered weight could be set at 40 kg and the target concentration reduced, for example a 10 kg child 0.8 $\mu g.ml^{-1}$, a 20 kg child 1.4 $\mu g.ml^{-1}$ and a 30 kg child 2.2 $\mu g.ml^{-1}$. Such manipulations increase the risk of practitioner or pump error and manual infusion schedules may be preferable.

Practical Approaches for Some Clinical Scenarios

Spontaneously Breathing Diagnostic Procedures (e.g. Radiology Investigations)

Anaesthesia and spontaneous respiration will generally be maintained at a target of 4 to 6 $\mu g.ml^{-1}$ in the absence of opioids or other adjuncts. Pressure supported respiration using either an endotracheal tube (ETT) or a supraglottic airway (e.g. LMA™) will generally maintain normal or near normal $PaCO_2$. In the absence of pressure support, $PaCO_2$ will increase.

Spontaneously Breathing Airway Procedures without an Endotracheal Tube (e.g. Flexible Respiratory Bronchoscopy, Rigid Laryngobronchoscopy)

The aim is to maintain spontaneous respiration during anaesthesia. If induction is inhalational then an initial propofol target of 3 $\mu g.ml^{-1}$ is reasonable to maintain spontaneous respiration and then be titrated against response. If IV induction is used then a plasma target of 4 to 6 $\mu g.ml^{-1}$ is reasonable but induction should be slow, especially if using an effect target model because of the relatively larger propofol bolus used to rapidly obtain the target effect-site concentration (C_e).

Remifentanil helps dampen airway reactivity and a 1 $\mu g.kg^{-1}$ bolus followed by an infusion at 0.02 to 0.03 $\mu g.kg^{-1}.min^{-1}$ is helpful, titrating upward against respiratory rate. If using the Minto C_e TCI, then starting at an initial target of 1 $ng.ml^{-1}$ is reasonable and then titrated to effect.

Laryngoscopy and topical anaesthesia with lidocaine can be carried out following induction. If using IV induction, it pays to bide your time before performing laryngoscopy and topical anaesthesia in order to allow effect-site equilibration.

Once the procedure has commenced, reactivity can be addressed by slow increments of propofol (1 $\mu g.ml^{-1}$ C_p or C_e if using TCI or 1 $mg.kg^{-1}$ bolus if using a manual regime) and by increasing the remifentanil infusion. Further topical anaesthesia may be useful. It is generally best to avoid large boluses of propofol as this may induce apnoea.

Spontaneously Breathing Procedures with an Endotracheal Tube (e.g. Adenotonsillectomy)

Induction may be either inhalational or intravenous. Tracheal intubation can be performed once the desired C_e has been achieved or after a bolus dose has been administered. The most stimulating part of the procedure is often the mouth gag (e.g. Boyle–Davis) placement. Propofol can be increased or a short-acting opioid administered in anticipation of this response to gag stimulation. This may cause apnoea but once surgery has commenced propofol can be slowly reduced until spontaneous respiration returns.

Spontaneously Breathing Surgical Procedures with a Supraglottic Airway (e.g. Orthopaedic and Peripheral Surgical Procedures)

Induction can be inhalational or intravenous. Commence propofol with an appropriate bolus if using a manual regime or use a TCI system. Remifentanil is a very useful adjunct to prevent movement in response to surgical stimulation.

pEEG monitoring is, again, a useful adjunct to titrate propofol. Generally, children will maintain spontaneous respiration with BIS in the 40 to 60 range and a remifentanil infusion of 0.1 to 0.2 $\mu g.kg^{-1}.min^{-1}$ or an effect concentration of 3 $\mu g.ml^{-1}$ C_e using the Minto model. Spontaneous respiration may not be adequate to provide CO_2 clearance and pulmonary ventilation may be required. Remifentanil remains a useful

agent even if regional blockade has been used. It facilitates rapid induction and ready performance of the block without response to needle placement. Furthermore, it provides analgesia while the block takes effect as well as reducing tourniquet pain. With the absence of surgical stimulation due to a functional block, propofol dose can generally be reduced. Remifentanil infusion or target concentration can also be reduced to assess block function.

Remifentanil is not necessarily useful if central blockade is employed. However, it is still helpful for induction and during airway management and block placement. Infusion rates or target can then be reduced or stopped once the block is established.

Major Invasive Procedures with Intubation (General, Thoracic, Neurosurgical or Major Orthopaedic Surgery, e.g. Posterior Spinal Fusion)

Commencement of TCI or a manual regimen can be followed by neuromuscular blockade and airway management. Remifentanil blunts the intubation response. Processed EEG monitoring in such patients undergoing major surgery is prudent. This may be achieved using the actual BIS score or the processed EEG waveform, especially if under three years of age. Remifentanil is useful to reduce the total propofol dose, obtund pain and avoid delayed awakening at the end of the procedure. Analgesia can be managed with multi-modal analgesia schemes and/or regional or neuraxial blockade.

Towards the later stages of the procedure the propofol infusion may be reduced by titration against the EEG. This allows for a more rapid return of consciousness. One approach at the end of the procedure is to reverse residual neuromuscular blockade and stop both propofol and remifentanil infusions. Generally, by the time the remifentanil effect has worn off, spontaneous respiration will have returned while anaesthesia is still deep, allowing safe tracheal extubation. This is attributable to propofol's longer context sensitive half-time than remifentanil.

Common Manual Infusion Schemes

Adolescents

Adolescents can generally be grouped as small adults. A manually controlled infusion scheme designed to achieve a propofol blood concentration of 3 $\mu g.ml^{-1}$ within two minutes and to maintain this concentration for 80 to 90 minutes is widely used. It consists of a loading dose of 1 $\mu g.kg^{-1}$ followed immediately by an infusion of 10 $mg.kg^{-1}.h^{-1}$ for ten minutes, 8 $mg.kg^{-1}.h^{-1}$ for the next ten minutes and 6 $mg.kg^{-1}.h^{-1}$ thereafter.[66]

Children

Children require higher infusion rates of propofol than adults to maintain the same blood concentrations as Vd and clearance are larger. Parameter estimates reported by Kataria[42] were used to determine infusion regimens that maintain a steady-state blood concentration of 3 $\mu g.ml^{-1}$ in children aged 3 to 11 years. A loading dose of 2.5 $mg.kg^{-1}$ followed by an infusion rate of 15 $mg.kg^{-1}.h^{-1}$ for the first 15 minutes, 13 $mg.kg^{-1}.h^{-1}$ from 15 to 30 minutes, 11 $mg.kg^{-1}.h^{-1}$ from 30 to 60 min, 10 $mg.kg^{-1}.h^{-1}$ from 1 to 2 hours and 9 $mg.kg^{-1}.h^{-1}$ from 2 to 4 hours was proposed. The context sensitive half-time in children was longer than in adults, rising from 10.4 minutes at 1 hour to 19.6 minutes at 4 hours compared to adult estimates of 6.7 minutes and 9.5 minutes, respectively.[56] Subsequent clinical assessment of the infusion regimen's performance was acceptable.[57] It is prudent to avoid the use of neuromuscular blocking drugs, if possible, in order to assess clinical response.

Infants

Clearance is reduced in infants and we might anticipate reduced infusion rates at steady state in this population. Infusion rates for children under three years of age, based on clinical experience from a pilot study of 50 patients, were used to develop dose regimens that were then evaluated in 2271 children undergoing anaesthesia with mechanical ventilation. Infusion changes were made every 10 minutes, similar to that proposed by Roberts in adults.[66] These are shown in Table 14.2. Few adverse effects were recorded (bradycardia 12%, blood pressure fall 8%, desaturation 1% which were easily countered by routine measures.[54] An alternative model and regimen for neonates and infants that uses less propofol has been recently published.[67]

Ready Mixes

Individual anaesthetists often have their own recipes using fixed drug mixes for some clinical scenarios. These have the advantage of simplicity but lack the

Table 14.2 Propofol dose requirements in children under the age of three years. Infusion rates are $mg.kg^{-1}.h^{-1}$. (Adapted from Steur et al. Dosage scheme for propofol in children under 3 years of age. *Pediatr Anesth* 2004; 14: 462–7.)

Time (min)	0–3 months	3–6 months	6–9 months	9–12 months	1–3 years
0–10	24.3	19.7	15.3	14.8	12.1
10–20	20.4	15.2	12.3	11.9	9
20–30	15.1	12	9	9	6
30–40	12	9	6	6	6
40–50	9	6	6	6	6
50–60	6	6	6	6	6

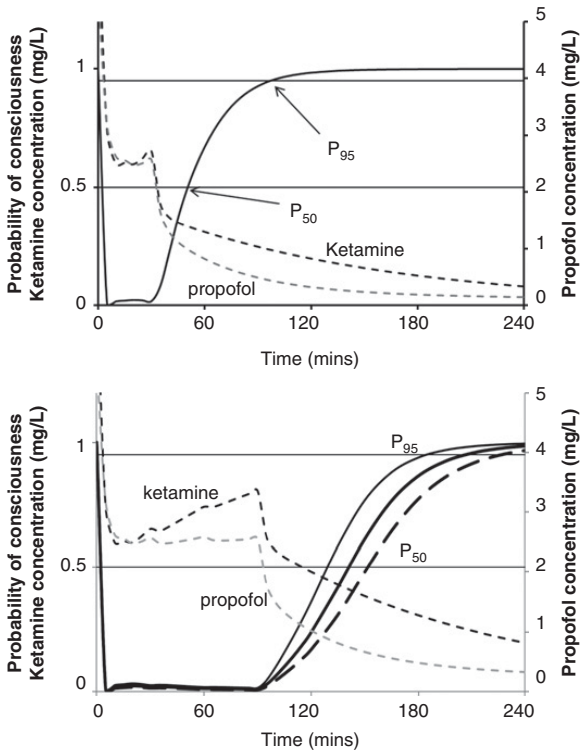

Figure 14.6 The upper panel shows the probability of response during anaesthesia using a propofol:ketamine ratio of 5:1. The loading dose for induction of anaesthesia was 2.5 $mg.kg^{-1}$ propofol and 0.5 $mg.kg^{-1}$ of ketamine. Infusion rate was 67% of that suggested by McFarlan.[56] The lower panel shows simulation results for a 90-minute infusion. This panel also shows the probability of response as age increases from a two-year-old (thin black line), to a five-year-old (bold black line) and for a ten-year-old (bold black hash line) child. (From Coulter, FL. *Paediatr Anaesth* 2014; 24: 806–12, with permission.)

versatility of separate infusions. There can be reluctance to make up such infusions by hospital pharmacies because of concerns about stability and the lack of clinical studies documenting these mixtures.

'Ketofol' is a mixture of ketamine and propofol (1:1) that is finding a niche for procedural sedation in the emergency room.[68] Stable haemodynamics, analgesia and good recovery are reported.[69] The additive interaction for anaesthesia induction in adults has been reported.[70] These data have been used to simulate the effect in children.[71] Optimal ratios of racemic ketamine to propofol of 1:5 for 30 minutes' anaesthesia and 1:6.7 for 90 minutes' anaesthesia were suggested (Figure 14.6).[71] The 'ideal mix' for sedation will depend on the duration of sedation and the degree of analgesia required. The context sensitive half-time of ketamine increases with infusion duration, resulting in delayed recovery.[72]

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