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## FOCUS ON: PAEDIATRIC ANAESTHESIA

## Total intravenous anaesthesia in children

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## S U M M A R Y

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The use of total intravenous anaesthesia (TIVA) in children has become a popular technique for the induction and maintenance of anaesthesia following the introduction of newer short-acting drugs and more elaborate delivery systems. Advances in microprocessor technology and increased complexity of pharmacokinetic modelling have further refined TIVA to target controlled infusions (TCI). TCI delivery systems offer a continuously variable rate of intravenous drug administration, conferring advantages including greater haemodynamic stability, a stable depth of anaesthesia, and a rapid recovery with a low incidence of post-operative nausea and vomiting. This review will describe the development of TIVA and TCI for paediatric anaesthesia, the pharmacology of the common agents used, and possible future directions for the use of TIVA.

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## 1. History of TIVA

Initial experimentation of propofol solubilised in Cremophor in the late 1970s found a high incidence of anaphylaxis,<sup>1</sup> prompting the search for an alternative carrier medium. This led to the introduction of lipid emulsion propofol into anaesthetic practice for induction of anaesthesia, rapidly followed by reports describing the use of propofol infusions for the maintenance of anaesthesia,<sup>2</sup> the term TIVA being subsequently applied to this technique. The apparent advantages of this rapidly titratable anaesthetic technique with a favourable recovery profile led to the exploration of pharmacokinetic models to account for the distribution of propofol. Increased understanding facilitated the development of guidelines for the manual administration of propofol by intravenous infusion to induce and maintain general anaesthesia in adult practice.<sup>3</sup> The concept of a “target” plasma concentration for propofol was introduced in 1989, heralding the development of TCI systems.<sup>4</sup>

Despite the rapid evolution of TIVA and TCI for the maintenance of anaesthesia in adults uptake into paediatric practice was initially limited. The original systems for children were based on adult models, developed primarily using indirect methods of anaesthesia depth monitoring in correlation with plasma propofol concentration measurement in the research environment. Fundamental differences in propofol distribution and metabolism in children prevent the direct extrapolation of adult models demanding the development of paediatric pharmacokinetic models for propofol infusions. Scope for further research was also hampered by reports of unexplained fatal acute myocardial failure, metabolic acidosis

and rhabdomyolysis in children sedated with propofol in intensive care units. Subsequent confirmation of a significant association, though importantly not causation, limited development of TIVA in children.<sup>5</sup> Further experience with this agent in the critical care setting has demonstrated that such adverse events are extremely rare when propofol is administered within the recommended dosage guidelines of less than 4 mg/kg/h for a maximum of 48 h.

## 2. Pharmacology

A highly lipophilic hypnotic agent presented as an emulsion for clinical use is 2,6 di-isopropylphenol. After intravenous administration of a bolus of 3–5 mg/kg loss of consciousness due to drug delivery to the central nervous system (CNS) reliably occurs within 30–60 s. As the CNS is the target organ for the hypnotic action of propofol it is termed the “effect site”. The time taken for the effect site propofol concentration ( $C_e$ ) to equilibrate with the plasma propofol concentration ( $C_p$ ) following a bolus loading dose is the equilibrium constant around 4 min. A bolus dose is effectively an infusion given at a very high rate for a short period of time. Most commercial TCI infusion devices deliver the loading dose of propofol at a rate of 400–1200 ml/h. It can be observed that even though a wide variation of  $C_p$  is seen when the rate of the loading dose is varied, there is a minimal variation in  $C_e$ . This information allows the anaesthetist to tailor the rate of induction to minimise undesirable effects of a rapid bolus of propofol, for example respiratory depression in a patient with anticipated difficult airway management, by slowing the infusion rate of the loading dose without significantly affecting the time to effective anaesthesia. The difference between  $C_p$  and  $C_e$  following a loading dose at variable infusion rates, and the time to  $C_e:C_p$  equilibrium are shown in Fig. 1.

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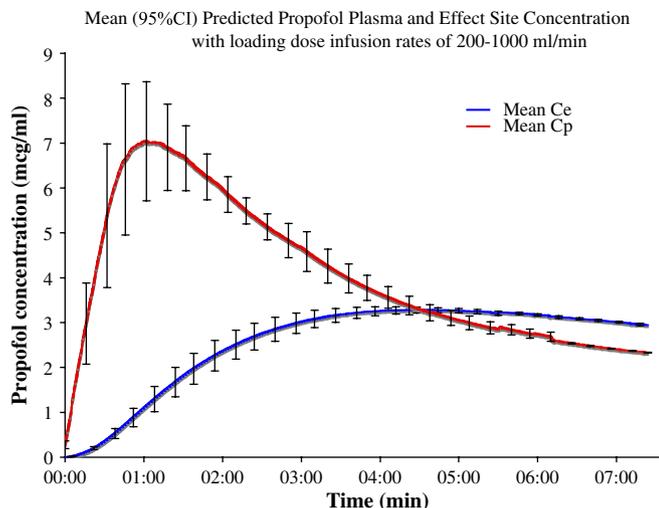


Fig. 1. Predicted  $C_e$  and  $C_p$  following a loading dose of 5 mg/kg in a 20 kg child, with loading dose infusion rates of 200–1000 ml/h.

With continued propofol infusion, redistribution occurs to the vessel rich and vessel poor tissues, termed shallow and deep peripheral compartments, which have equilibrium constants of 30–45 min and 3–63 h respectively. Propofol metabolism is primarily by hepatic glucuronide conjugation, with renal excretion of the conjugates. This is an extremely high capacity flow independent system, with a plasma clearance of up to 50 ml/kg/min. Propofol may reduce its own metabolism at high doses, as cardiovascular depression may reduce hepatic blood flow to such an extent that clearance becomes flow dependent.

The pharmacodynamic effects of propofol on the cardiovascular and central nervous systems in children have been extensively documented previously.<sup>6,7</sup> Hypotension is less marked in children, though caution should be exercised in patients with cyanotic congenital heart disease. The effects of a propofol bolus on the respiratory system are less well described in children but it is known that propofol causes a dose-dependent depression of minute ventilation<sup>8,9</sup> which is mediated by blunting of the chemoreceptor response to PaCO<sub>2</sub>.<sup>10</sup>

### 3. Principles of TIVA

The attractive concept of a drug delivery system which offers a continuously variable rate of propofol infusion led to the development of pharmacokinetic models, these being mathematical expressions which relate the administered dose of drug per unit time to the plasma concentration achieved. This is dependent on the rate of transfer of propofol between various theoretical “compartments” of the body. Rather than discrete organs, these compartments are groups of tissues or organs with similar blood flow and lipophilicity. Following an intravenous bolus, propofol is immediately distributed from the vascular pool to the highly perfused tissues, the brain being the key target organ for clinical effect, but this compartment also including the liver. On completion of bolus administration, the fall in plasma levels generates a concentration gradient resulting in rapid redistribution from the CNS to organs with intermediate perfusion, mainly the abdominal viscera and muscle tissues. Finally, distribution to the poorly perfused but extremely high capacity adipose tissues occurs. This compartmental concept explains the rapid onset and offset of the clinical action of propofol despite an elimination half-life of up to 44 h and volume of distribution of nearly 4000 l.<sup>11</sup>

Integration of propofol distribution, elimination and inter-compartmental transfer is described by a tri-exponential model:

calculated by the superimposition of three separate exponential decay curves with different rate constants ( $k$ ), Fig. 2. Elimination of the drug from the body happens only via the central compartment, after hepatic or renal excretion. Despite the high clearance and rapid metabolism, it must be noted that propofol does accumulate, primarily within adipose tissue, with a context sensitive half-time (time for  $C_p$  to fall by 50% after stopping a steady state infusion) of around 20 min at 4 h, increasing to a maximum of 35–50 min after 12 h of steady rate infusion.<sup>12</sup>

The bolus-elimination-transfer (BET) principle, as described by Tackley et al., was used to develop a TIVA infusion scheme aiming to deliver and maintain a constant  $C_e$  of 3 mcg/ml.<sup>4</sup> This comprised a bolus loading dose, followed by manual adjustment of an infusion pump to deliver a decreasing rate of propofol infusion, aiming to address the tri-exponential characteristics of propofol distribution. A manual replication of this was suggested, equating to a 1 mg/kg bolus dose followed by an infusion of 10 mg/kg/h for the first 10 min, 8 mg/kg/h for the next 10 min, and then 6 mg/kg/h thereafter. This regime delivers a bolus to rapidly raise effect site concentration inducing loss of consciousness, an initially high infusion rate to maintain adequate plasma concentrations during the early rapid redistribution phase, and a subsequent lower infusion rate to prevent accumulation of propofol and delayed recovery. This concept has been validated by several groups, although to date there continues to be disagreement regarding the exact equilibrium constants. The largest study, performed by Schüttler et al.,<sup>14</sup> analysed propofol concentrations in over 4000 plasma samples, and whilst generally concurring with previous work, concluded that a significant variability existed in compartment volumes and half-lives.

### 4. Principles of TCI anaesthesia

TCI infusion pumps are computer controlled syringe drivers which aim to electronically replicate the principles of the BET regimen by constantly adjusting the infusion rate to maintain the desired  $C_p$  as selected by the anaesthetist. These devices deliver a similar initial bolus and high infusion rate, but as the duration of infusion increases, the rate of propofol delivery automatically progressively reduces to prevent excess accumulation. In healthy children, the volume of distribution is about 50% larger than in adults and the clearance can be up to twice that in adults.<sup>15</sup> However, differences in the cardiac output, affecting primary compartment distribution and subsequent delivery to the liver and kidney accelerating elimination, must be considered. Despite paediatric models delivering a higher loading dose, the time to peak plasma propofol concentration has been demonstrated to be significantly longer in children than in adults, at 132 compared with 89 s ( $p > 0.01$ ).<sup>16</sup> One of the most widely available devices is the Graseby Diprifusor® (Fig. 3), which employs algorithms described by Kenny<sup>17</sup> and Marsh.<sup>18</sup>

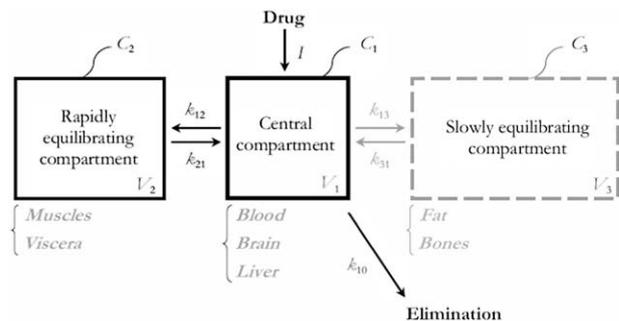


Fig. 2. Three-compartment distribution model and rate constants, adapted from Glass et al.<sup>13</sup>



Fig. 3. Graseby Diprifusor<sup>®</sup> TCI device loaded with a pre-filled propofol syringe.

The accuracy of TCI delivery for many intravenous anaesthetic drugs, including fentanyl, alfentanil, sufentanil, remifentanyl, propofol, etomidate, thiopental, midazolam, dexmedetomidine, and lidocaine has been demonstrated.<sup>19</sup> There are two mechanisms by which TCI devices can account for biologic variability. Firstly, TCI devices may incorporate patient covariates such as weight, height, age, sex, liver function, or cardiac output into the pharmacokinetic model. Secondly, the pharmacokinetic property of drug redistribution and accumulation in peripheral tissues is compensated for by adjusting the infusion rate. As a result of the pharmacokinetic modelling of tissue accumulation, setting a particular target propofol concentration on a TCI device typically results in achieving a predictable steady concentration in the patient. In contrast, manually setting a particular rate on a conventional infusion pump results in increasing drug concentrations over time as drug accumulates in peripheral tissues.

The original Diprifusor<sup>®</sup> algorithms were designed to target plasma drug concentrations. As the plasma is not the effect site of the drug control of  $C_p$  is not necessarily an optimal target. More recently, pharmacokinetic-pharmacodynamic models have been developed that predict the concentration of propofol at its site of action in the brain, this being termed the effect site concentration.<sup>20</sup> The Paedfusor<sup>®</sup> model, which has been specifically developed and validated for children, is designed to predict the effect site concentration and provide a concentration–effect relationship with greater accuracy with regard to clinical responses.<sup>21</sup> Recently infusion devices have become commercially available in Europe that allow  $C_e$  targeting based on the Paedfusor<sup>®</sup> model using generic propofol syringes, for example the Alaris PK syringe driver, Fig. 4.

The performance of TCI devices is gauged using a number of characteristics. The median performance error or bias (MDPE) represents the direction (over or under) of the error in the predicted concentration when compared to the actual measured value and the wobble measures the potential of the infusion system to maintain a constant setpoint. The MDPE and median value for wobble of the Paedfusor<sup>®</sup> system were found to be 4.1% and 8.3% respectively compared to the measured plasma concentrations.<sup>21</sup> Put into perspective these were less than those found in adult studies using the Diprifusor<sup>®</sup> TCI system, where values for bias are of the order of 16%,<sup>22</sup> and that end-tidal volatile agent concentration has a bias of around 20% compared to arterial isoflurane or halothane concentrations.<sup>23,24</sup>

TCI systems can thus be used to increase or decrease the depth of anaesthesia, by altering infusion rates to achieve the chosen effect site concentrations. A natural extension of this capacity is to predict time to awakening from anaesthesia, which many TCI infusion devices also display. Accurate prediction of recovery prevents unnecessary administration of drug, improves safety by facilitating rapid return of protective airway reflexes and



Fig. 4. Alaris PK syringe driver, loaded with generic propofol, with an indication of both  $C_p$  and  $C_e$  on the display: the solid line representing the predicted  $C_p$  and the dotted area representing  $C_e$ .

contributes to the efficiency of the operating suite. Recovery from propofol anaesthesia following discontinuation of an infusion depends on  $C_e$  declining to an “awakening value”. The time taken to reach an awakening  $C_e$  depends upon the steady state  $C_e$ , the CSHT, and the individual awakening  $C_e$ . The CSHT for propofol is longer in children than in adults due to the larger volume of distribution.<sup>15</sup> This, combined with the greater inter-individual pharmacokinetic variability in young children makes it more difficult to predict when children will emerge from anaesthesia. TCI models can accurately estimate the time required for  $C_e$  to decline to a particular level; however, the exact  $C_e$  at which children will awaken is not yet known. An example of the estimated  $C_e$  values and the clinical plane of consciousness these correspond to are shown in Table 1.

In clinical practice the models determine the estimated volumes of distribution for each of the three compartments, and calculate the loading dose, post-induction infusion rate and maintenance infusion rate based on operator input values for weight and age. These calculations relate to algorithms assuming relatively constant volumes of distribution and equilibrium constants dependent on body mass, which may be prone to error in patients with extremes of body habitus for the actual body mass. It has been recommended that lean body weight should be used for these calculations.

## 5. TIVA in paediatric anaesthesia

The advantages of intravenously infused propofol over conventional volatile anaesthetic agents used in children are quicker recovery,<sup>25</sup> reduced nausea and vomiting,<sup>26</sup> decreased post-operative delirium,<sup>27</sup> and less environmental pollution.<sup>28</sup>

Table 1

Propofol  $C_e$  and clinical stages of anaesthesia in adults. The exact values in children have not yet been described

Target $C_e$ (mcg/ml)	Plane of anaesthesia	Clinical application
<0.5	Light sedation	Insertion of invasive pressure monitoring lines Adjunct to awake fibre-optic intubation
0.5–1.5	Heavy sedation	Radiological imaging or endoscopic interventions Sedation for surgery under regional anaesthesia
1.5–3.0	Light anaesthesia	Anaesthesia for surgery with analgesic adjuncts
4.0–6.0	General anaesthesia	Anaesthesia for major surgery

Organ specific effects, such as reduced airway reactivity and improved post-operative ciliary function,<sup>29</sup> lower heart rate and reduced level of stress hormones,<sup>30</sup> maintained cerebrovascular reactivity,<sup>31</sup> and preserved middle ear pressure<sup>32</sup> confer significant advantages in specific clinical settings. At lower doses, propofol may also be used to maintain a level of sedation for radiological imaging or endoscopic investigations.

At present two popular systems for TIVA delivery in paediatric anaesthesia are readily available, the Paedfusor<sup>®</sup> (Marsh model) and the Kataria model. Despite widespread experimental and clinical use for over 15 years in Europe these systems are not yet licensed for use in clinical practice in North America and Canada due to concerns over the accuracy of the pharmacokinetic models. Difficulties in programming infusion devices to deliver propofol in a target controlled manner have been compounded by a lack of agreement between previously published studies. However, the reliability of both the Paedfusor and Kataria models has recently been confirmed by both mathematical modelling and clinical measurement.<sup>16</sup>

## 6. Paedfusor<sup>®</sup> TCI system

The Paedfusor<sup>®</sup> system was developed in the early 1990s as a variant of the Diprifusor<sup>®</sup> specifically for use in paediatric anaesthesia, incorporating modified pharmacokinetic models to improve the accuracy of propofol delivery. Using this system it was found that a bolus dose approximately 50% greater and maintenance infusion rates approximately 25% greater than that required for adults, on a weight basis, are required. The Paedfusor<sup>®</sup> model has been shown to have an acceptable bias with the measured plasma concentrations.<sup>21</sup> The Paedfusor<sup>®</sup> device was originally designed to deliver propofol supplied in pre-filled syringes which were “tagged”, being for single use only and which could not be refilled. The increasing availability of generic propofol over the last few years has led to the development of infusion devices that do not require pre-filled tagged propofol syringes. To facilitate the continued use of the Paedfusor<sup>®</sup> model the authors have published the pharmacokinetic data set for use with various infusion devices and generic propofol.<sup>33</sup>

## 7. Kataria model

An alternative to the Paedfusor<sup>®</sup> system is the eponymously named Kataria model.<sup>34</sup> To develop this, over 600 plasma propofol samples were taken from 53 children at various stages of induction, maintenance and recovery from anaesthesia. Kataria et al's investigation revealed that the child's weight accounted for around 25% of the inter-patient variability in the performance of the system. The authors found that standard three-compartment modelling provided reliable constants, the accuracy of which was further improved by weight, and to a lesser degree, age adjustment. The input of age and weight when preparing the infusion device allows the calculation of a tailored bolus dose and infusion rates which are validated for use in patients aged 3–16 years with a minimum weight of 15 kg.

## 8. Children under 3 years

Children less than three, and in particular less than 1 year of age have very different and more variable propofol requirements.<sup>35</sup> Steur produced a dosage scheme for propofol used as a TIVA technique in children of less than 3 years of age. After a 50 patient validation study, based on the BET principle described previously, the model was trialled in over 2200 patients over a period of 8 years. After a bolus dose of 3–5 mg/kg for induction, the maintenance infusion rates required in the first 10 min are shown in Table 2. This

**Table 2**

Manual infusion scheme for propofol requirements by age and duration of infusion, values in mcg/kg/min.<sup>35</sup>

Duration (min)	Age				
	0–3 months	3–6 months	6–9 months	9–12 months	1–3 years
0–10	405	328	255	247	202
10–20	340	253	205	198	150
20–30	252	200	150	150	100
30–40	200	150	100	100	100
40–50	150	100	100	100	100
50–60	100	100	100	100	100

demonstrates that the very high initial infusion requirements of children aged less than 3 months are twice that required by children aged 1–3 years. Similarly, the authors also found that the awakening time was approximately doubled in neonates, at around 25 versus 11 min in children aged 1–3 years.<sup>35</sup>

## 9. Established uses of TIVA

The list of areas where propofol TIVA for paediatric anaesthesia and sedation has been successfully used is comprehensive and there are now few clinical scenarios where TIVA cannot be employed. Most studies have employed controlled ventilation with or without intubation as part of the technique; however, TIVA has also successfully been used to maintain anaesthesia during spontaneous ventilation through an open airway in children, an advantage for diagnostic airway procedures where tracheal intubation impedes surgical access.<sup>36</sup> TIVA has also been administered to facilitate gastrointestinal endoscopic procedures under conscious sedation, where the favourable pharmacological profile facilitates rapid recovery and early discharge with a minimal risk of post-operative nausea and vomiting.

## 10. TIVA sedation

Advances in medical technology demand that increasing numbers of children are given sedation to facilitate non-painful investigations or for minimally invasive procedures. A large majority of these sedations in children are performed by non-anaesthetists outside the operating suite, with intensivists and emergency physicians administering over 55% of the sedation episodes, and only 19% performed by anaesthetists.<sup>37</sup> It is well documented that the risks of complications during sedation exceed those experienced during the much more controlled environment of general anaesthesia, with a 12-fold increased risk of mortality when sedation is administered outside the operating room.<sup>8</sup> It is anticipated that expanding the use of propofol TCI in this role will enhance the safety of sedation procedures in children.

## 11. Adjuncts to propofol TIVA

The modern intravenous opioid remifentanyl has a rapid onset of action, is easily titratable and is cleared rapidly by metabolism making this a useful adjunct for TIVA with propofol. Remifentanyl is an ultra short-acting potent opioid metabolised by non-specific plasma and tissue esterases. This results in a rapid clearance that is independent of renal or hepatic function and a short elimination half-life (less than 6 min in children). It has a potency 20–30 times greater than alfentanil; however, this potency also applies to its respiratory depressant effects, which are dose dependant. In combination with remifentanyl, propofol TIVA results in less CVS stimulation and the same or quicker recovery times than propofol and alfentanil.

**Table 3**Target  $C_e$  of propofol with various analgesic adjuncts

Propofol $C_e$	Nil	Remifentanil	N <sub>2</sub> O	Regional anaesthesia
Sedation	1–1.5 mcg/ml	<1 mcg/ml	N/A	<1 mcg/ml
Maintenance of anaesthesia	4–6 mcg/ml	3–4 mcg/ml	4–5 mcg/ml	3–4 mcg/ml

Several studies have demonstrated the synergistic effects between remifentanil and propofol, such that the propofol requirements are reduced. In spontaneously breathing adults, TIVA using propofol and remifentanil results in an increased incidence of respiratory depression when the rate of remifentanil exceeds 0.05 mcg/kg/min. Moreover, the combination of remifentanil and propofol has a synergistic effect on respiration at relatively low concentrations resulting in increased respiratory depression.<sup>38</sup> In children, a large variation in the dose of remifentanil tolerated while breathing spontaneously has been observed during anaesthesia for fibre-optic bronchoscopy and MRI scanning. Of note smaller children breathe well, if not even better than older children using this combined regimen.<sup>39</sup>

The pharmacodynamic synergy between propofol and remifentanil has been well described, and a dose-dependent relationship is evident. To maintain a steady state depth of anaesthesia, as defined by bispectral index values (BIS) targeted to 35, propofol target  $C_e$  fell from 4.96 mcg/ml with low dose remifentanil (2 ng/ml) to 3.0 mcg/ml with the higher dose of 8 ng/ml remifentanil.<sup>40</sup> A similar synergistic effect will be expected if patients anaesthetised with TIVA propofol have analgesic adjuncts, either inhaled nitrous oxide or regional anaesthesia, and the  $C_e$  target should be reduced accordingly. An example of dose alterations with analgesic adjuncts is given in Table 3.

## 12. Disadvantages of TIVA

Many of the disadvantages of TIVA relate to practical rather than pharmacological applications of the technique, and in general are as applicable to adult practice as paediatric patients. In most countries propofol is more expensive than volatile anaesthetic agents. A balanced argument would propose that this short term increase in cost at the point of care may be offset against savings from unplanned admissions due to post-operative nausea and vomiting in paediatric patients anaesthetised with volatile agents. Equipment costs relating to the purchase and maintenance of infusion pumps must also be acknowledged, but are unlikely to be different from acquisition costs for plenum vapourisers.

The most obvious disadvantage is the requirement for intravenous access prior to induction of anaesthesia. In elective situations where there is an inability to obtain IV access in an uncooperative infant, it would be common to defer to inhalational induction to prevent prolonged cannulation attempts. However, it is still entirely feasible to maintain anaesthesia with TIVA in this situation by commencing a TCI infusion once IV access is established and discontinuing inhalational anaesthesia. Second to this, the pain on injection from the propofol bolus on commencing the infusion may further upset the child, though this can be minimised by the addition of 0.1 mg/kg lidocaine into propofol, or the use of the newly released propofol-lipuro preparations. These issues, and the fact that the induction time from a TIVA infusion is longer than that of the traditional bolus induction, require a degree of cooperation from the patient that may not be attainable in younger infants.

## 13. Future directions

Continued and expanding interest in the use of TIVA and TCI for paediatric anaesthesia will likely see a growth in its use over the

coming years. It is likely to be applied in most areas of practice for surgical operations and interventional procedures where equipment is available. Yet there remains vast scope for the refinement of techniques available. Work continues into analysing the pharmacokinetics of propofol in children, and yet more sophisticated models may be available for infusion devices.

One of the biggest drawbacks of TIVA is the lack of feedback on drug delivery. Plasma level sampling is not possible outwith the research environment and apart from clinical parameters there is no way to confirm adequate propofol administration. The risk of awareness during paediatric anaesthesia is low, recently shown to be 0.2% with TIVA (compared to up to 5% with volatile anaesthesia)<sup>41</sup> but attempts should continue to reduce any potential risk of awareness in paediatric anaesthesia. One possible solution to this may involve depth of anaesthesia monitoring, such as the BIS monitoring system, which has been correlated well with clinical end points during propofol anaesthesia and improve overall peri-operative care.<sup>42</sup>

Titration of propofol delivery against BIS values has been shown to reduce anaesthetic use (and hence cost) without adverse events, and to reduce recovery time by up to 40% and discharge time by up to 33%.<sup>43</sup> The limitations of the use of depth of anaesthesia monitors must be recognised, with inaccuracies in BIS values seen in patients who are hypothermic following cardiac bypass or have cerebral hypoperfusion of any aetiology.

An advancement of the TIVA and BIS combination presently under development is a closed loop anaesthesia delivery system, where a TCI pump receives input from an EEG based depth of anaesthesia monitor, titrating the infusion rate accordingly. It has been suggested that these “closed loop” anaesthesia delivery systems actually perform more accurately than experienced clinicians, with a median fluctuation around a BIS setpoint of 9 BIS points, versus 16 points when humans are introduced into the loop.<sup>44</sup> Closed loop systems inherently lack anticipation, and hence the presence of a trained anaesthetist will always be required; nevertheless the release of these devices may further enhance patient safety during the delivery of total intravenous anaesthesia in paediatric practice.

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