Target controlled infusion anaesthesia in children

Wilson G
Consultant, Groote Schuur Children's Hospital, UCT
Correspondence to: Dr Graeme Wilson, e-mail: greame.wilson@uct.ac.za

Introduction

Total intravenous anaesthesia (TIVA) has grown rapidly in popularity over the last two decades in both adult and paediatric anaesthesia. This rapid increase in popularity is in part due to the widespread availability of drugs with favourable pharmacological properties and the development of new concepts in pharmacokinetic modelling, as well as advances in computer technology that have allowed the development of sophisticated anaesthetic delivery systems. This has led to refinements in blood plasma concentration targeting and dosing adjustments. A target controlled infusion (TCI) is an infusion controlled by a real time pharmacokinetic model that achieves a user defined blood or tissue concentration of a drug.

Early TCI devices did not cater for the paediatric population. Application of these early pumps in children aged 1 - 12 years resulted in plasma concentrations that were less than predicted by the adult delivery system algorithm.[1] Clearly adult parameter estimates required redefinition for target controlled concentration in younger patients. Two paediatric propofol infusion targeting data sets are now available on commercially available TCI systems in South Africa. They are based on the data sets published by Kataria et al and Marsh et al.[1,2]

Why use TIVA in children?

A recent survey of propofol infusion use by paediatric anaesthetists in Great Britain and Ireland found that only 26% used propofol infusions on at least a monthly basis.[3] Although the authors did not collect data on why paediatric anaesthetists were reticent to use propofol in children, they did speculate that the lack of availability of TCI devices, coupled with the fear of awareness, may contribute to the anaesthetists' reluctance.

The advantages of TIVA over conventional volatile anaesthetic agents used in children are quicker recovery, reduced nausea and vomiting, decreased postoperative delirium, and less environmental pollution.[4] Organ specific effects, such as reduced airway reactivity and improved postoperative ciliary function, lower heart rate and reduced level of stress hormones, maintained cerebrovascular reactivity, and preserved middle ear pressure, 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.

Basic infusion pharmacokinetics

When a drug such as propofol is administered as a bolus, the blood concentration rises to a peak. then falls as the drug is redistributed into other tissue compartments and eliminated from the body (Figure 1). If the bolus is followed by an infusion, the infusion will help maintain the plasma concentration as the drug is redistributed to other tissues and cleared (Figure 2). An infusion on its own will result in a slow increase in the blood concentration, reaching a steady state after approximately five elimination half-lives, when redistribution to other organs has ceased and clearance equals the rate of drug administration (Figure 3).

Table 1: Advantages and disadvantages of TIVA[5]

Advantages	Disadvantages
• Large ke0 in children results in very quick induction and rapid equilibration between plasma and effect site. • Rapid onset of action independent from alveolar ventilation. • Improved quality of emergence from anaesthesia. • Decreased environmental pollution. • Reduction in the incidence of postoperative nausea and vomiting. • Increased patient comfort and parental satisfaction in the postoperative period. • Propofol reduces brain metabolism and cerebral blood flow. • Method of choice in patients at risk of malignant hyperthermia and in some patients with congenital myopathies. • Propofol does not suppress somatosensory evoked potentials.	• Needs sophisticated infusion pumps. • Pain during injection of propofol. • Greater pharmacokinetic and pharmacodynamic interindividual variability. • Depth of anaesthesia monitoring using BIS/AEP has interindividual variability. • Difficult to estimate blood concentration of propofol in real time. • Difficult to monitor continuous administration of intravenous agents. • Prolonged context-sensitive half-time in children when compared to adults. • Propofol infusion syndrome.

Figure 1: Plasma concentrations of propofol following a single bolus dose.

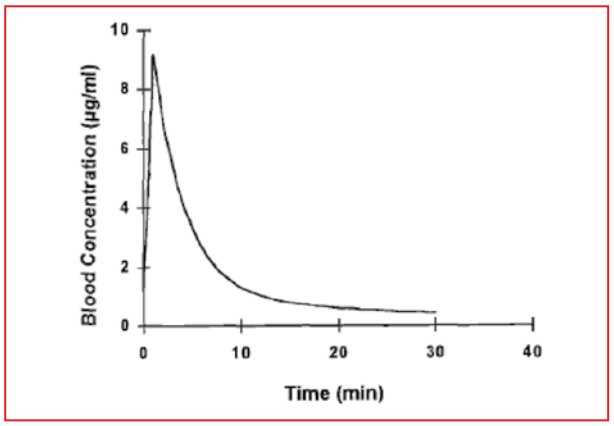


Figure 2: Plasma concentrations following a bolus and constant infusion of propofol.

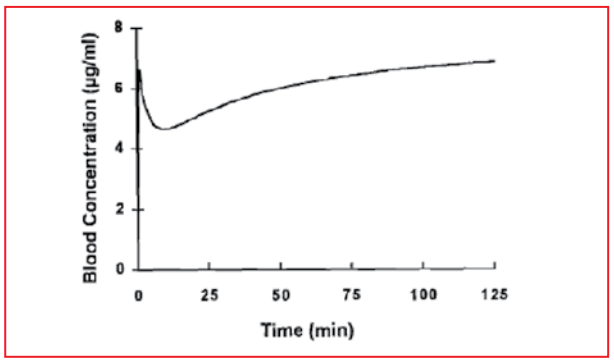
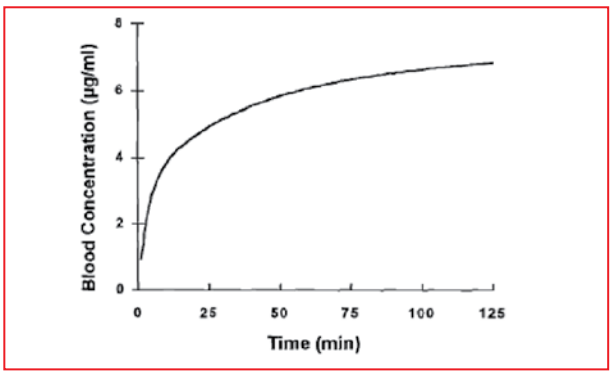


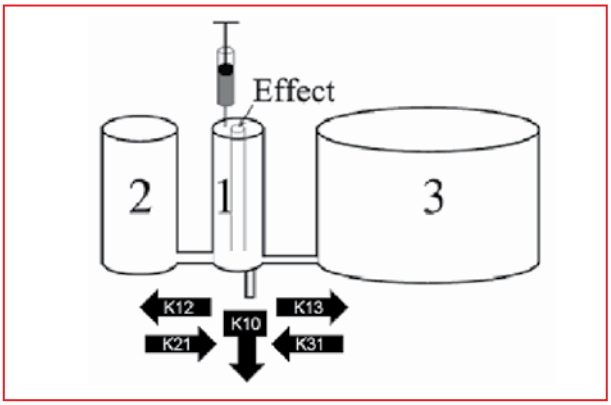
Figure 3: Plasma concentration of propofol following a continuous infusion.



These changes are best explained by a three compartment model (Figure 4). The drug is administered to the central compartment 1, represented by the blood. It then redistributes into two peripheral compartments 2 and 3, the rate of which is determined by the rate equilibration constants K12 and K13. Drug will also move in the opposite direction back into the central compartment, as described by the rate equilibration constants K21 and K31.

Clearance is described by the rate constant K10, and represents metabolism of the drug or elimination of drug from the body. The central nervous system (CNS), not the plasma, is the effect site of hypnotic and analgesic drugs. There is a delay in their onset of action as the drugs diffuse into the CNS, and this can be described by the rate constant Ke0 which represents the rate of equilibration of the plasma and CNS.

Figure 4: Graphical representation of a three compartment model



Basic principles of TCI anaesthesia

A typical TCI system consists of three main components: a user interface incorporating a display and method to input data, a microprocessor to run the pharmacokinetic modelling software and control the third component, namely the infusion device. The infusion device must be able to deliver high infusion rates, typically up to 1 200 ml/hour, within a precision of 0,1 ml/hour. When a new target concentration is selected, the TCI pump administers a bolus to rapidly fill the central compartment. The size of the bolus is calculated from the initial volume of distribution and, if applicable, the difference between the pre-existing compartment concentration and the target concentration. When the pharmacokinetic model determines that the target concentration has been reached, the infusion rate decreases. The new infusion rate will be determined by the elimination of the drug and the redistribution of the drug to peripheral compartments. As the peripheral compartments fill up with drug, the pump will recalculate the infusion rate needed to maintain a steady plasma concentration and sequentially decrease the infusion rate of the pump. Eventually, when the peripheral compartments are saturated (i.e. at steady state), the infusion rate will match the clearance of the drug. If a target concentration less than the present blood concentration is selected, the TCI pump will stop infusing drug until the target or plasma concentration has declined to the new value as estimated by the pharmacokinetic model.

The pharmacokinetic principles of TCI anaesthesia in infants and children

TCI models are not yet available for children under a year of age. Infants have immature hepatic enzyme systems, resulting in decreased metabolic elimination or transformation of drugs. This decrease in elimination significantly decreases the clearance of many drugs, including propofol. Glucuronidation is the major metabolic pathway of propofol metabolism and this pathway is immature in neonates. Multiple CYP isoenzymes, including CYP2B6, CYP2C9, and CYP2A6, also contribute to its metabolism.[6] Maturation of each of these enzyme

systems occurs independently, contributing to the complexity of predicting clearance of propofol in this group. Furthermore, maturation starts before birth, suggesting that postconceptual age is a better predictor of drug metabolism than postnatal age. The development of a TCI model for neonates and infants would require a complex equation, taking into account the postnatal age of the patient, as well as the maturation profile of the various phase 1and phase 2 reactions needed for propofol metabolism.

Pharmacokinetic modelling becomes easier in children over the age of one, when the hepatic enzyme systems can be considered mature. In children, the application of adult TCI propofol algorithms adjusted for weight results in significant underdosing.[1] This is because there are changes in cardiac output, regional blood flow, body composition, and body proportions in children when compared to adults. Children have a larger apparent volume of distribution due to their relatively large cardiac output, which results in rapid redistribution of drug away from the central compartment. The rapid redistribution of drug from the central compartment also accounts for the increased clearance seen in children. Variations in drug concentrations may be reasonably accurately predicted using allometric scaling calculations and become more accurate when age is used as a co-variate. Normal, healthy children will require a relatively larger induction dose (to compensate for the increased volume of distribution) and larger maintenance dose (to compensate for the increased clearance) to maintain the same plasma concentration of a drug as compared to an adult. The increase in induction and maintenance doses results in a large total dose in mg/kg of drug being given which, in turn, leads to a prolongation of the context sensitive half-time. Prolongation of the context sensitive half-time also accounts for the slower awakening of children following a TIVA, although children will awaken at a similar effect site concentration of propofol as adults.[7]

Effect or plasma concentration targeting

The plasma effect site equilibration rate is determined by several factors. These include the rate of delivery of drug to the effects site (cardiac output, cerebral blood flow) as well as the pharmacological properties of the drug (degree of ionisation, protein binding and lipid solubility).

The plasma-effect site concentration can be described mathematically by a rate constant usually designated Ke0. Commercially available TCI devices do not allow the user to target effect site concentrations, as the original data sets by Kataria and Marsh did not include Ke0 values for children. Ke0 values are age dependent, and adult Ke0 values cannot be used for children; the younger the child, the higher the Ke0 value for each given pharmacokinetic model.[8] The decrease in Ke0 with increasing age reflects the relative decrease in cardiac output and cerebral blood flow in children. Interestingly, despite having a higher Ke0 (suggesting a rapid onset of action of propofol), children have a tendency to an increased time to peak effect (TTPE).[9] This is probably a reflection of the differences in the front end kinetics of propofol in children, resulting in very rapid early redistribution and clearance of propofol. Including effect site targeting options on TCI devices would necessitate the addition of an age dependent Ke0, and clinicians should be cautious of devices using either a single fixed paediatric Ke0 or adult Ke0 values.

Paediatric models

Most pharmacokinetic models that could be used for paediatric TCI have been developed for propofol, namely the Kataria, Schuttler and Paedfusor models.[1,2,10] Of these models, only the Paedfusor model has been prospectively tested in TCI mode.[11]

Only the Kataria and Paedfusor models are available on TCI devices in South Africa. The reliability of both these models has recently been confirmed by mathematical modelling and clinical measurement.[9] The Kataria model has some limitations; the database was developed from a study in 53 children aged 3 to 11 years, with a weight distribution of 15 - 61 kg. The Kataria model has been validated for use in patients aged 3 – 16 years with a minimum weight of 15 kg. Extrapolation of these data to children outside these parameters cannot be recommended.

The Paedfusor model was developed as a variant of the Diprifusor model, specifically for use in paediatric anaesthesia. This model has been shown to have an acceptable bias with the measured plasma propofol concentrations in otherwise normal children undergoing cardiac surgery.[11] Further studies are presently underway to validate the performance of the Paedfusor in children under the age of 3 years.

Conclusion

Paediatric TCI is still in its infancy. No ideal paediatric TCI model exists, although the current commercially available TCI software is adequate for most healthy children above the age of 3 years. Improvement on the currently available techniques and software is essential if paediatric TCI is going to become widely accepted in everyday anaesthetic practice. Further research on pharmacodynamic-pharmacokinetic links, and especially depth of anaesthesia monitoring, in children is needed to optimise the delivery of TIVA to minimise its adverse effects and to maximise its safety.

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