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Paediatric total intravenous anaesthesia

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Key points

- Paediatric total i.v. anaesthesia (TIVA) can facilitate surgery, reduce airway responsiveness, and minimize complications such as postoperative nausea and vomiting and emergence agitation.
- Bolus doses of propofol are largely determined by the volume of distribution, while required infusion rates are predominantly determined by the clearance.
- Manual infusions remain an important option in clinical practice due to variability within and between target-controlled infusion models.
- Adjuvant agents, such as remifentanil and dexmedetomidine, play an important role in minimizing propofol requirements.
- Avoidance of neuromuscular block, and the adjuvant use of processed EEG, is recommended to aid titration and lower the potential risk of awareness.

Total i.v. anaesthesia (TIVA) has been used in adult practice since 1982 with target-controlled infusion (TCI) regimes available since 1989. Conversely, the use of TIVA in paediatric practice is far less routine with a survey finding only 10% of paediatric anaesthetists using it weekly or more.[1] It has previously been the subject of a special edition of the journal *Pediatric Anaesthesia*[2] and the use for paediatric anaesthesia care is an increasing component at international meetings: educational sessions at the European Society for Paediatric Anaesthesia (2013), ASA (2014), and the Society for Intravenous Anaesthesia meeting in November 2015.

Despite a number of obstacles (including interindividual pharmacokinetic and pharmacodynamic variability and safety concerns regarding propofol infusion syndrome—PrIS), there are notable benefits to TIVA and particular areas where it is indicated for anaesthetic or surgical reasons, where it may surpass volatile anaesthesia.[3] It is a mandatory technique when inhalation agents are contraindicated.

Indications (see Table 1)

Advantages and disadvantages

For physiological and clinical[3] reasons (Table 2), TIVA has increasingly established a significant role in surgery in or around the airway (e.g. ENT) by obtunding airway reflexes (Table 2). The changes in airway reactivity facilitate extubation and result in a minimal incidence of laryngospasm and stridor after extubation. It is readily titratable, so that spontaneous ventilation (SV) may be maintained.[4] It does not rely on the airway for delivery or on airway and pulmonary dynamics for anaesthetic maintenance. Therefore, there is no risk of ambient pollution and exposure of surgical and operating theatre staff to volatile anaesthetics when the airway is shared. TIVA has been seen to be beneficial in those with preoperative respiratory symptoms by reducing the frequency of complications.[5]

Emergence delirium (or agitation) (ED/EA) is common, especially subsequent to sevoflurane anaesthesia, and may

precipitate maladaptive behaviour, memory impairment, and problems with subsequent anaesthetic experiences in paediatric practice. Propofol use, at induction and as maintenance of anaesthesia, has been seen to reduce the risk of ED in comparison with sevoflurane.[6]

Prevention of postoperative nausea and vomiting (PONV) with propofol improves patient experience and may avoid associated complications such as dehydration, electrolyte abnormalities, and delayed discharge. The incidence of PONV in children over 3 yr is double that of adults. Propofol reduces early PONV with number needed to treat quoted as 5.53 in adult practice and is therefore felt likely to benefit children over 3 yr old.[7]

With the current concern surrounding the effects of anaesthesia on the developing brain, propofol may exert some neuroprotective effects; animal studies have shown reduced 'hypoxia-mediated increases in lactate dehydrogenase' and increased neurogenesis.[4] The reduced incidence of emergence delirium has been hypothesized to be a result of this neuroprotective effect. This is thought not to be true for the neonatal brain as propofol does cause apoptosis similarly to isoflurane and ketamine in this population in animal studies.[8]

Table 1 Indications for use or consideration of TIVA in paediatric cases

Patient	Malignant hyperthermia history, susceptibility, or risk
	Muscular dystrophy, core myopathy, or neuromuscular disease
	Previous history of PONV or motion sickness
	Risk or previous history of emergence delirium
	History of acute or chronic reactive airways
	Fear of facemask
	Minimization of allergy risk
Surgical	Airway surgery or shared airway procedures
	Requirement for evoked potential monitoring, e.g. scoliosis surgery
	Neurosurgical procedures
	Middle ear surgery
	Procedures with high PONV risk, e.g. strabismus, T&A
Procedural	Remote site anaesthesia, e.g. MRI
	Muscle biopsy for neuromuscular diagnosis

The disadvantages of TIVA in children include practical issues such as pain on injection and others seen in Table 2. If i.v. access, without undue distress, is not possible in the awake child, then a TIVA infusion may still be used for maintenance of anaesthesia subsequent to an inhalational induction once the cannula is placed. Methods of preventing the pain of injection include co-administered lidocaine (0.2–0.5 mg kg^{-1}, common practice), pre-treatment with other agents such as opioids (e.g. 0.5 μg kg^{-1} remifentanil),[9] use of a larger vein, lower initial infusion rates, or alternative propofol formulations with altered lipid content (the addition of lidocaine nullifies the differences between formulations).[7]

Overall cost-effectiveness is difficult to assess with drug costs, disposables, equipment, and patient outcomes all requiring consideration. Propofol and remifentanil have decreased in cost since their introduction and usage is inversely proportional to weight; becoming cheaper in comparison with sevoflurane or desflurane anaesthesia as weight decreases[3] (cost for 60 min: sevoflurane $54.75, TIVA 10 kg patient $2.95, TIVA 20 kg patient $5.91—unpublished hospital data).

There are concerns about awareness when TIVA is used in children, although one study has shown the risk to be lower with TIVA compared with inhalation anaesthesia in paediatric practice.[3] In the recent Fifth National Audit Project, the incidence was higher with TIVA (compared with volatile anaesthesia) in adults, but there was only one paediatric vignette, in a 15 yr old, associated with TCI propofol and neuromuscular block. The risk may be reduced by avoiding neuromuscular block and by using processed EEG (pEEG) monitoring in patients over 2 yr of age or dependent on the monitor available (monitors are not well validated in children and are not valid in infants less than age 2 yr). Caution should be exercised in the light of the recent publication regarding pEEG in awake patients.[10]

Pharmacokinetic and pharmacodynamic variability between paediatric patients,[11, 12] the effect of maturation on propofol metabolism in early life and specific issues in the critically ill, limits use; the extremely variable pharmacokinetics of propofol in neonates and the non-linear changes in both volume of distribution and clearance indicate that it should be used with extreme caution in neonates and ex-premature infants and in the critically ill with organ dysfunction. Caution is also required where vasodilatation would be hazardous, such as in the shocked child or those with certain types of congenital heart disease.

Table 2 Advantages and disadvantages of TIVA in paediatrics[3]

	Advantages		Disadvantages
Clinical	Reduced airway reactivity, laryngospasm and bronchospasm	Clinical	Risk of bacterial contamination
	Improved ciliary function		Pain on injection
	Bronchodilation and preserved hypoxic pulmonary vasoconstriction		Risk of associated metabolic phenomena; PrIS, lactic/metabolic acidosis
	Reduced emergence delirium	Practical	Need for i.v. access and infusion pump(s)
	Reduced PONV		Potential for disconnection, risk of awareness
	Use in neuromuscular disease, core myopathies		Lack of EEG monitoring availability or reliable depth of anaesthesia monitor
Practical	No interference with evoked potential monitoring		No practical, cost-effective point–of-care propofol measurement systems
	Titratable, ease of delivery via pump		
	Maintenance of SV for remote site anaesthesia	Other	Caution in prolonged procedures or obese patients due to long context-sensitive half-life of propofol
Other	No vapour atmospheric pollution		Environmental effect of plastic waste and waste propofol
	Associated with overall reduced costs		Disposables may be costly

Propofol infusion syndrome is a concern with the use of propofol for TIVA; it is associated with high propofol infusion rates (>4 mg kg^{-1} h^{-1}) for a prolonged period (usually >48 h).[7] It has been seen in the sedated intensive care unit population, but there are no reports in healthy children undergoing routine anaesthesia. Care is required in those with defects in lipid metabolism[7] or with metabolic disorders. Restricting duration, using regional or local anaesthesia and using adjunct agents (opiates, α-2-adrenergic agonists), will reduce the propofol requirement and associated potential risk. The use of a 2% propofol preparation can also reduce the lipid load; 1% and 2% solutions have 0.1 g ml^{-1} of lipid, the volume required for the same dose may be halved with the use of 2% preparation. Hospital guidelines suggest a maximum of 3–4 g kg^{-1} day^{-1} of lipid may be given to children on parenteral infusions, greater than the above rate associated with PrIS.

Pharmacology

Propofol and pharmacokinetic modelling in adults has been described recently in this journal.[13] Manual and TCI techniques in children have been described.[14] The differences in propofol pharmacokinetics in children vary with age.

- There is a larger central compartment and volume of distribution; greatest in infants and decreasing with age to adult levels. This requires a higher bolus dose and initial infusion rate.
- There is a greater rate of clearance, peaking at around 1 yr of age. This requires higher maintenance rates.

Manual infusion regimens for children, as seen in Tables 3 and 4, are markedly different when compared with adult regimens. The former, McFarlan and colleagues,[15] based on the Kataria pharmacokinetic data for 3–11 yr olds. The latter, Steur and colleagues,[16] proposed more recently for children under 3 yr of age. These suggestions cannot be applied rigidly to the clinical setting without taking into account other factors such as the level of preoperative anxiety of the child, the desired depth of anaesthesia for the specific surgical stimulus, the use of adjuvants or regional blocks, and, perhaps most importantly, the significant variability between individual children. Initial bolus doses may need to be much higher in toddlers, but then maintenance infusion rates may decrease below those of older children with increased infusion duration. In children, the dose is typically modelled as an allometric relationship (typically to the power of 0.75) between weight and volume of distribution or clearance. Maturation and organ dysfunction are also crucial covariate factors.[17] In the obese population, propofol induction doses are proportional to lean body mass, while maintenance doses are linked to total body weight.[3] Processed EEG feedback may be particularly useful for titration of anaesthesia in this population.

TCI models are commonly used for adults in Europe. Numerous paediatric TCI models have been developed but two are widely available: the Paedfusor and Kataria (Fig. 1). Paedfusor uses age and weight as covariates; it can be used between 5 and 61 kg, and 1–16 yr of age. Kataria can be used from 3 to 16 yr of age and works with a minimum weight of 15 kg.

There is a marked degree of variability both within and between population-based pharmacokinetic models; as much variation may be seen within a model as between models and so they are not generalizable. There is a good concordance with projected Paedfusor infusion rates when using typical simple manual infusion techniques.[18] The context-sensitive half-life in children has been derived to be longer than in adults; 10.4 *vs* 6.7 min after 1 h infusion, 19.6 *vs* 9.5 min after 4 h.[15] This is infrequently clinically significant, but infusion rates can be tapered towards the end of longer cases to avoid prolonged recovery times.

Anaesthetists may titrate infusion rates to traditional clinical signs of depth of anaesthesia, such as vital signs, and use pEEG for titration in lengthier cases or where neuromuscular block is required; titrating to a target and recognizing potential limitations of the monitor.[10] Investigation continues into the 'closed loop' systems where physiological data and pEEG provide feedback directly to infusion pumps with anaesthetic supervision. These systems may lead to less variability in titration of anaesthesia, lower drug requirements, improvement in haemodynamic stability, and more rapid smooth emergence from anaesthesia.[19]

Remifentanil is the ultra-fast-acting titratable opioid that has a unique synergistic effect with propofol and is a valuable adjunct. There is an associated incidence of respiratory depression with its use, but a higher dose is tolerated for SV in children compared with adults; between 0.05 and 0.3 μg kg^{-1} min^{-1}, with younger children maintaining SV more effectively at higher doses. The reduction in respiratory rate can be used as a marker for titration (see airway example), either aiming for a respiratory rate of <15 or a 50% reduction in younger children. Remifentanil can be given as a weight-based infusion or via TCI models; a weight-based infusion has an almost linear relationship between target level and infusion rate. The Rigby-Jones and Davis models are not widely available. The Minto model has a minimum weight of 30 kg, minimum age of 12 yr, and uses height as a covariate. This makes it less practical in a large proportion of the paediatric population.

Propofol and remifentanil can be combined in the same syringe in varying proportions for practicality and ease of delivery depending on the clinical situation (see example); concentrations of 2.5, 5, and 10 μg of remifentanil per millilitre of propofol are infused. They can be weaned or stopped together for emergence. The practice is endorsed by clinicians but not by regulators. The combination of agents is not recommended for patients under 10 kg or where individual agent titration is required (see Example 1).

Table 3 Propofol infusion rate recommendations in children aged 3–11 yr targeting blood concentrations of 3.0 μg ml^{-1}, McFarlan and colleagues[15]

Bolus dose Propofol infusion rates	2.5 mg kg^{-1} μg kg^{-1} min^{-1}	mg kg^{-1} h^{-1}
0–15 min	250	15
15–30 min	215	13
30–60 min	185	11
1–2 h	165	10
2–4 h	150	9

Table 4 Steur recommendation for propofol dosing in under 3 yr.[16] Doses in mg kg^{-1} h^{-1}

Time	0–10 min	10–20 min	20–30 min	30–40 min	40–100 min	Remaining time
<3 months	25	20	15	10	5	2.5
3–6 months	20	15	10	5	5	2.5
6–12 months	15	10	5	5	5	2.5
1–3 yr	12	9	6	6	6	6

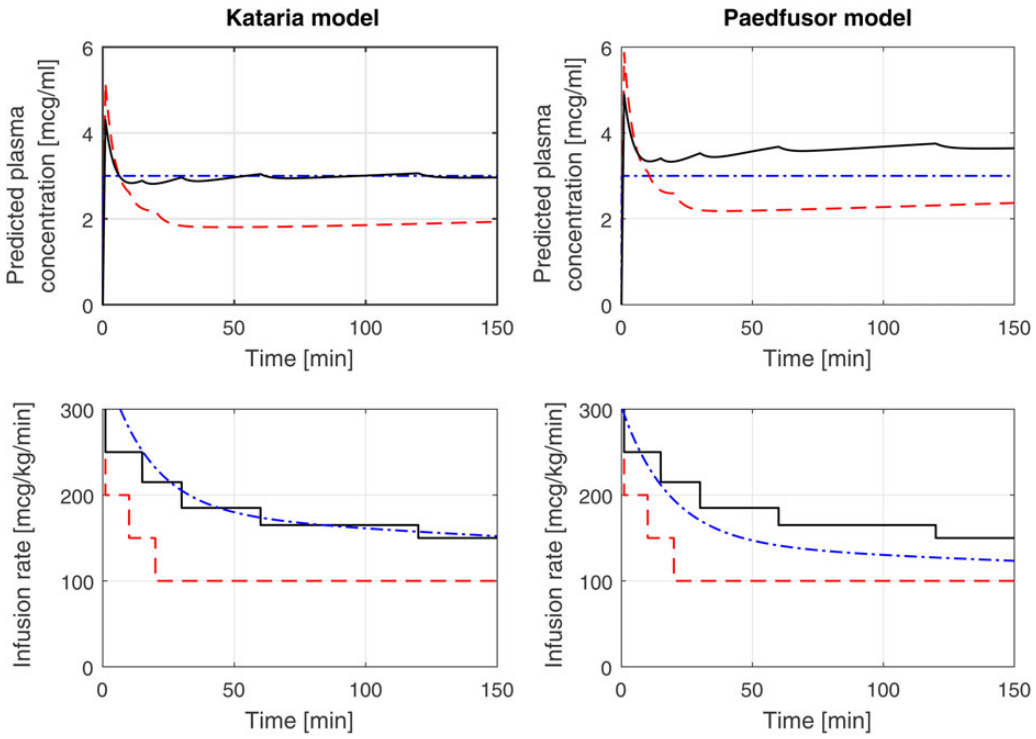

Fig 1 Modelled plasma concentrations and infusion rates for a 3 year old weighing 18 kg targeting 3 mcg/ml; using the Kataria model (left, blue) and Paedfusor model (right, blue) in comparison to manual Mcfarlan (black) and Steur (red) schemes.

Other adjuvants to consider utilizing are the α-2-adrenergic agonists, clonidine or dexmedetomidine, depending on availability. These agents have been seen to add further analgesic, sedative, and anxiolytic properties. Dexmedetomidine is around 8 times more selective but is not licensed anywhere for use in the paediatric population. Despite this, it is in increasing use and has been found to be a valuable adjunct at this centre in reducing propofol and remifentanil requirements and also further enhancing the quality of recovery.[3]

Newer agents such as fospropofol and other propofol, etomidate, and midazolam-related compounds are in development; PF0713 and AZD3043, MOC-etomidate, carboetomidate, remimazolam (CNS7056), and JM-1232.[3]

Clinical examples

(1) Airway surgery (maintaining SV and avoiding an airway device)

Coordination and communication with the surgeon is required regarding the anticipated surgical plan and the use of a ventilating laryngoscope/bronchoscope. The aim is to achieve an appropriate depth of anaesthesia with SV and the avoidance of an airway device to distort the airway or increase the risk of fire

Attach the monitoring, including a pEEG monitor. Proceed with inhalation or i.v. induction followed by separate propofol and remifentanil infusions. Titrate propofol boluses to maintain SV and then 200–400 μg kg^{-1} min^{-1} titrated against a target pEEG index of 30–40

Use remifentanil 0.2–0.3 μg kg^{-1} min^{-1} (less with increasing age) titrated to target a respiratory rate at the low end of normal for the age of the child; beware of marked tidal volume variation as this may indicate imminent apnoea. The margin between an awake and an apnoeic patient becomes narrower with age. The addition of 0.5–1 μg kg^{-1} bolus of dexmedetomidine widens this margin

Adequate topical anaesthesia of the airway is vitally important. Coordinate handover of the airway to the surgeons and provide continuing oxygenation supplementation to the spontaneously breathing patient. Minimize oxygen levels based on S p_{O_2} if laser is being used. Transcutaneous CO2 monitoring is useful if available. An accessory monitor of respiratory rate, such as a hand on the abdomen or ECG impedance, can be very useful

(2) Anaesthesia for an MRI scan

Aiming for settled conditions for MRI with a well-maintained airway and SV

Routine pre-assessment with standard monitoring attached as tolerated. I.V. cannula placement with cooperation of the parent if present. Subsequent slow, titrated i.v. induction with propofol 2–3 mg kg^{-1} (with lidocaine 0.5 mg kg^{-1}) aiming to maintain SV. Gas induction if i.v. access not possible. The use of nasal cannulae providing oxygen with carbon dioxide sampling. Attach complete monitoring if not already present. Stop sevoflurane if used. Commence propofol 1%, with 2.5 μg ml^{-1} remifentanil added, initially at 180 μg kg^{-1} min^{-1} but titrated down in response to respiratory rate

Top tips

- Patient, parent, and support staff preparation is invaluable in achieving i.v. access awake while avoiding distress to the patient or family. Distraction techniques and assistants may facilitate this.

- Similar precautions as in adults should be used;[20] reliable access, visible infusions or concurrent fluid infusion, anti-reflux valves. Infusion line dead-space should be especially minimized in children.
- To avoid pain on induction: lidocaine (before or mixed with propofol) may be administered, the rate of induction can be slowed, or use of opioid analgesia.
- Propofol alone will not provide good surgical conditions. The use of an opioid, with or without other adjuncts (e.g. dexmedetomidine), or good regional blockade will limit the required dose of propofol and improve surgical conditions.
- The use of an inhalation induction is not a contra-indication to TIVA use: techniques of conversion after inhalation induction include slower loading dose administration or starting TCI at a lower target and slowly increasing it. Beware the potential for severe bradycardia associated with administration of remifentanil after inhalational induction when there is significant residual sevoflurane present.
- Be cautious in the critically ill, or shocked, patient and those with congenital heart disease, metabolic disorders, or abnormal lipid metabolism.
- Processed EEG monitoring is a useful adjunct to aid titration of TIVA, especially for lengthy procedures and where neuromuscular block is indicated. Continue using clinical judgement and do not rely only on the infusion pump.

Conclusion

TIVA in paediatrics is an accessible technique with published advantages for the patient in terms of facilitating specific surgical procedures, optimizing surgical conditions, and reducing postoperative complications. It has previously been infrequently used, but in order to gain the benefits, it may be advantageous to develop expertise as part of paediatric anaesthetic practice. Familiarity with the technique is required when inhalational agents are contraindicated.

There is no single method for using TIVA in paediatrics. A variety of techniques can be seen in the literature and have been described at international meetings. What is safe and practical in different centres with different anaesthetists can be derived from these examples. We hope this provides a starting point for the development of individual practice with the 'top tips' and safety issues taken into account.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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