Total intravenous anaesthesia in children: a practical guide

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Abstract

Total intravenous anaesthesia (TIVA) is increasingly used for maintenance of anaesthesia in both adults and children. This article will discuss topics relevant to administration of TIVA in children – the potential benefits of TIVA, challenges and some clinical examples of its use.

Keywords Children; intravenous; pharmacology; propofol; remifentanil; TIVA

Royal College of Anaesthetists CPD Matrix: 1A02, 2D02, 2D06

Learning objectives

After reading this article, you should be able to:

- describe the pharmacology of TIVA
- discuss the benefits of TIVA in children
- recognize the limitations of TIVA

What is TIVA?

Total intravenous anaesthesia (TIVA) is the use of intravenous agents for induction and maintenance of anaesthesia. The most frequently used agent is propofol (2,6 di-isopropylphenol). Other agents used for TIVA include ketamine, midazolam, dexmedetomidine and opioids. In recent years, most TIVA systems use propofol with or without adjuvants.

Propofol is a highly lipophilic hypnotic agent formulated in a lipid emulsion and is an excellent hypnotic. Propofol has minimal or no analgesic properties, so any TIVA technique involving propofol requires a clear analgesic management plan, be that intravenous or regional anaesthesia. Intravenous analgesia is often given in the form of opioids or α_2 agonists; however, many other agents have also been used. This article will principally focus on the use of propofol alongside remifentanil.

Remifentanil is a short-acting synthetic opioid working on μ-receptors. It is highly lipid soluble and undergoes rapid blood–brain equilibration. It has an ester linkage that undergoes rapid hydrolysis by non-specific tissue and plasma esterases. This means it is does not accumulate and its context-sensitive half-time (the time for plasma concentration to fall by 50% after stopping a steady state infusion) remains fairly constant even after prolonged infusions. It is metabolized to remifentanil acid that has virtually no clinical effect. This quick offset means it is not be suitable for postoperative analgesia. The use of opioids such as remifentanil allows anaesthesia with lower concentrations of propofol.

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Pharmacology of propofol

Propofol follows a three-compartment model (Figure 1), in which anaesthesia is achieved by an initial bolus of 3–5 mg/kg. This quickly crosses the blood–brain barrier to lead to the hypnotic effect in the central nervous system (the effect site). Modern infusion pumps can deliver these bolus infusions with rates of up to 1200 ml/h.[1]

Maintenance of anaesthesia is by continuous infusion at a lower rate. The rate of infusion depends on the rate of transfer between the various theoretical compartments of the body. These compartments consist of organs with similar blood flow or lipid solubility. After the initial bolus, propofol distributed to the central compartment (C1), a very well perfused compartment including the liver and the brain. There is then redistribution to organs with good perfusion (C2), with further redistribution to the poorly perfused adipose tissue (C3) with its large volume.

The relatively quick emergence from a bolus of propofol occurs because of this redistribution into the other compartments, rather than elimination. Redistribution will be higher in healthy children than adults due to their high cardiac index. To prevent emergence, the propofol in the central compartment has to be replaced.

Elimination (clearance) is only from the central compartment and occurs after propofol is metabolized by the liver, mainly by conjugation with renal excretion of the conjugates. Because clearance is only from the central compartment, propofol does accumulate, especially in the poorly perfused adipose tissue. After a long infusion, even after stopping propofol, propofol will make its way along a concentration gradient (now reversed) from the adipose tissue back into the well-perfused tissues and continue to contribute to hypnotic effect on the brain. This increases wake-up time after a long infusion. Propofol has a context-sensitive half-time of 20 minutes after an infusion of 4 hours or up to 45 minutes after 12 hours of an infusion.[1]

Target-controlled Infusions (TCI)

Pharmacokinetic models: TCI pumps are programmed with pharmacokinetic algorithms based on parameters for compartment models (e.g. a two-compartment model might contain clearance, intercompartment clearance, central and peripheral volumes). These programs determine infusion rates to maintain a

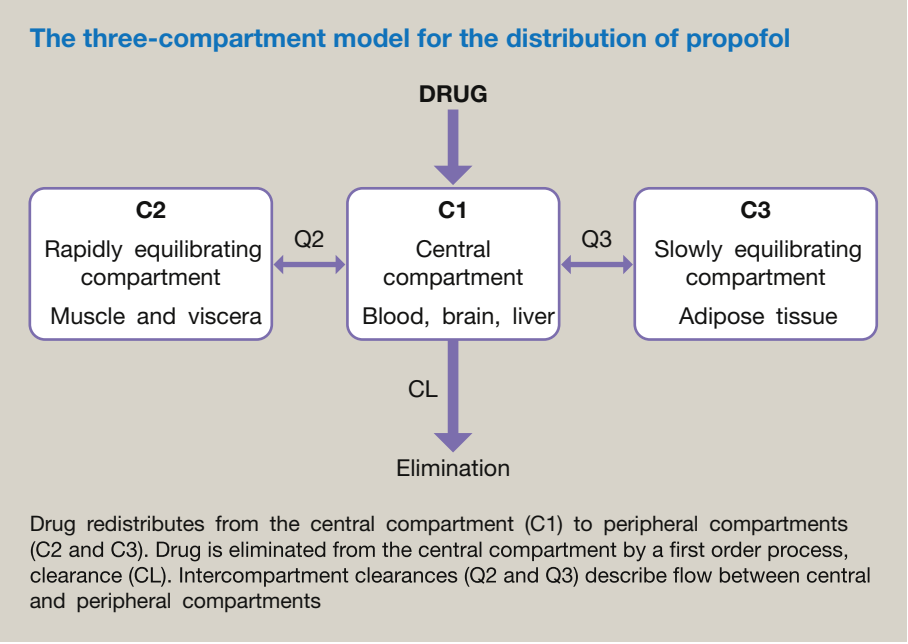

Figure 1

certain plasma concentration (Cp) or effect site concentration (Ce) in the CNS. Original TCI models were designed using pharmacological data derived from tests in healthy adults. Adult data is not suitable for children due to the increased volume of distribution and higher clearance values exhibited by children. There is now data available from healthy children over the age of 1 year; and this data has been incorporated into newer pharmacokinetic algorithms and these have been incorporated into available programmable infusion pumps. Fundamentally, children tend to require higher initial boluses and maintenance infusion rates due to having higher volumes of distribution, cardiac outputs and clearance rates, and the pharmacokinetic models recognize this and deliver these parameters within their programmes. There are to date over twenty published pharmacokinetic models for paediatrics patients; however, there is still limited data in the neonatal and infant populations where pharmacokinetics have been shown to be variable and unpredictable partly due to the immature hepatic enzyme system.[3]

Infusion regimens have been described that allowed anaesthesia and suitable operating conditions with simple manual pumps and mass-rate infusion. Making adjustments to increase depth of anaesthesia requires further boluses plus an increase in infusion rates. The introduction of TCI pumps has simplified this process. TCI pumps require patient demographics (age, weight) and then use modeling based on pharmacokinetic data to predict dose. Given the widespread availability of these pumps, we recommend their use where possible.

The most widely used paediatric pharmacokinetic parameter sets ('models') used in TCI pumps are the Kataria and Paedfusor models, although many others have been described. The Kataria model has a lower limit of 3 years or 15 kg, whereas the Paedfusor has limits of 1 year or 5 kg. They have both been widely used and seem to perform well, although the Paedfusor model has had the more extensive investigation. They may overestimate initial boluses so care should be taken especially in patients who are potentially haemodynamically unstable. Unlike most adult TCI models, these have no effect site prediction (Ce), so plasma concentration will not reflect the concentration in the brain until equilibration has occurred. This is particularly relevant after a bolus, where it may take up to 5 minutes for the Ce to be equivalent to the Cp. Therefore care should be taken to confirm loss of consciousness prior to insertion of an airway device or administration of neuromuscular blockade at the start of anaesthesia.

One challenge facing the anaesthetist is the increasing incidence of obesity in children. The dose for obese children does not increase in a linear fashion with weight. This is because there is not a linear correlation between clearance and the volume of the central, well-perfused compartment and body weight. It has been suggested that ideal body weight should be used for induction doses and then an allometric scaling factor of 0.75 on total body weight be used to calculate maintenance infusion.[2] However, the use of two weights is not practical for a TCI pump. A rule of thumb is to calculate the ideal body weight and add 20% — this additional weight aliquot takes into account the increased muscle mass that is present in obese patients.

There are TCI models for remifentanil but these have been derived from a very limited populations. The rapid equilibration means that a steady state is achieved very quickly so a selected rate can be used — a microgram per kilogram body weight per minute rate (μg/kg/min) is commonly used. A rate of 0.1 μg/kg/min will provide reasonable intraoperative analgesia while rates can be increased up to 0.5 μg/kg/min for very stimulating procedures.

Between-individual PK variability means that patients will still require different drug concentrations. TCI modelling does not make adjustments for covariates such as anxiety, concurrent opioid use or co-morbidity that may increase or decrease

requirements. Closed-loop systems that adjust infusions in response to changes in clinical measurements, using processed EEG monitors or auditory evoked potentials, are in development and may further aid safe administration of TIVA. They are unlikely to be predictive so would still need external, medical input; these are not yet available in clinical practice.

Other drugs: There are a variety of intravenous agents that can induce anaesthesia or can be given alongside propofol. Fentanyl and alfentanil both can be given intermittently or as infusions. Unlike remifentanil, they accumulate and cause increased recovery time after prolonged infusion.

Dexmedetomidine and clonidine are α_2 agonists that can be used preoperatively or intraoperatively. They have analgesic and anxiolytic effects with limited respiratory depression. However, they can cause hypotension and their sedative effect can lead to a slower, more unpredictable wake-up. Midazolam, a benzodiazepine, has good sedative and anxiolytic qualities. It can also cause hypotension and unpredictable recovery.

The use of ketamine for TIVA has the advantage of relative maintenance of respiratory function. There are manual dosing regimens available but there is no TCI equivalent for ketamine. Ketamine can cause an increase in airway secretions, although this can be counteracted by an antimuscarinic drug. The current debate around potential apoptosis in neural cells means that ketamine infusions, especially in younger children, may not be acceptable.

Why use TIVA?

TIVA has general and specific advantages over inhalational anaesthesia.[3]

Airway

Propofol reduces airway reactivity, decreasing the risk of bronchospasm or laryngospasm. Anaesthesia and spontaneous ventilation can be maintained using TIVA without requiring tracheal intubation and this makes it the preferred option for shared airway cases such as bronchoscopy or laryngoscopy. The development of high-flow humidified nasal oxygen delivery devices has further enhanced the potential for using TIVA in these cases.[4]

TIVA has a relatively predictable wake-up therefore reducing the risk of postoperative complications. The possible avoidance of neuromuscular blocking drugs further reduces the potential risk of postoperative respiratory problems.

Postoperative nausea and vomiting

There is robust evidence that TIVA with propofol lowers rates of postoperative nausea and vomiting (PONV) compared with inhalational agents. TIVA should be considered for those with a history of severe PONV or during surgery associated with high PONV rates, such as middle ear or strabismus surgery.

Emergence delirium

Propofol use with TIVA is associated with less emergence delirium than sevoflurane. Unfortunately this effect seems to be negated if a preceding gaseous induction is required before maintenance with TIVA.

Co-morbid conditions

The impact on the airway reflexes mean TIVA should be considered for those children with more reactive airways (e.g. concurrent upper respiratory tract infections or asthma).

TIVA should be used for those at risk of malignant hyperpyrexia or MH-like reactions in children with muscular dystrophies. Furthermore, TIVA can give suitable intubating conditions without using neuromuscular blocking drugs (NMBDs). This is very pertinent for neuromuscular conditions where it may be helpful to avoid NMBDs.

Propofol can cause myocardial depression but unlike volatile agents it is not arrhythmogenic.

Specific operative circumstances

Propofol reduces cerebral metabolic rate and demand for oxygen. It preserves cerebral autoregulation relatively well compared to volatiles and may offer some neuroprotective effects following brain injury. This makes it an appropriate anaesthetic for neurosurgery, particularly when dealing with raised intracranial pressure. TIVA with propofol and remifentanil displays the least interference with monitoring of sensory or motor evoked potentials making it the method of choice for spinal cord monitoring, for example during scoliosis surgery.

The portable nature of TIVA makes it an appropriate choice for anaesthetized patients requiring inter-hospital or intra-hospital transfer, for radiological investigations or for procedures that take place outside of the main operating theatre complex. TIVA can be adjusted to give safe, controlled and easy sedation for procedures such as colonoscopy or endoscopy. The maintenance of spontaneous ventilation, relative cardiovascular stability and quick recovery using propofol and remifentanil are all advantageous.

Environmental impact and cost

There are arguments about the environmental impact and cost of TIVA. TIVA requires disposables and there is an initial outlay for TCI pumps. Some of the advantages of TIVA (less PONV and better emergence) may save costs by shorter patient stays. The larger volume of disposables will have a carbon load; however, TIVA does not require any volatile agents and can be administered without nitrous oxide, avoiding their contribution to the greenhouse effect.

Potential problems with TIVA

Appropriate use of TIVA should not increase the risk of intraoperative awareness. There is believed to be a lower rate of awareness in the paediatric population. The fifth National Audit Project[5] did highlight potential difficulties with inappropriate and incorrect use of intravenous anaesthesia. The NAP5 report states that, where possible, infusions should be connected to cannulae that are visible – this can be more challenging in children due to their size relative to drapes. Where this is not possible, infusions should be connected to easily flushable intravenous lines and maintenance fluids given through a pump can give early indication of a tissued cannula. Depth of anaesthesia monitors should be considered when using TIVA with NMBDs in older children.

Propofol does accumulate with infusion duration and the TCI target concentration may be very gradually reduced during a long

case. Accumulation can lead to prolonged recovery times during long cases, especially as children require higher doses that were calculated for age bands rather than specific ages; clearance is higher in the younger children than the older children within the age band.

The modeling of TCI for neonates has not been developed. Inhalational anaesthesia, with or without a remifentanil infusion may be a more practical choice.

Propofol can cause pain on injection, especially in the initial bolus phase. This can be eased with a small amount of intravenous local anaesthetic and cannulation of as large a vein as possible.

As with many anaesthetic agents, there is a dose-dependent impairment of cardiovascular function and TIVA should be used cautiously in patients with cardiac impairment.

Propofol is presented in a lipid emulsion. This can lead to a high lipid load, especially after long-term infusions. Propofol infusion syndrome (PRIS) is defined as acute refractory bradycardia leading to asystole with one or more of: metabolic acidosis, rhabdomyolysis, myoglobinuria, lipaemia or fatty liver enlargement. Given their reduced body weight, low glycogen storage, higher fat metabolism and high sedation requirements, children are more prone to this condition. PRIS is thought to be a consequence of alterations in carnatine use by mitochondria and successful survival has been reported following replacement of this substrate, haemofiltration and critical care support.

Current guidelines suggest that propofol should not exceed 4 mg/kg/h for periods greater than 48 hours. We suggest the PRIS is another reason that TIVA should be used with caution for long duration neonatal anaesthesia or at rates greater than 10 mg/kg/h for more than 8 hours. Prolonged fasting increases the risk of PRIS, so glucose infusions may reduce the risk. Head injury and sepsis are also risk factors.[6]

How to use TIVA?

The first step administering TIVA is to secure intravenous access. Preoperative application of topical local anaesthetic alongside distraction allows intravenous access to be established in the majority of cases. The topical agent is normally well tolerated, although can cause redness and itch. If there is no obvious IV access or an attempt is unsuccessful, then gaseous induction may be required prior to securing IV access and switching from inhalational anaesthesia to TIVA. The target concentration needs to be increased gradually to avoid apnoea if spontaneous ventilation is required or if there is risk of cardiovascular instability. As the volatile agents dissipate, the target concentration can be increased to those required for surgery.

Induction does take slightly longer when using a TCI pump compared to a manual single (often larger) propofol bolus. The patient will often remain spontaneously breathing and will remain well saturated provided the airway is held open. This reduces the need for 'bagging' and potential insufflation of the stomach. Once anaesthetized, an airway device can be inserted — endotracheal intubation requiring deeper anaesthesia and a higher target concentration than a supraglottic airway. If spontaneous ventilation is a requirement, as for removal of an inhaled foreign body or for a potentially challenging airway, then the TIVA should be increased slowly, which will reduce the rate of the initial bolus. The target concentration should be adjusted during the anaesthetic in accordance with to clinical signs and magnitude of surgical stimulation. Regional anaesthesia and adjuvant analgesia can allow a lower target concentration; this manipulation is similar to how an anaesthetist would change MAC during inhalational anaesthesia. ◆

Case examples

Example 1. TIVA for microlaryngoscopy and bronchoscopy

A 3-year-old, 13-kg boy with history of recurrent stridor. He is currently well, although being investigated for laryngomalacia.

- Local anaesthetic cream applied to hands on ward
- Establish intravenous access
- Single infusion of propofol 10 mg/ml combined with remifentanil 5 μg/ml co
- Start infusion at Cp 2.0 ug/ml propofol and titrate up and down by 0.5 ug/ml to a satisfactory level of anaesthesia
- The child should remain breathing, support airway and maintain oxygenation with high flow nasal oxygen
- Topical local anaesthesia to the pharynx, larynx and subglottis with 2% lignocaine through a mucosal atomizer device
- Propofol/remifentanil infusion can be titrated throughout the procedure to maintain anaesthesia
- Oxygenation during procedure can be maintained by high-flow nasal cannula, a nasopharyngeal airway, intermittent oral oxygenation or insufflation depending on preference remembering that when using a bronchoscope an anaesthetic circuit will be required. We use high-flow humidified nasal oxygen and transcutaneous CO_2 monitoring

Example 2. Deep sedation for endoscopy and colonoscopy

A 12-year-old, 34-kg boy with history of diarrhoea, abdominal pain and weight loss. There is no history of reflux or vomiting.

- Local anaesthetic cream applied on wards
- Explain to child they may be aware of nasal prongs being applied or being positioned during case
- Establish intravenous access
- Single infusion of propofol 10 mg/ml with remifentanil 5 μg/ml combined
- Start infusion at Cp 2.0 ug/ml propofol
- Apply nasal prongs — some also allow detection of carbon dioxide
- Ask patient to turn on side
- Gradual increase rate of infusion (usually 2—4 ug/ml) until patient will tolerate gentle jaw thrust to allow insertion of bite block and then endoscope
- Infusion can be varied throughout the procedure to maintain deep sedation while maintaining spontaneous ventilation

Example 3. Target-controlled infusion for posterior spinal fusion

A 15-year-old, 50-kg girl with idiopathic adolescent scoliosis who is otherwise well.

- Oral premedication: clonidine (1 μg/kg); midazolam (0.5 mg/kg up to 20 mg); local anaesthetic cream to hands
- Establish intravenous access and attach TIVA giving set

- Intraoperative monitoring with arterial line and depth of anaesthesia monitoring
- Use Marsh model for propofol (lower age limit is 16 years)
- Start propofol at Cp off 2.0—3.0 μg/ml, titrate up to 4.0 μg/ml; this will give a slow bolus of ~150 mg
- Concurrently start remifentanil at 0.2 μg/kg/min
- Once anaesthesia induced, can give small dose of short-acting muscle relaxant (atracurium 15 mg) to facilitate intubation, while still allowing neurophysiological monitoring in 30 min
- Maintenance of anaesthesia with propofol at Cp 3—5 μg/ml (approximately 6—15 mg/kg/h) and remifentanil 0.2—0.4 μg/kg/min
- Once neurophysiological monitoring has been discontinued (normally during closing) propofol target concentrations can be gradually reduced to allow for a quicker recovery
- Volatile anaesthesia can be then be used if required to maintain anaesthesia; desflurane allows the quickest recovery
- Adminster analgesics during the case — IV paracetamol, morphine 100—200 μg/kg, further clonidine as indicated

Note: For spinal surgery, we use remifentanil at a concentration of 100 μg/ml and propofol 20 mg/ml to minimize the number of syringe changes during these long cases. The higher concentration of propofol can cause more discomfort that can be alleviated by a small dose of lignocaine (10 mg) and gradual increasing the effect concentration.

We have reported doses when using TIVA, these should be used with caution and medical acumen. As with using MAC for inhalational anaesthesia, there is significant between-individual variability so target concentration will need to be adjusted using clinical judgement.

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