South African Family Practice 2016; 58(3):S6-S9

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

NWU REFRESHER COURSE

Paediatric TIVA and TCI

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Any drug administered will have a gradual predictable decay in concentration while surgical stimuli do not follow this predictable time course. The major difficulty with anaesthesia is to accommodate these two totally different patterns to produce rapid induction, smooth maintenance and rapid emergence in concert with the varying degrees of stimuli and patient response.

At present there is no method of reliably matching the amount of drug delivered with the surgical stimulus so we have to rely on mathematical models of pharmacokinetics to determine how to give an anaesthetic hoping this is adequate for the procedure.

General principles

1. We assume the amount of drug present at the receptor is proportional to the effect that is produced by that drug.
    a. Unfortunately – the amount of drug we deliver is not equal to the amount of drug reaching the receptor and as a result is not equal to the final effect produced.
2. The concentration of any drug administered as a bolus will decay over time.
3. Drugs administered as continuous infusions will accumulate over time.
4. The rate of decay or accumulation is multifactorial depending on properties of the patient and the agent.
5. Pharmacokinetics attempts to produce mathematical models to explain the changes in concentration, decay and accumulation using the principles of absorption, distribution, metabolism and elimination.

TIVA vs TCI

TIVA

Total intravenous anaesthesia really just means that all agents are given intravenously and can be performed by bolus or infusion techniques. For the rest of this presentation TIVA will mean a manually calculated bolus and infusion anaesthetic where the anaesthetist determines the amount of drug needed to be delivered.

TCI

Target controlled infusion uses a pharmacokinetic based algorithm where the expected drug concentration in the blood is calculated and infusions of drug are contolled according to this algorithm taking into account the pharmacokinetic factors of elimination, metabolism and accumulation.

Work is being done to close the loop in these TCI systems using cerebral monitors, but due to a poor correlation between response and pharmacokinetic modelling this technology still appears to be a future development.

Some basic pharmacokinetics

Absorption

This depends on the route of drug administration – with a total intravenous anaesthetic (TIVA) all drug administered is available in the blood.

Distribution

Volume of distribution (Vd) Is the apparent volume of blood into which the drug has distributed. (Actually how much drug remains in the blood after it gets there)

This is determined by the plasma binding and lipid solubility of the agent. If a drug is protein bound it will remain in the vascular space producing a Vd similar to the total blood volume (5 litres). A lipid soluble drug will move out of the vascular space rapidly leaving a low concentration in the blood and the agent will appear to have dissolved into more than the total blood volume. (VD greater than 5 litres).

Metabolism and elimination

Metabolism and elimination are often interrelated pharmacokinetically, occurring via the liver, kidneys and enzyme pathways.

As a general guide –

- Ultra short acting agents are eliminated by blood enzymes (usually cholinesterases)

- Drugs having a short half-life are liver metabolised.
  - Rapidly metabolised drugs being dependent on hepatic blood flow
  - Slower metabolised drugs depending on liver enzyme activity.
- Drugs with a long half-life are usually excreted via the kidney.

Half-Life ($t_{1/2}$) is the time taken for the plasma concentration to decrease by 50%.

A drug is considered to be eliminated when 5 half-lives have passed after a single bolus.

Different rates of drug elimination occur after the administration of a single bolus. These can be separated into many exponential equations, but for practical purposes the 3 most important are distribution, elimination and terminal half-life.

Clearance (CL) is the volume of plasma from which the drug is removed per unit time.

In first-order pharmacokinetics the rate of elimination of drug is proportional to the amount in the body. Meaning that if administration of the drug increases so will elimination. So at **steady states** the rate of elimination will equal the rate of administration.

With multiple identical doses the concentration will continue to increase until the rate of elimination equals the rate of administration. This should occur after 5 doses.

Zero order kinetics has a constant rate of elimination despite the amount of drug in the body. (e.g. alcohol)

Applying pharmacokinetics to TIVA

Induction

3 things need to happen at induction - the patient needs to be anaesthetised rapidly, intubation achieved and a blood level of drug reached that approaches steady state to maintain the patient.

This could be achieved with a constant infusion, but it will take five half-lives to reach steady state.

A better approach is to use a bolus loading dose to rapidly get an adequate blood level of drug.

When giving a manual TIVA a simple formula to achieve this is to give a bolus dose of 2mg/kg of Propofol while starting your infusion at 10mg/kg/hour (1 ml/kg/hour).

In TCI the pharmacokinetic algorhythm takes these principles into account, giving a bolus which saturates the blood allowing the required concentration to be reached rapidly before decreasing the infusion rate to the required infusion rate.

Maintenance

After induction the aim is to get a steady state blood level of drug.

Various regimens exist using boluses or infusions. All have one thing in common. To maintain a steady state the rate of elimination of drug must match the rate of administration. Certain drugs like Thiopentone, fentanyl and to a much lesser degree Propofol start to accumulate after the initial dose is given resulting in a regimen that either increases the dosing interval or continuously decreases the dose using the same interval.

The practical approach to this differs for TIVA and TCI

TIVA – As Remifentanil does not accumulate a constant infusion of 0.25 to 0.5 µg/kg/hr (about 0.25ml/kg/hr or 20ml/hr in a 70 kg patient) can be given throughout the anaesthetic.

With Propofol the infusion rate needs to decrease slowly over time to allow for accumulation. Various regimens have been described (12, 10, 8, 6 mg/kg/hr decreasing at 10 minute intervals). I have found that an infusion rate of 50-60% of the patients body weight in an anaesthetic lasting up to 4 hours does not seem to produce prolonged emergence so I run an infusion of about 40ml/hr in a 70kg patient).

TCI – The algorithm continuously decreases the infusion rate using the formulae from above, but amazingly the infusion rates are very close to 40ml per hour.

Emergence

Emergence after a TIVA anaesthetic depends on the elimination time from stopping an infusion or the last bolus. As most drugs accumulate when given as repeated boluses or as an infusion the concept of context sensitive half-life is important here.

Context sensitive half-life is the time taken for the concentration to drop by 50% after an infusion of a certain time. i.e. the half –life increases in context to the duration of infusion.

Remifentanil is the only agent that does not have a context sensitive half-life that increases with an infusion while Propofol accumulates very slowly.

Practically if Propofol is stopped 2 to 3 minutes before Remifentanil, awakening and the start of breathing occur almost together after 8 to 10 minutes from stopping the infusions.

A necessity is to ensure that the patient has adequate analgesia before stopping the infusions as Remifentanils' effect wears off exceedingly quickly.

TIVA and TCI in paediatrics

While these are probably not the cases to refine ones skills on, the following are a list of indications for TIVA or TCI to be used in paediatrics: Malignant hyperthermia, anaesthesia outside theatre, The Floppy child, ICU anaesthesia, cardiac catheterisation and the child in cardiac failure.

Differences between adult and paediatric TIVA/TCI

Despite the pharmacological principles for adults and paeds TIVA/TCI being identical certain practical aspects of doing these techniques in paediatrics need to be overcome:

- Intravenous access needs to be secured pre induction
  - Master a technique of putting up drips in children using tricks like pre-medication, EMLA, distraction, positioning.
- Everything is "off label"
  - Very few agents can be ethically tested in children.

- Pumps, connections and drugs
  - These all need to be ready prior to induction and of a size and calibre adequate for the childs size.
- Volume of fluid given
  - This can become a problem in small children especially if drugs are diluted in large amounts of sterile water.
- Nitrous oxide?
  - Is used in some centres to decrease the amount of propofol needed and speed up emergence as well as providing a ""safety net" to reduce the risk of awareness.

Propofol infusion syndrome (PRIS)

In the early 1990's Parke (BMJ 1992) described a number of childhood deaths associated with lengthy propofol infusions in children less than 6 years old, who developed a metabolic acidosis, hyperkalaemia, rhabdomyolysis, hyperlipidaemia, sudden onset bradycardia and cardiovascular collapse. It is suggested that the cause is the interaction of propofol's carrier lipid and mitocondrial oxidation preventing ATP production. The risk doubles with every hour that dose exceeds 5mg/kg/hr.

Differences with paediatric pharmacokinetics

- Pharmacokinetics change markedly with age
  - Greatest changes being seen up to 5 years old after which pharmacokinetics start to approach those of adults.
- Volume of distribution changes throughout childhood
  - Alters the induction dose which is usually far larger than in adults (up to 3 times greater)
- Clearance increases with age as enzyme maturity develops
  - Alters steady state infusion rate which is often lower than adults.
  - Emeregence is much slower than in adults.
- The perfect pharmacokinetic model needs to incorporate age, weight, height and organ function and as a result does not exist.
- Currently both paediatric and adult models have been evaluated for propofol TCI in children.
  - Most models use weight only to develop their algorhythm.
  - Adult models start at above 16 years of age and 30 kilograms.
  - The best fit model for paediatric propofol above the age of 6 years appears to be the adult Schnider model. (Agnes Rigouzzo et al Anesthesiology 2010)
- The result is most children get a TIVA rather than a TCI
- Remifentanil has a very small volume of distribution and predictable elimination so the Minto model works well in both adults and children.

Drug choices

Induction agents

Propofol

- Good TIVA and TCI agent.
- Bolus redistributes rapidly after induction, with a short predictable half-life.
- Need large induction doses in children
  - 2.5 to 5mg/kg
- Small amount of accumulation over time.
  - 15,13,11,9,7 mg/kg/hr decreasing every 15 minutes
- Context sensitive half-life has a small increase with prolonged infusion.
  - Paeds take longer to emergence.
- Kataria and paedofuser models available with the adult Schnider model appearing to work well in children over 6.
- Concerns with long duration infusions in paediatrics leading to PRIS.

Midazolam

- Slow onset of action
- Accumulation and increase in context sensitive half-life with infusions which make it a very unpredicatble agent in children.
- Bolus dose of 0.1mg/kg every 15 minutes

Ketamine

- Ketamine is used as an intravenous agent especially during cardiac catheterisations as it reduces systemic vascular resistance less than propofol and cardiac contractility less than sevoflurane.
- It does not produce complete immobility and is often used with midazolam (0.1mg/kg) or propofol - so called keta-fol.
- Ketamine is dosed as 1-5mg ivi or imi bouls initially and then 2 -4.5 mg/kg/hr infusions.
- Keta-fol is ketamine 50mg added to 200mg propofol given according to propofol dosing requirements – ie 2.5 to 5mg/kg bolus at induction and then 15,13,11,9,7 mg/kg/hr decreasing every 15minutes

Etomidate

- Infusions associated with adrenal suppression.

Analgesics

Remifentanil

- Ideal TIVA agent as no accumulation after repeated doses.
- Context sensitive half-life remains the same despite the duration of infusion.
- Needs addition analgesia post operatively as it has a very short half-life.

Alfentanil, Sufentanil and Fentanyl

- All accumulate to some degree with repeated doses or infusions.
- Alfentanil has the shortest context sensitive half-life in infusions less than one hour.
- Sufentanil is slightly better in infusions longer than one hour as it is the least fat soluble of the synthetic opioids and has TCI algorithms written for it.

Muscle relaxants

- All accumulate with infusions.
- Sugammadex reverses rocuronium infusions rapidly and has been used in paediatrics.

Doses for Paediatric TIVA

	Propofol*	Remifentanil#
Induction	2.5 – 5mg/kg	No bolus needed
Maintenance	15mg/kg/hr for 15 min	0.1-0.25µg/kg/min
	13mg/kg/hr for 15 min	
	11mg/kg/hr for 30 min	
	9mg/kg/hr for 15 min	
Emergence	10-30 minutes	8 – 10 minutes

* Propofol 1%

Remifentanil diluted to 50 µg/ml (2mg Remifentanil in 40ml water for injection.)

Further reading

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