Pharmacokinetics of TIVA/TCI

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Total intravenous anaesthesia (TIVA) can be defined as a technique of general anaesthesia using a combination of agents given solely by the intravenous route and in the absence of all inhalational agents including nitrous oxide. The availability of short-acting, potent hypnotic and analgesic drugs and modern target controlled infusion (TCI) systems make the process of administering TIVA now a practical and straightforward alternative to conventional inhalational anaesthesia. Rapid and precise titration of anaesthetic drugs to provide smooth onset and short, predictable drug offset is now feasible. This may be advantageous in the context of a cost-conscious health service moving towards ever shorter inpatient stay and more patients treated as day cases. Competency in TIVA is also vital for safe management of patients with contraindications for inhalational anaesthesia who require general anaesthesia.

The main objectives in the administration of TIVA are rapid loss of consciousness and lack of awareness during the operation; the level of anaesthesia and analgesia should closely follow the level of surgical stimulation to ensure haemodynamic stability; the drug effects should rapidly wear off at the end of the operation so that the patient has no residual sedation, no respiratory depression and no painful sensation from the surgical trauma. TIVA is particularly concerned with an understanding of the time course of drug effect, and subsequently the practitioner to have a sound understanding of the pharmacokinetics involved. Poor understanding of the pharmacokinetics underlying TIVA has caused accidental awareness as documented in the Fifth National Audit Project on accidental awareness during general anaesthesia (NAP5) report. In this report, there were 28 probable reports of awareness involving intravenous anaesthesia. In 21 of them total intravenous anaesthesia (TIVA) was used for induction and maintenance of anaesthesia. In these cases, the commonest cause of awareness was the administration of an inappropriately low dose infusion, usually as a fixed-rate infusion regime.

The pharmacokinetics of induction and maintenance of TIVA

The administration of a bolus dose of a drug results in a peak (central compartment) concentration, which then decreases rapidly with time as the drug is redistributed into the peripheral compartments. (Fig 1.)

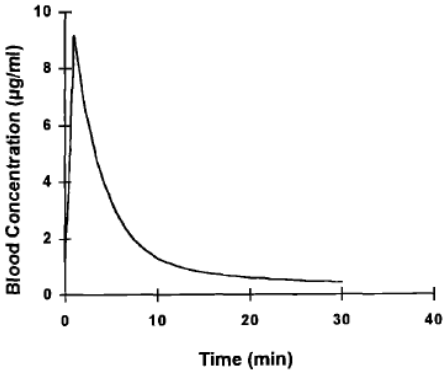


Fig 1 Plasma concentrations of propofol following a single bolus dose

Early drug distribution kinetics (front-end kinetics) determines the rate and extent of both drug distribution to the brain and its dilution by distribution to indifferent tissues. Following rapid injection there is a delay between the time drug is administered and the time drug appears at the sampling site. This is because drug is diluted by the venous return before entering the pulmonary circulation. The lungs delay the passage of drugs and even sequestrate significant amounts of drug. The systemic cardiac output then distributes drug to various organs and the drug becomes detectable in the arterial blood before being returned by the venous flow for recirculation. The exposure of the various organs to anaesthetic drug will be therefore determined by both the cardiac output as well as the distribution of the cardiac output. Both cardiac output and its distribution are important determinants of the early drug concentration versus time relationship of intravenously administered drugs and inter-individual variability in response to rapidly acting intravenous anaesthetics.

These plasma drug changes are best described by a three-compartment model (Fig 2.) 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 at which is determined by the rate constants K12 and K13 drug will also move in the opposite direction back into the central compartment as described by the rate constants K21 and K31. Clearance is described by the rate constant K10. The central nervous system, 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 which can be described by the rate constant Ke0

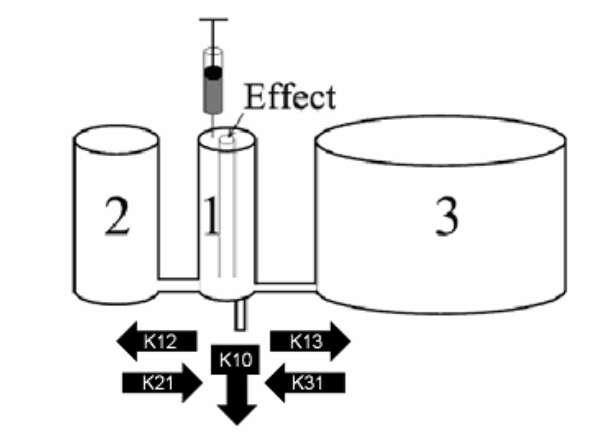


Fig2. Graphical representation of a three-compartment model

Although a rapid onset of action is desirable for the induction of anaesthesia with an intravenous agent, recovery of consciousness would be rapid without some form of maintenance. Repeated single bolus doses can be used to maintain a drug's effect, but it is easy to understand how such 'peaks and troughs' in drug concentration can result in both toxic and sub-therapeutic effects (Fig 3.) Another approach would be to simply run a constant infusion of drug. When drugs are given by infusion at a constant rate, a steady state drug concentration can be achieved, but to achieve such stability, a considerable period is required. Many of the drugs that we use have long elimination half-lives and steady state is approached only after the drug has been infused for approximately 5 elimination half-lives (Fig 4.) In terms of how long it will take to reach steady state, the answer is simple - infinity. The reason is that the steady state concentration is asymptotically approached, but never reached. For a propofol infusion this would mean that the plasma concentration would continue to slowly increase before approaching a steady state at somewhere around 24-36 hours.

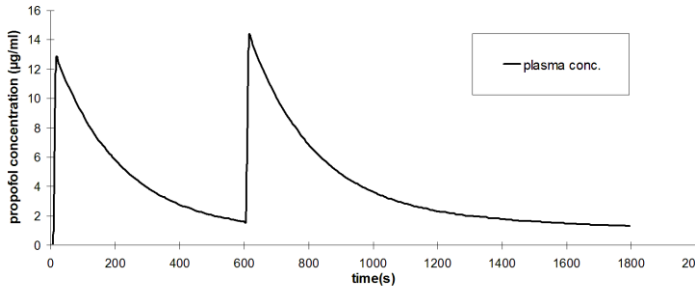
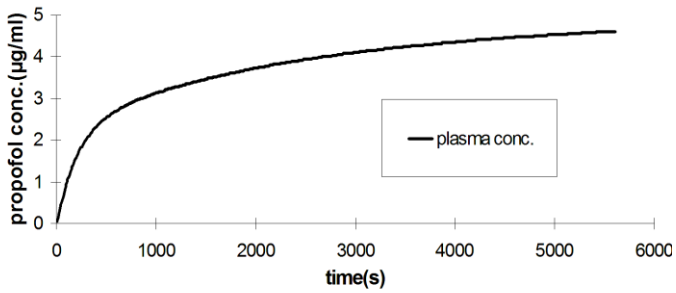


Fig 3. Plasma concentration of a drug following multiple boluses

Fig 4. Plasma concentration of a drug infused at a fixed rate.



Achieving a steady plasma concentration is the chief goal or aim when administering a TIVA. To achieve an almost constant plasma concentration in a drug whose pharmacokinetics are reliably represented by a three-compartment model, will require a loading dose and variable infusion rate.

In 1968 Kruger-Thiemer described a theoretical approach to achieving and maintaining a steady blood concentration of a drug. Briefly to achieve a steady state it is necessary to administer –

1) An initial bolus dose e to 'fill' the central compartment (and provide rapid induction of anaesthesia)

2) A constant final infusion rate maintaining central compartment concentration by matching the elimination of drug once redistribution is complete and drug concentrations in peripheral and central compartments have equilibrated

3) An interim infusion rate maintaining central compartment concentration by matching the rates of transfer of drug from central to peripheral compartments.

This became known as the BET scheme – Bolus Elimination Transfer scheme. This concept was instrumental in the development of the first TIVA recipes and TCI systems. In 1988, Roberts et al. proposed such a regimen for the delivery of propofol anaesthesia in adults. The manual infusion scheme for a target blood propofol concentration of 3 micrograms/ml, consisted of a loading dose of 1 mg/kg followed immediately by an infusion of 10 mg/kg/hour for 10 minutes, 8 mg/kg/hour for the next 10 minutes and 6 mg/kg/hour thereafter. An overall mean blood propofol concentration of 3.67 micrograms/ml was achieved within 2 minutes and maintained stable for the subsequent 80-90 minutes of surgery. Unfortunately, this regimen fails to provide adequate anaesthesia for all patients in all circumstances, risking excessive doses in some and proving inadequate in others. Subtle pharmacokinetic and pharmacodynamic variability between patients dictate the clinical effect of any given drug concentration and these differences, coupled with the need to vary depth of anaesthesia to combat changing levels of surgical stimulation, necessitate the ability to quickly and reliably titrate drug concentration to effect.

The pharmacokinetics of emergence from anaesthesia.

At the termination of a drug infusion plasma drug levels start to fall - this is due to clearance. Clearance is defined as the amount of plasma cleared of drug per unit time and consists of two main components namely redistribution and metabolic elimination of drug. As described above during an infusion drug is simultaneously metabolised and redistributed to peripheral compartments. Drug will continue to redistribute to peripheral compartments until a true steady state is achieved (after approximately 5 elimination half-lives) where clearance will be solely due to metabolism of drug. For most drugs, elimination occurs in an exponentially declining manner, the rate of elimination being proportional to the plasma concentration, as the downstream end of the gradient remains at zero. This system (i.e. the amount of drug being removed is a constant fraction in unit time rather than a constant amount) is known as first-order kinetics. As most of our anaesthetic agents usually follow first order kinetics clearance at true steady state will match the infusion rate.

Target controlled infusion (TCI)

TCI provides an accurate and user friendly method of delivering a TIVA. Alterations to the plasma or effect site concentration can be made rapidly and without the need for complex calculations and manual changes in the infusion rate. One feature of TCI pumps that contributes greatly to the anaesthetist's ability to accurately time the offset of drug effect is the ability of the pumps to calculate the "relevant effect-site decrement time". 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 needs to be able to deliver high infusion rates typically up to 1200ml/hour within a precision of 0.1ml/hour.

Achieving a steady plasma concentration with TCI

When a 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 calculated clearance of the drug and the redistribution of the drug to peripheral compartments. 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 the infusion until the target concentration is reached as estimated by the pharmacokinetic model used.

Pharmacokinetic models

There is a mathematical relationship between an administered dose of a drug and the resulting observed changes in plasma concentration. This relationship allows mathematical pharmacokinetic models to be constructed that may then be used to facilitate the calculation of dosing regimens and to guide pharmacotherapeutic management. A pharmacokinetic model is a mathematical model that predicts the plasma concentration of a drug after administration by infusion or bolus. The data for these models are derived by plasma concentration measurement in volunteers given a bolus or infusion of the drug being studied, and the model is derived using statistical techniques.

As the pharmacokinetics of different drugs varies, each drug will obviously need its own pharmacokinetic model. Similarly, when significant pharmacokinetic differences exist within the population, such as the difference between adults and children, different pharmacokinetic models will be needed.

Several pharmacokinetic models exist for adult and paediatric propofol TCI and several adult TCI models exist for the short acting opioids.

Choosing a TCI model

Most confusion arises when using propofol as the user is requested to choose between different pharmacokinetic models. The two main adult models in use are those described by Marsh and Schnider. The use of a weight-proportional pharmacokinetic model, (Marsh model), means that all the volumes and clearances of a multi-compartment model are proportional to only the weight of the patient. Interestingly, when using a weight-proportional pharmacokinetic model with a TCI pump, a doubling of the weight has the same effect on the infusion rates as a doubling of the targeted concentration. The Marsh model will adequately predict the plasma and effect site concentrations in most non-elderly adults who are of a normal body habitus. In the elderly, the Marsh model will typically display a wide variability. The Schnider model uses age and lean body mass as co-variates, and it may be a safer model to use when administering propofol to both elderly and overweight patients. The Ke0 values of the Marsh and Schnider result in differing times to peak effect (TTPE). The TTPE of Schnider's model is 1.6 min whereas the TTPE with the Marsh model is 4.57 min. When using Schnider's model for effect site targeting there is less plasma overshoot and better cardiovascular stability in compromised or elderly patients.

Two paediatric models are available for use at present in South Africa - one developed by Kataria et al and the second adapted from the preliminary models developed by Schüttler and incorporated in the Paedfusor software.

Kataria's model is based on a relatively small population (53 children) ranging from 3 to11 years. It uses both weight and age as covariates in determining infusion rates. There are no peer reviewed publications validating the accuracy of this model. The Paedfusor model is the newest paediatric model and has recently become commercially available in South Africa. The Paedfusor model is validated for children from 6 months (min 5 kg) to 16 years. A recent peer reviewed publication show that the Paedfusor model performed well in children undergoing cardiac surgery or cardiac catheterisation.

In practical terms the Kataria model has a smaller calculated volume of distribution and faster clearance and redistribution compared to the Paedfusor model. This equates to a smaller initial bolus and faster infusion rate when increasing the plasma target concentration.

At present the there is only one pharmacokinetic model available for remifentanil, sufentanil and alfentanil each on the commercially available TCI pumps. These are the Minto, Gepts and Maitre models respectively. None of these have been validated for use in children.

Effect site

So far we have focused on plasma drug concentration. This may be misleading, because the plasma is not the site of drug effect. For example, even though the plasma concentration following an intravenous bolus peaks nearly instantaneously after the bolus, no anaesthesiologist would induce a patient with an intravenous bolus of a hypnotic and immediately proceed with intubation. Figure 5 shows the time delay between plasma concentration and EEG effect of fentanyl and alfentanil, as reported by Scott and Stanski.

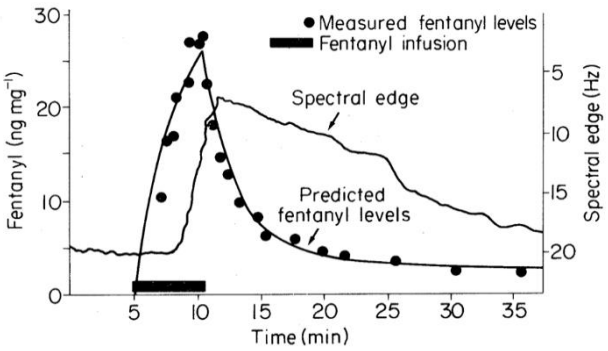


Fig. 5 the EEG effect is delayed nearly 3 minutes after the plasma concentrations of fentanyl rise. The EEG effect of alfentanil follows the rise in drug concentration much more closely, suggesting more rapid equilibration between the plasma and the site of drug effect.

This delay between peak plasma concentration and peak effect is called hysteresis. Hysteresis is the clinical manifestation of the fact that the plasma is not the site of drug action, only the mechanism of transport. Drugs exert their biological effect at the effect site, which is the immediate milieu where the drug acts upon the body, including membranes, receptors, and enzymes. The rate of equilibration between blood and effect site depends on several factors – cardiac output, cerebral blood flow, lipid solubility degree of ionisation etc.

The concentration of drug in the effect site cannot be measured. First, it is usually inaccessible, at least in human subjects. Second, even if we could take tissue samples, the drug concentration in the microscopic environment of the receptive molecules will not be the same as the concentration grossly measured in, say, ground brain or CSF. Although it is not possible to measure drug concentration in the effect site, using rapid measures of drug effect we can characterize the time course of drug effect. Knowing the time course of drug effect, we can characterize the rate of drug flow into and from the effect site. Knowing these rates, we can characterize the drug concentration in the effect site in terms of the steady state plasma concentration that would produce the same effect. Starting with the 3-compartment model we can incorporate the effect site as an additional compartment.

The effect site is the hypothetical compartment that relates the time course of plasma drug concentration to the time course of drug effect. ke0 is the rate constant of drug elimination from the effect site. The effect compartment receives such small amounts of drug from the central compartment that it has no influence on the plasma pharmacokinetics.

Effect site vs plasma targeting

The problem with targeting the plasma concentration is that when the target concentration is changed there is a temporal delay before the concentration at the effect site changes. When targeting the plasma concentration, the user determines the plasma concentration and the effect site concentration follows passively with a time delay determined by the Ke0 It is possible to target the effect site concentration using the Ke0 in combination with the other pharmacokinetic parameters. The TCI system then manipulates the blood concentration to change the effect site concentration as rapidly as possible. This will necessitate an “overshoot” in the plasma concentration to achieve a plasma-effect site gradient to cause rapid effect site equilibration. As it is the plasma concentration that determines the cardiovascular side effect profile care should be taken when effect site targeting in elderly or compromised patients.

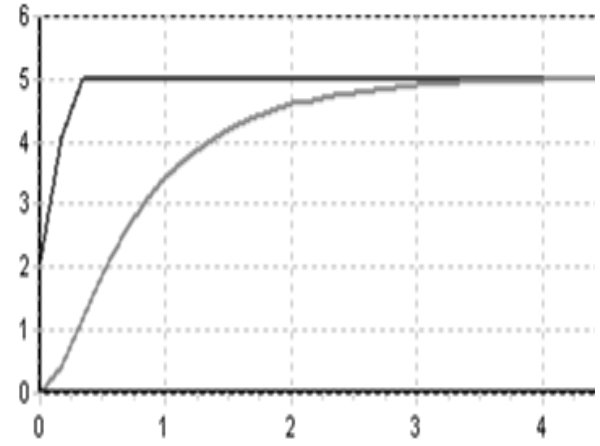


Fig 6. Plasma targeting. Targeting plasma concentration results in a slower induction

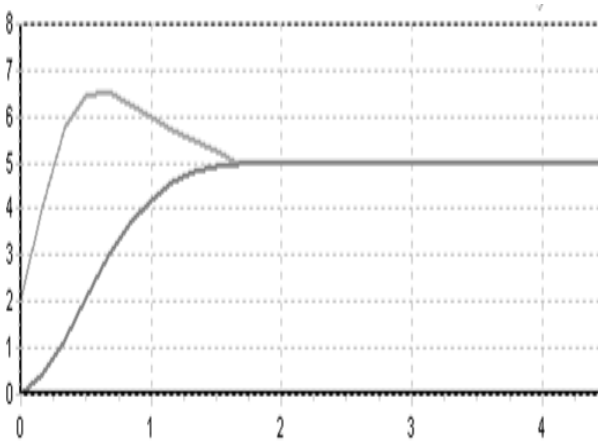


Fig 7. Effect site targeting. Targeting effect site results in overshoot of the plasma concentration

Conclusion

TCI and TIVA do not change the properties of drugs. Target concentrations are calculated, not measured. TCI pumps maintain three superimposed infusions, one at a constant rate to replace drug elimination and two exponentially decreasing infusions to match drug removed from central compartment to other peripheral compartments of distribution. Nowadays TCI technology is becoming a part of routine anaesthesia technique for the practitioner rather than a research tool for specialists and those who are enthusiasts of intravenous anaesthesia. Besides clinical application in anaesthesia, target controlled systems will play a significant role as research tools in the evaluation of drug interactions in anaesthesia and in the development of new control techniques for the administration of sedative and analgesic drugs in the peri-operative period.

FURTHER READING

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