

Total intravenous anaesthesia (TIVA) I: Pharmacokinetic principles and methods of delivery

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Introduction

In the past decade the popularity of total intravenous anaesthesia (TIVA) has increased as new hypnotic and analgesic agents, with improved pharmacokinetic profiles, particularly suitable for intravenous administration, have become available. This has coincided with greater understanding of the pharmacokinetics of intravenous infusions and huge advancements in microprocessor and infusion pump technology, leading to the development of commercial infusion pumps such as the Diprifusor, which has made the administration of intravenous anaesthesia more user-friendly for the practicing anaesthetist.

Pharmacology

The traditional triad of anaesthesia, hypnosis, analgesia and muscle relaxation, can all be achieved by intravenous techniques. However, the increasing use of the laryngeal mask airway, and the realisation that muscle relaxation is not always necessary merely to facilitate tracheal intubation, has led to the more rational use of neuromuscular blocking agents.

Hypnosis

Hypnosis is defined as "a state of altered consciousness during which perception and memory are altered". Any intravenous anaesthetic can be used for hypnosis by infusion, however their practical value is determined by their individual characteristics. For instance, thiopentone accumulates leading to delayed recovery and etomidate is not recommended by infusion because it has been associated with increased mortality when used for prolonged sedation in the critically ill. Currently propofol is the hypnotic of choice for infusion, because of a rapid recovery profile even after prolonged infusion, and particularly because of the good quality of recovery.

Analgesia

Most injectable opioids have been used by infusion during anaesthesia. Alfentanil has gained some popularity for infusion, particularly in patients with renal failure. However, the new μ -opioid receptor agonist remifentanil is metabolised by non-specific plasma and tissue esterases making its elim-

ination independent of renal or hepatic function and duration of infusion. In this respect, it can be considered as having a context *insensitive* half-life of only three to five minutes. This allows excellent titratability of analgesia over a wide range of infusion rates and blood concentrations. Consequently, it is becoming increasingly popular as a component of a total intravenous technique in day-case surgery, neurosurgery, and cardiac surgery. Its major limitation is that alternative analgesia (by longer acting opioid, non-steroidal anti-inflammatory or local anaesthesia) needs to be in place when the infusion is discontinued.

Basic pharmacokinetics for TIVA

Pharmacokinetics is the study of 'what the body does to the drug', i.e. the distribution and elimination of the administered drug, together known as drug disposition. A distinction must be made between the clinical concepts of drug movement between organs and tissues that anaesthetists carry in their head, and the mathematical models that describe the observed concentration-time relationship.

Mathematical concept of drug handling

Pharmacokinetic models attempt to describe the relationship between dose and blood concentration with respect to time. The quoted pharmacokinetic parameters are useful for calculating the loading doses and rates of infusion necessary to maintain a steady-state *plasma* concentration. They do not, however, describe the concentration in any particular tissues, and as such are not 'organ orientated.' In particular the pharmacokinetic compartments do not relate to any particular organs. The rate of change in blood concentration is calculated from the slope of the curve at any point in time (Figure 1). Hence, by separation of the different components of the curve we can describe the decline in plasma concentration in the terms of various half-lives such as distribution half-life ($t_{1/2\alpha}$) or elimination half-life ($t_{1/2\beta}$). Mathematical analysis of the graph of concentration against time, for most anaesthetic drugs reveals that the decay of plasma concentrations is tri-exponential. Tri-exponential drugs are best described by a three-compartment model (Figure 2).

Figure 1 Drug disposition in a two compartment model

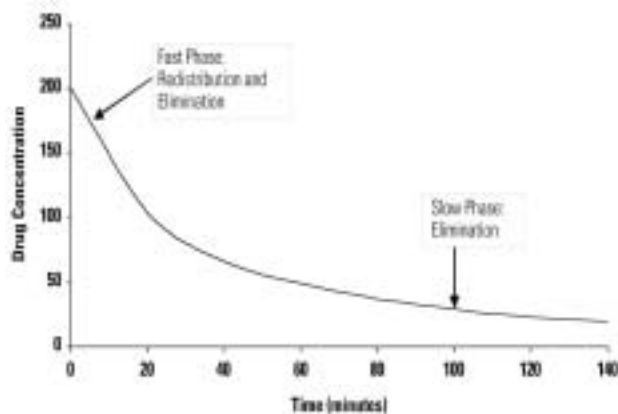
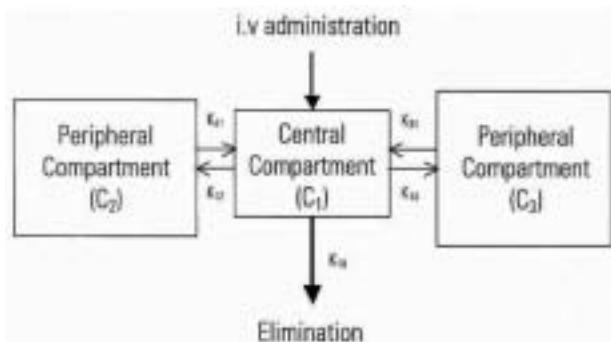


Figure 2 A three compartment pharmacokinetic model, consisting of a central compartment (C_1), and two peripheral compartments (C_2 and C_3). Drug is delivered into (with i.v. administration), and eliminated from the central compartment. Rate constants k_{12} , k_{21} , k_{13} , k_{31} , determine the transfer of drug between the central and peripheral compartments. The elimination rate constant is k_{10}



Mathematical models generate some theoretical pharmacokinetic parameters such as volume of distribution and clearance. These describe the body’s handling of the drug, and can be used to calculate the loading dose and rate of infusion necessary to maintain a steady-state *plasma* concentration at equilibrium.

Volume of distribution (V_d)

This is simply the apparent volume in which the drug is distributed. It is calculated by the formula:

$$V_d = \text{dose}/\text{concentration of drug}$$

Its value depends on whether it is calculated at time zero after a bolus (V_d) or at steady state after an infusion (V_{ss}).

Clearance (Cl)

Clearance represents the volume of plasma from which the drug is eliminated per unit time to account for its elimination from the body. It can be calculated from the formula:

$$\text{Clearance} = \text{Elimination} * V_c$$

Clearance can be calculated as elimination from the body (Cl), or to describe the clearance from one compartment into the central compartment, Cl_2 , Cl_3 . It is mathematically related to the half life:

$$t_{1/2} \propto V_c / Cl$$

In other words, as clearance increases the half-life reduces, and as the volume of distribution increases so does the half-life. Clearance can also be used to describe how quickly the drug moves between compartments.

Loading dose

The drug is initially delivered into the central compartment, so that C_1 is the initial volume of distribution (V_c). If the desired concentration for therapeutic effect (C_{ther}) is known, it is possible to calculate the loading dose to achieve that concentration:

$$\text{Loading dose} = C_{ther} * V_c$$

It can also be used to calculate the bolus dose required to rapidly increase the concentration during a continuous infusion:

$$\text{Bolus dose} = (C_{desired} - C_{actual}) * V_c$$

However, in reality most anaesthetic drugs fit a 3-compartment model, hence following administration of a bolus dose the drug will be redistributed to C_2 and C_3 , and will also be eliminated from the central compartment.

Continuous infusions

To achieve a desired concentration ($C_{desired}$), the required dose rate can be calculated:

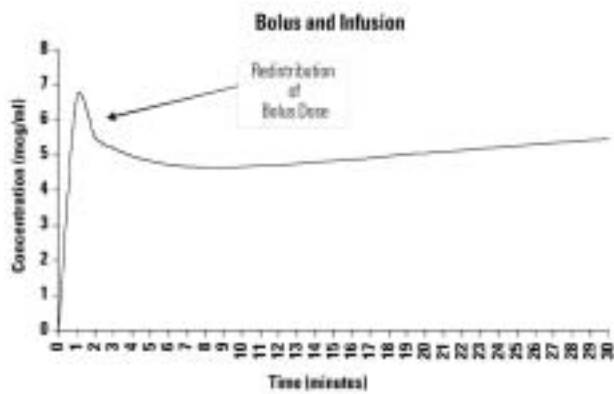
$$\text{Dose rate} = C_{desired} * \text{Clearance}$$

However, it will take five to six half-lives to achieve steady state. The desired concentration can be achieved more quickly if a bolus dose is followed by this infusion rate (Figure 3). But the concentration will still fall below the desired concentration for some time because of redistribution.

Correlation of observed drug disposition with traditional half-lives

The half-life describing drug disposition changes depending on when it is measured. For instance after a bolus dose, the reduction in concentration will be as a result of redistribution and elimination acting concurrently. While the observed initial decline in blood concentration will be close to the distribution half-life ($t_{1/2\alpha}$), it will be closer to the

Figure 3 The propofol blood concentration after a bolus followed by an infusion



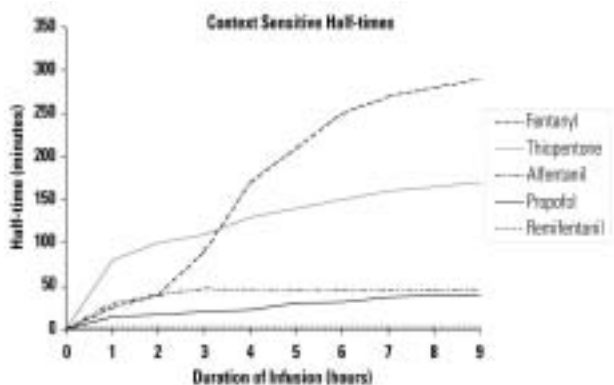
elimination half-life ($t_{1/2\beta}$) after a prolonged infusion. In short, the observed fall in blood concentration or indeed duration of clinical effect is poorly predicted by either of these half-lives. Hence these are not particularly useful terms for the practicing anaesthetist.

The situation with drug infusions is more complicated. It has become clear that the observed half-life at any particular time depends on the duration that the infusion has been running, this is the context sensitive half-time (CSHT).

Context sensitive half-time

This is a more clinically useful term and has been defined as ‘the time for the drug concentration to decline by 50% in the context of the duration that the infusion has been running.’ It is not a single figure but a range of figures which are better considered as a graph (Figure 4). This clinically relevant half-life increases with the duration of the infusion until all compartments or body tissues are in equilibrium. This reflects the peripheral compartments becoming filled with drug. The context sensitive half-time eventually

Figure 4 Context sensitive half-time. The time required for drug concentrations of thiopentone, fentanyl, alfentanil, propofol and remifentanyl to decrease by half their value as a function of the duration of the infusion



plateaus at steady state. At this point it is the same as the elimination half-life, and is no longer context sensitive. The context sensitive half-time graphs provide better comparisons to the clinically observed drug disposition than the traditional pharmacokinetic parameters. The context-sensitive half-life increases for some drugs over time but is relatively constant for a drug such as as remifentanyl.

Varying depth of anaesthesia

It can be seen that it is no simple matter to provide and maintain a desired concentration of a drug. If the anaesthetist wants to increase or decrease the depth of anaesthesia in response to patient response or surgical stimulus, it becomes even more difficult to calculate.

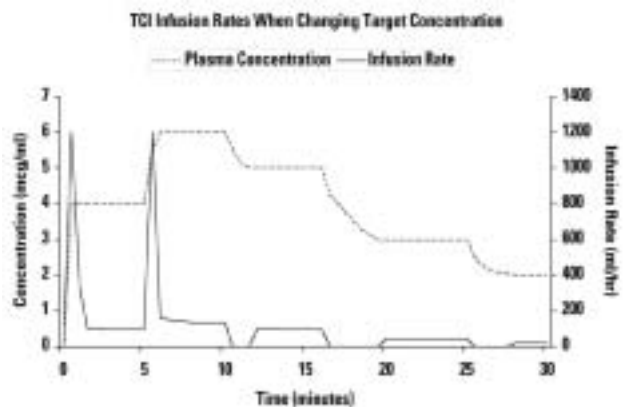
Delivery of TIVA

Target controlled infusions

Target Controlled Infusion (TCI), uses a real time pharmacokinetic model to calculate the bolus dose, infusion rates or indeed for how long to stop the syringe pump, to achieve a desired or ‘target’ blood concentration (C_T) at any point in time. TCI systems have become a powerful research tool, and systems have been developed for many drugs. However the only commercially available TCI system to date, is the Diprifusor for propofol. It uses a 3-compartment pharmacokinetic model of propofol, and some basic data about the weight of the patient, to calculate and control the infusion rates required to reach the desired C_T .

An increase in the target concentration entered into the pump, results in a bolus dose followed by an increased infusion rate, whereas a reduction in the target results in the infusion being suspended until the concentration reaches the target, then the pump re-starts at a lower rate (Figure 5).

Figure 5 Propofol blood concentrations and infusion rates generated by Diprifusor TCI pump when the concentration is titrated from 4 to 6 $\mu\text{g}\cdot\text{ml}^{-1}$ and then back to 2 $\mu\text{g}\cdot\text{ml}^{-1}$ in increments



Comparing manual infusion and TCI

When propofol was introduced in the early 1980s it became apparent that its pharmacokinetics, and in particular its recovery profile were particularly suited to infusion anaesthesia. At this time equipment to administer a computer controlled infusion was not available to most anaesthetists. Several studies have compared the use of manually controlled infusion with TCI, and while the designs have differed, the results are broadly comparable: with the TCI system induction of anaesthesia is achieved with less propofol over a longer time, insertion of laryngeal mask airway is more rapid, there is less patient movement in response to surgical stimulus, though recovery times and total propofol dose are generally greater (possibly reflecting a more appropriate anaesthetic depth). Significantly, the majority of anaesthetists prefer the TCI system.

Performance of TCI systems

While the TCI systems deliver propofol to achieve a target concentration entered by the anaesthetist, this is calculated based on the population pharmacokinetics with which the microprocessor is programmed. In practice, the actual measured blood concentration is likely to differ from predicted. This can be quantified as the performance of the system.

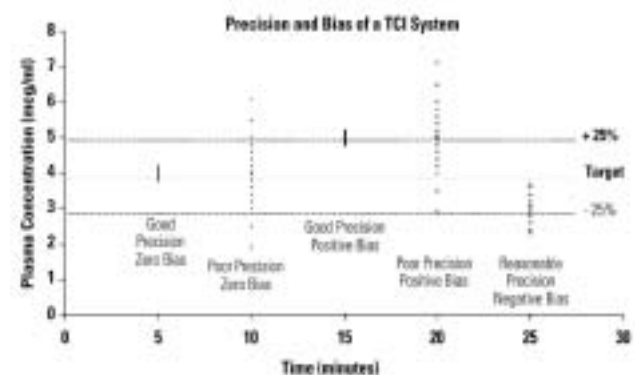
For each individual observation, this is usually expressed by the term 'performance error'; this is calculated from the difference between the measured concentration (C_M) and the calculated concentration (C_{CALC}).

$$\text{Performance error (\%)} = \frac{C_M - C_{CALC}}{C_{CALC}} \times 100$$

For a population of patients, these observations are pooled, and expressed as a 'median absolute performance error' (MDAPE). This represents the scatter or spread of measurements, also known as the **precision** of the system. This gives an indication of how close the calculated value is to the measured value. Another descriptor of performance is the **bias** of the system. This describes whether the system over-estimates (positive bias) or under estimates (negative bias) the measured concentration (Figure 6). For the Diprifusor, in healthy patients within 20% of their ideal body weight, the precision is generally 20–25%, and appears consistent across most age ranges. Generally the system has minimal bias at $2\mu\text{g ml}^{-1}$; it underestimates at lower values, and overestimates at higher values.

When criticising the performance of TCI systems, anaesthetists often forget that the difference between end-tidal volatile anaesthetic partial pressure and arterial partial pressure is of a similar magnitude. End-tidal monitoring usually over-estimates arterial partial pressure by around 20–25%.

Figure 6 The relationship of measured plasma concentrations (dots) with the target concentration of a TCI system (solid line) can be described in terms of precision and bias. This graph shows hypothetical measured blood concentrations for a target controlled infusion of propofol at $4\mu\text{g}\cdot\text{ml}^{-1}$



Individual variability

Pharmacokinetic variability

There can be variations in the plasma concentration of drug between patients because they differ from the population pharmacokinetic model used. This pharmacokinetic variation results in a variable plasma concentration being achieved. Potential confounding factors for the pharmacokinetic data set used are sex, body weight, age and systemic disease.

For propofol administered by the Diprifusor, body weight correlates well with clearance and volume of distribution, and surprisingly, this applies even in obese patients. Volume of distribution and clearance are disproportionately greater in children, with volume of distribution being increased more than clearance. Therefore children require different pharmacokinetic settings. If the adult system is used then the problem of divergence is encountered. This describes the phenomenon where the difference between the measured and target propofol concentration becomes greater the longer the infusion is running. A commercial TCI system for children is not yet available; accordingly the Diprifusor is currently not licensed for children less than 16 years. Despite the decreasing V_d associated with ageing in adults, the MDAPE is remarkably consistent across age groups.

For remifentanyl the important pharmacokinetic variables are sex, age and lean body mass. Accordingly these have been included in a TCI Remifentanyl pump 'Remifusor' available only for research at this time.

Pharmacodynamic variation

In addition to pharmacokinetic variation, there can be marked variation in individual patient's response at the same blood concentration. This is pharmacodynamic variation.

As well as affecting drug disposition and elimination, systemic disease can affect response to the drug also. For instance, there is increased sensitivity to sedative and hypnotic drugs in patients with renal, hepatic and cardiovascular disease. It appears that pharmacodynamic variation is greater than pharmacokinetic variation. Indeed for propofol it is estimated to be six to seven times greater. This explains why there is no 'correct concentration' of propofol. Therefore, in these patients it is appropriate to start with a low target concentration and titrate to effect slowly.

Further reading

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Glass PSA. Intravenous infusion techniques: how to do it and why we should do it. Canadian Journal of Anaesthesia 1998;45:R117–127.

Minto CF et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl: I. Model Development. Anesthesiology 1997;86:10–23.

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TRAINEES' TOPICS Editor Dr M J Garfield, The Ipswich Hospital, Suffolk

The trainees' topics section for this issue has been reduced in size, in order to allow more space for National Anaesthesia Day. The 'How the College works' series will continue in the next issue. This month, there is an account by Dr Padma Rao, of her experience as an overseas trainee (and a working mother), and a review of the College's Primary FRCA book, by Dr Sally Wilmshurst, a recent Macintosh Prize winner.

An experience of an overseas trainee

Dr P Rao, Specialist Registrar, North Thames

It was in January 1997 that I landed in the United Kingdom to join my husband, a qualified surgeon from India who had taken up a Senior House Officer (SHO) post in one of the North London hospitals – with a lot of expectations, ambitions and goals.

As I walked through the narrow corridors of the hospital accommodation, my heart just sank. The tiny studio flat that we were offered was in a condition far from my expectations. The first thing that I did was to cover the furniture with throws to conceal the unsightly stains. Hours of shampooing could not get rid of the peculiar smell from the carpets. My husband soon mastered the art of balancing on a three-legged chair at the dining table. We managed to survive. (I was later delighted to know that those buildings were demolished and new ones built).

By then, I was not a bad anaesthetist by any standards, even without mentioning the gold medal I had been awarded for my performance in the postgraduate exam at the state level. I managed to get a SHO post in the friendly anaesthetic department at the same hospital as my husband. Having learned to administer a 'safe anaesthetic' within limited resources, I then faced the challenge of making appro-

appropriate use of these available resources. Not knowing exactly what was expected of me, I did almost everything I was asked to do including intravenous cannulations on the wards during the late hours. I worked relentlessly to get through the exhausting emergency lists. I soon learned to follow the instructions of seniors who had better organisational skills, if not always better clinical skills. The regulations of the College are such that most overseas trainees end up working at SHO level for at least two years before obtaining the specialist training that they are aspiring for. So did I. Exams, interviews, failure and success – the cycle went on.

Life outside anaesthetics was fabulous. The world seemed smaller and closer than ever. We could afford the holidays that very few people at home can even dream of, and eventually moved out of the hospital accommodation. Then came along our first child, long awaited. Eight months of motherhood away from work shook the confidence I gained over time. However, before long I was back on the track facing clinical commitments, audit projects, presentations, and the next milestone: the 'Final FRCA'. Just as I was gearing up to it, came the news that my husband