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Review Article

Review of pharmacokinetic models for target controlled infusions in anesthesia

Subash Kennedy Sivasubramaniam*

Department of Anaesthetics, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

*Correspondence to:
Dr. Subash Kennedy Sivasubramaniam,
Email: subashken@gmail.com

ABSTRACT

Intravenous injection of anesthetic drugs dates back to the 17th Century when opium and chloral hydrate have been injected intravenously. It was not until the 1930s intravenous anesthesia became popular with the invention of barbiturates. Early intravenous anesthetic agents such as barbiturates were ideal for induction of anesthesia, but not suitable for maintenance of anesthesia. Most of these drugs accumulated significantly with increasing durations of infusion and also resulted in cardiorespiratory depression. The invention of propofol and shorter acting opioid analgesics such as remifentanil and alfentanil have revolutionized intravenous anesthesia. The rapid onset and offset of these drugs lends itself to being suitable agents for maintenance of anesthesia over prolonged periods of time.[1,2] Detailed understanding of the pharmacokinetics of propofol and remifentanil, combined with technological advances in intravenous pumps capable of accurate delivery of drugs have resulted in great development of the field of total intravenous anesthesia and target controlled infusions. I would like to discuss, in this article, the pharmacokinetics and pharmacokinetic models behind these intravenous infusion pumps.

Keywords: Pharmacokinetic model, Target controlled infusion

INTRODUCTION

The basic goal, while administering intravenous anesthetic agents is to accurately administer a dose of drug aiming to produce a specific therapeutic concentration of the drug at specific sites and obtain a desired clinical effect. In order to achieve this, we will need a detailed understanding of the drugs dose-response relationship, pharmacokinetics, and dynamics of the drug. The most accurate way of measuring the drug concentration is to obtain plasma and end organ concentrations of the drug, which is feasible in experimental studies, but not in daily anesthetic practice. Moreover, measured concentrations of the drug in the body does not necessarily translate in to predictable clinical effect due to various factors such as age, individual variability, etc.

Anesthetists usually are able to control the blood concentration of inhalational anesthetic agents by using a vaporizer and measuring the actual end tidal concentrations of the volatile agent. A similar model to measure the concentration of intravenous anesthetic agents during routine anesthetic practice is not feasible. Consequently, anesthetists calculate the dose and infusion rate of the anesthetic agent according to patient's body weight and other physiological parameters. Moreover, there is a complex relationship between dose and effect site concentrations. A simple infusion will not be able to maintain a steady state blood concentration until at least five times the elimination half-life of that the drug has prevailed. This is illustrated in the Figure 1. Hence, this requires an accurately estimated bolus dose and an estimated maintenance rate of the anesthetic drug delivered by an infusion pump.

Propofol lends itself to be used for target controlled infusions, while administering anesthetics. This includes rapid onset and recovery from the anesthetic, including early recovery of psychomotor function and "home readiness" to be discharged from the post anesthesia care unit. Remifentanil is an ultra-short acting opioid, which virtually never accumulates in the body even with very prolonged durations of infusion.
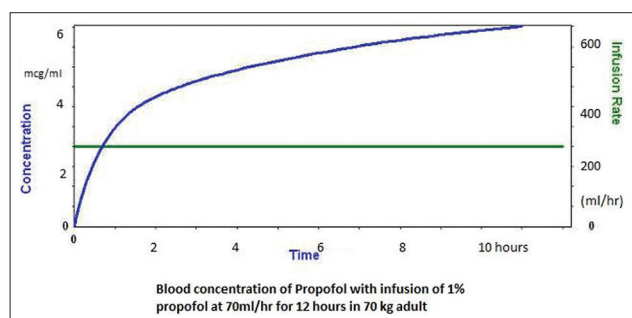
Figure 1: Blood concentration of propofol after infusion does not reach steady state after 12 hours of infusion.

TARGET CONTORLLED INFUSIONS (TCI)

This is an infusion controlled in such a manner as to attempt to achieve a user defined concentration in a body compartment or effect site tissue. Multi-compartment pharmacokinetic models, derived from previously performed population pharmacokinetic studies are used by TCI pumps to calculate bolus and infusion rates required to deliver a target concentration. A microchip computer in these pumps is able to calculate the complex poly-exponential equations of the multi-compartmental pharmacokinetic models for a specific drug.

An anesthetist using these systems relies on clinical observations and monitoring of the patient rather than measuring the actual concentrations of the drug in progress. This exposes the system to some errors between the true concentration of the drug and the estimated concentration of the drug. Moreover, drug concentration may not reliably translate in to desired clinical effect and overall clinical observations and monitoring help the experienced anesthetist determine the right amount of anesthetic.

TCI systems are programmed with pharmacokinetic models that mathematically illustrate the process of drug distribution and elimination.

PHARMACOKINETIC MODELLING

Pharmacokinetics is "what the body does to the drug", which is the relationship between the administered dose and resulting blood concentrations. TCI machines have a microchip programmed with an infusion algorithm based on one or more pharmacokinetic models for one or more drugs.

A pharmacokinetic model is a mathematical model that is used to predict the blood concentration profile of a specific drug after a bolus and/or infusion of carrying duration. These are derived from experimental studies where arterial or venous concentrations of the drug are measured after a bolus or infusion in a group of patients or volunteers and subject to standardized statistical approaches and software.

Figure 2 illustrates what happens to blood concentration of propofol after a single bolus dose. The rapid onset and
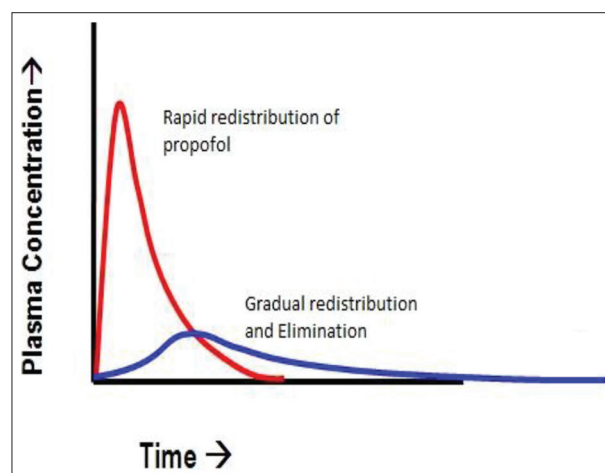

Figure 2: Propofol concentration in blood after single bolus.

offset of the clinical effect after a single bolus is due to rapid redistribution of propofol from the central, highly perfused compartment of the body to the less perfused parts of the body. The central highly perfused compartment would include the heart, main arteries, lungs, brain, and kidneys. The lesser perfused compartments would include the muscles, gut, and other parts of the body. The fat stores are very poorly perfused. It is important to note these compartments are not strict physiological boundaries, but they help us conceptualize the pharmacokinetics of a drug in a detailed manner and enable us to apply mathematical models to explain them.

A two or three compartmental model[3,4] can be used to mathematically to describe the behavior of most anesthetic drugs with reasonable accuracy. A model describes the number of compartments, their volumes, and rate of transfer between compartments and the metabolism and elimination of the drug. This is illustrated in Figure 3, showing a multi-compartmental model that could be used for propofol.

Conventionally, the compartment into which the drug is drug is injected is called the central compartment Vc or V1 and can also be called the initial volume of distribution.

The second compartment (V2) is the vessel rich or fast redistribution compartment. There is a rapid distribution of drug from Vc to V2.

The third compartment V3 is the vessel poor or slow compartment where there is a slow distribution between Vc and V3.

The sum of Vc (V1), V2 and V3 is the "Volume of distribution at Steady state", Vd_{ss}.

The central compartment may be thought of as including the blood volume and often Vc may be far larger than the blood volume. The volumes V2 and V3 in the multi-compartment models are theoretical volumes that are used to predict
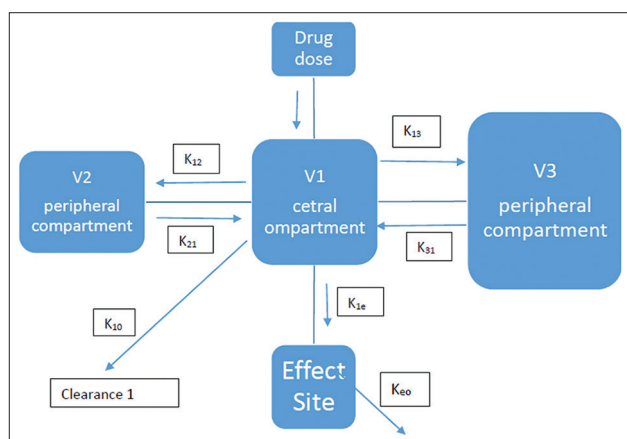
Figure 3: Three compartment pharmacokinetic model.

blood concentrations and they have no real anatomical or physiological correlates.

The rates of drug metabolism and distribution are described by rate constants or clearances. A rate constant is the proportion of drug in a compartment undergoing a process during a unit of time and is represented as units per minute or units per hour. Conventionally, the symbol K_{10} is used to denote the rate constant for metabolism or elimination and rate constants K_{12} and K_{21} are used to denote rate constants for drug transfer between V1 and V2 and between V2 and V1, respectively.

Clearance describes a volume of a compartment that is "cleared" during a unit of time. They are represented as ml/min or ml/hr. If the compartment volumes and the rate constants are known the clearance can be determined as:
Elimination clearance = V1 × K_{10}
Clearance 2 = V2 × K_{21}
Clearance 3 = V3 × K_{31}
Usually V2 and V3 re deduced from the rate constant V1.

PHARMOACOKINETIC MODELS

One of the first models to be developed for propofol is the Marsh model[5] which was most popular until recent years. It is incorporated in the Diprifusor (by AstraZeneca) where a microprocessor was used in the TCI pump. This model was derived from the model originally proposed by Gepts et al.[6] In this model, the central compartment volume is a linear function of the actual weight of the patient. The Marsh model does not incorporate age in to account; although, the diprifusor software requires the age to be entered.

It is now evident from several studies that age, gender, height, site of blood sampling (venous vs. arterial) all influence the pharmacokinetic model parameters. Schüttler et al. analyzed the data from several from several individual studies of propofol pharmacokinetics and produced a model that incorporates age, height, gender and infusion characteristics.[7] In Schüttler's model, all parameters except for V3 are derived

from equations that include a power function of body weight. Elimination clearance and V1 are also influenced by age.

Schnider et al. developed a model that includes a fixed V1, with age as a covariate in the calculation of V2 and clearance. It also used weight, height, and lean body mass (LBM) as covariates for elimination clearance.[8]

Several studies of the predictive performance of the Marsh model shows that Marsh model under-predicts the blood concentration of propofol. Most studies of Marsh model included young and middle-age patient.

The Schnider model uses age and LBM as covariates and it may be safer to use when administering propofol in elderly patients.

For most drugs in clinical practice, the doses and infusion rates recommended are calculated on a weight adjusted basis. Most pharmacokinetic studies involve healthy, non-obese patients and there are very few pharmacokinetic studies in obese patients. We all intuitively know that two patients of similar weight but, markedly different age and height do not require the same dose of anesthetic drug to achieve a desired effect.

The common practice of reducing weight adjusted dose in obese patients is supported by studies that have shown a good correlation between dose requirements and LBM for propofol,[9] thiopentone,[10] and atracurium.[11] Egan et al[12] showed that remifentanil pharmacokinetics in obese and non-obese showed significantly higher doses of remifentanil in obese patients if doses were calculated based on actual body weight. This study showed that if compartmental volumes and clearances are adjusted for LBM, then the pharmacokinetics among obese and non-obese are similar, thus confirming that remifentanil dose regimens should be based on ideal body weight or LBM.

Older models like the Marsh model used the total body weight in the pumps, which in turn makes assumptions about clearance rates and volumes of distribution, which will have a significant effect on the infusion rate and total dose of drug infused.

More recent models like the Schneider model for propofol and minto model for remifentanil use the LBM as covariables. In these models, based on the total body weight, height, and gender, the LBM is calculated according to the following formulae.[13]
Males: LBM = 1.1 × weight − 128 × $(weight/height)^2$
Females: LBM = 1.07 × weight − 128 × $(weight/height)^2$

Though the lean body weight appears to give a sensible approximation of the ideal body weight, they do not reliably calculate the ideal body mass in extremely obese patients. Most of the modern TCI pumps are programmed in such a way they would not accept more than a certain upper weight

limit in order the TCI pump operates based on generation of realistic approximation of ideal body weights.

EFFECT SITE TARGETTING

The earlier models of TCI pumps were programmed to target blood concentrations. Although some models were able to display the calculated effect-site concentration, they were unable to directly target the effect-site concentration. The main issue with this is there is always a temporal delay between the concentration at the effect-site and the blood concentration when the target concentration is adjusted in the pump. The clinical effect of the drug is dependent on its concentration at its effect site and there is usually a hysteresis in clinical effect when the target blood concentration of the drug is either increased or decreased.

The rate of equilibration between the blood and effect site depends on several factors. These include the factors that influence the rate of delivery of the drug to the effect site, such as cerebral blood flow and cardiac output. They also depend on the pharmacological properties of the drug such as lipid solubility and degree of ionization, which determine the transfer of drug across the blood brain barrier.

The time course for blood to effect site equilibration is described as K_{eo}. Strictly speaking the K_{eo} should be used to describe the rate of removal of the drug from the effect site, but the effect site is usually regarded as a volume-less additional compartment, so that there is no need for a separate constant describing the rate constant for movement into and out of the effect compartment.

The concentration at the effect site is not feasible to measure directly and the blood concentration most of the time is not known either. However, the time course of changes in the effect site concentration can be estimated from measures of clinical effect such as electroencephalographic (EEG) parameters. When the blood concentration is known the pharmacodynamics measures can be used to estimate the K_{eo}.

A bolus administration of a given drug will result in the rapid increase in blood concentration, followed by a bi- or tri-exponential decline in concentration, the rate of which is determined by the drug distribution and metabolism. The rate of change of drug concentration in the various compartments depends on the concentration gradient between the central and other compartments and by their inter compartmental drug distribution rate constants.

After a bolus of a drug the maximal effect-site concentration occurs at a point when the blood and effect site curves cross (Figure 4).

As the clinical effect is determined by the effect site concentration, there is a time delay between the bolus injection and the time at which the blood and effect site
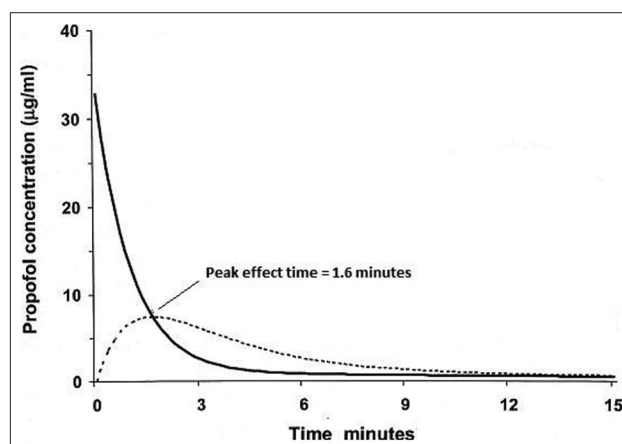

Figure 4: Point of maximal effect site concentration after single bolus of propofol.

curves cross. This is referred to as the "time to peak effect" (TTPE). The TTPE of a given drug is usually is independent of the size of the bolus dose.

If the same dose of propofol is administered to two different patients, simpler models like the Marsh model will predict the same peak blood concentration and the same time course of blood drug concentration. Hence, the same TTPE will generate the same K_{eo} for all patients.

When more complex models such as Schnider or Minto are used, they tend to predict different peaks and time courses of blood concentrations for patients with different characteristics. When a more complex pharmacokinetic model is used, and the TTPE for the drug and population are known, then that particular TTPE can be used to derive the unique K_{eo} for each patient.

With a blood targeted TCI system, the user defines the blood concentration and the effect site concentration follows passively with a time delay determined by the K_{eo} or TTPE for that particular drug.

When the K_{eo} is used along with the pharmacokinetic parameters, it would be possible to target the effect site rather than the blood concentration. With effect site targeting the system manipulates the blood concentration to bring about the target effect site concentration as rapidly as possible. When the target effect site concentration is increased by the operator the system calculates an optima peak blood concentration that would achieve the desired effect site rapidly and administers a bolus to achieve that blood concentration and eventually with effect site concentration with the shortest possible time lag. Similarly, if the effect site concentration is decreased by the operator, the system stops delivering drug for a short period allowing with blood concentration to fall below the level which would allow a gradient driving the drug out of the effect site in to the blood. As soon as, the effect site concentration is assumed to have been reached, the infusion restarts. We need to be aware that with effect site targeting, there are several layers

of assumptions inherent in there effect site targeting model.

Pharmacokinetic parameters and models, based on population studies, may not apply to an individual and measured blood concentration may be quite different to those predicted.

The choice of K_{eo} value used is very important in effect site targeting, because it will overshoot and undershoot in blood concentration used to steer the effect site concentration when the target effect site concentration is increased or decreased respectively.

If two different systems use the same pharmacokinetic data set, but with different K_{eo} values, different drug doses will be administered leading to different peak and trough blood concentrations.

Hence, it is important to use a fixed K_{eo} for effect site targeting when both the kinetic and dynamic models have been calculated from the same study population. If this is not possible, then a TTPE algorithm should be used.

Currently with the Marsh model, two different values of K_{eo} are used, a fast (Keo of 1.2 min^{-1}) and a slow K_{eo} (K_{eo} of 0.2 min^{-1}) values. In fit young patients, slow K_{eo} values are less likely to cause problems whereas in the elderly the large overshoots can cause cardiovascular instability. Hence, effect site targeting if used in elderly patients, it is safer to use a faster K_{eo}.

The Schnider model is more complex than the Marsh model as it incorporates age, height, weight and LBM. The TTPE for propofol was 1.6 min in the studies, which led to this model. This value is then used to calculate the individualized K_{eo} for each patient.

A TTPE of 1.6 min implies a much quicker time to maximum effect site concentration and clinical effects after a bolus, compared with the values used in the Marsh model. (4.57 min). Thus when effect site targeting is used in a Schneider model, a relatively less "overshoot" and "undershoot" of blood concentrations around the target effect site are required. For these reasons, effect site targeting in the Schneider model results in lower doses of propofol than when the Marsh model is used for blood concentration targeting. Hence Schneider model is desirable in elderly and frail patients.

Remifentanil, a relatively newer opioid drug is metabolized by no specific esterases and is not dependent on the liver of kidney for its metabolism and elimination. The model most commonly used for remifentanil is the three compartmental model by minto.[14] This model was developed from a study of the pharmacokinetics of remifentanil in a heterogeneous population. The covariates used included weight, height, gender, and age.

With remifentanil, equilibration between blood and effect site concentration are virtually complete within 5 min. With blood concentration targeting, rapid increases in effect site concentration can be achieved by brief periods of overshoot. When effect site targeting is used, the overshoot is calculated and controlled automatically. If the Minto model is used for effect site targeting, an initial effect site target of 6 ng/ml will require a blood concentration of 17 ng/ml, a level which may cause undesired side effects like chest wall rigidity and bradycardia. Hence, the argument to use effect site targeting with remifentanil compared with blood site targeting is less compelling.

ACCURACY OF TARGET CONTROLLED INFUSIONS

A TCI system administers drugs at rates determined by a model derived from pharmacokinetics of that drug in a population of patients or volunteers. The concentration shown in the machine screen is only an estimate and there is no method of measuring actual drug concentrations analogous to the measurement of end-tidal concentrations for volatile agents.

There are several factors that can influence the actual drug concentration achieved. Apart from physical factors such as machine malfunction or IV cannula disconnection, there would be some degree of inaccuracy as to how the model applies to that particular patient. As discussed earlier some models tend to be more accurate than the others.

CLINICAL APPLICATION OF PHARMACOKINETIC MODELS

During induction of anesthesia with propofol, it is best to choose an initial blood target that is above the anticipated effect site concentration required for loss of consciousness. Typical blood concentrations of propofol required to produce loss of consciousness in fit and young patients are around 6-8 mg/ml. Elderly patients are likely to require a blood target concentration of around 4 µg/ml. The target concentrations used should be carefully adjusted according to the clinical responses.

One major difference between the Marsh and Schneider models is the size of the central compartment. For example for an average adult of 70 kg, the Marsh model uses the value of Vc which is 15.9 l, whereas, the Schneider models uses a Vc of 4.27 l. This results in significant difference in the estimated blood and effect site concentrations for the first 10 min of commencing the TCI pumps. After 10 min the differences are less significant. It is best to use a Marsh model in a blood target concentration mode and Schneider model in an effect site concentration target mode.

While using propofol and remifentanil combinations, it is best to start the propofol infusion for induction of anesthesia

and start the remifentanil, whilst the propofol is taking effect and the patient is beginning to lose consciousness. This is because effect site concentration of remifentanil rises more rapidly than propofol and if remifentanil is used early, it is likely the patient will stop breathing earlier before loss of consciousness and also more likely to result in chest wall rigidity.

An effect site target concentration of 4-6 ng/ml of remifentanil is required to produce conditions adequate for laryngoscopy and intubation.

While using TCI systems in very elderly and unwell patients one should be aware of the altered pharmacokinetics where the volume of distribution and metabolic clearance, cardiovascular reserve are significantly different, thus producing significantly different and exaggerated responses the TCI systems if they are used without taking these factors into account.

With the use of remifentanil in TCI systems, one should be ware it produces no lasting analgesia and may in fact contribute hyperalgesia in some. Hence, adequate postoperative analgesia cover with multimodal drugs is important. If morphine is given for postoperative analgesia, it is best given at least 30-40 min before the end of the procedure.[15]

There are some other practical aspects to take into account, whilst delivering TCI for patients. It is generally advisable to have a dedicated cannula for the administration on the TCI and regular inspection of the cannula site is advised to ensure patency of the cannula and identify disconnections.

One should use dedicated infusion lines with minimal dead space to avoid inadvertent boluses and avoid the time lag and delay between the programmed bolus and the actual delivery of the drug in the blood. If fluids are co-administered in the sane cannula, it is best to use fluid administration sets with one way valves to avoid any backflow. One should also be aware of the residual dead space at the end of the procedure which may have been flushed before sending the patient to the recovery area.

Recent guidelines from the National Institute of Clinical Excellence, UK have highlighted the importance of the use some mode of EEG monitoring in an attempt to reduce accidental awareness.[16]

CONCLUSION

The TCI and total intravenous anesthesia are being increasingly used by anesthetists and are a part of established practice for several anesthetists. It is important to realize the target concentrations are calculated and predicted and there would always be a degree of error when compared with the true measured concentration. Improved understanding of pharmacokinetics and creating models, which have lesser inter patient pharmacokinetic variability would reduce this gap. Auditory evoked potential and bispectral index have been used in some closed loop TCI systems for propofol sedation.[17] More progress with anesthesia depth monitoring could see the use of computerized control of anesthesia in the future.

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