Overview of Target-Controlled Infusions and Total Intravenous Anaesthesia

Third Edition

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General and historical background

Total intravenous anaesthesia (TIVA) – when anaesthesia is induced and maintained with intravenous anaesthetic drugs – has been a relatively recent addition to the anaesthetists' repertoire. Although intravenous induction of anaesthesia became common in the 1930's after the discovery of the barbiturates, intravenous maintenance of anaesthesia only became practical, safe and popular after the introduction of propofol into clinical practice in the 1990s. First used clinically in 1977, propofol is the only currently available intravenous hypnotic agent suitable for induction and maintenance of anaesthesia. The discovery, in recent decades, of the shorter-acting opioid analgesics alfentanil and remifentanil, which have a rapid onset and offset of action and are eminently suitable for use by infusion, coupled with technological developments (such as more reliable and accurate intravenous pumps), and advances in our understanding of pharmacokinetic principles have enabled the development of the technique of TIVA in which anaesthesia is administered exclusively via the intravenous route.

Propofol-based TIVA techniques have many advantages. These include rapid recovery of consciousness and psychomotor function, earlier recovery and discharge from the post-anaesthesia care unit and shorter times to achieve 'home-readiness' than inhalational anaesthetic techniques.[1 2] Propofol has an anti-emetic affect,[3] and is thus associated with a lower incidence of postoperative nausea and vomiting.[4-9] Intravenous agents have no known adverse effects on theatre staff. Whereas exhaled inhalational agents contribute directly and significantly to the greenhouse gases, the greenhouse gas emissions arising from propofol use are miniscule (four orders of magnitude less than N_2O and desflurane) as they only arise during manufacture, transport, and the syringe pump operation.[10] It should however be mentioned that unused propofol should always be incinerated with clinical waste. If discarded into the water drains it is toxic to the aquatic environment.[11]

Significant advances during the past decades in our understanding of the pharmacokinetics and pharmacodynamics of the anaesthetic drugs has generated the knowledge required for rational administration of these drugs. The ultimate goal, when administering a particular dose of drug, is a specified clinical effect, for which a specific therapeutic concentration at the site of drug action is

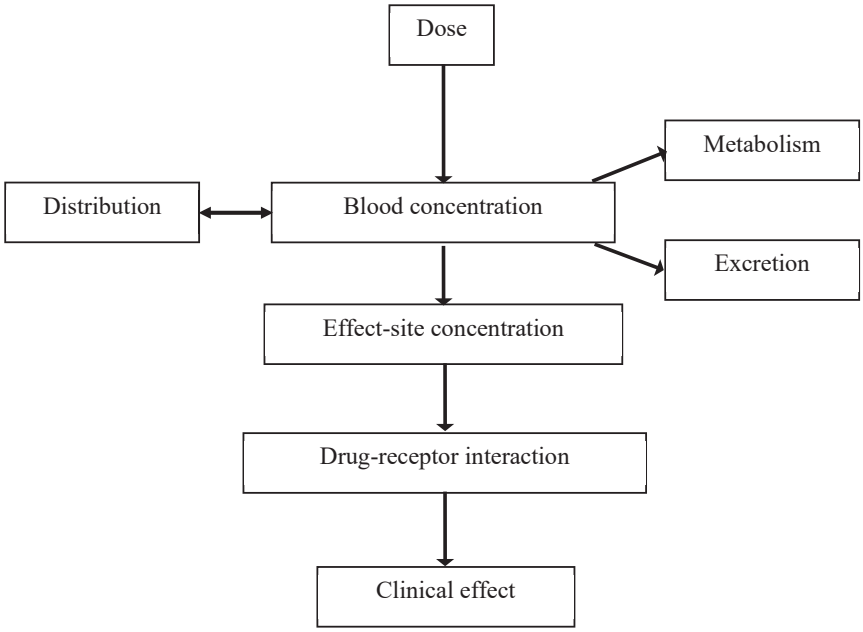

Figure 1: Schematic representation of the pharmacokinetic and dynamic processes determining the relationship between administered dose and resulting clinical effect.

necessary. This dose-response relationship, summarised in Figure 1, can be divided into three parts: the relationship between dose administered and plasma concentration (the pharmacokinetic phase), the relationship between effect organ concentration and clinical effect (the pharmacodynamic phase) and the coupling between pharmacokinetics and dynamics.

For several decades anaesthetists have been able to titrate the blood concentration of the inhalational anaesthetic agents by using a vapouriser to administer the drug and by measuring the end-tidal concentration (a moderately accurate estimate of blood concentration). In this way, anaesthetists who use inhalational anaesthesia need mainly to concern themselves with the pharmacodynamic phase of the dose response relationship.

The introduction of target-controlled infusion (TCI) technology in the late 1990s provided a similar facility to administer stable predicted plasma concentrations of the intravenous anaesthetic agents. Before this anaesthetists administering intravenous anaesthetic agents tended to calculate the dose or infusion rate according to the weight of the patient. The problem with this is the complex relationship between dose, plasma and effect-site concentrations. Simple infusion regimens do not yield steady state plasma concentration profiles until at

least 5 multiples of the elimination half-life. Also, the calculations required to estimate the plasma and effect-site concentrations are complex and not amenable to mental arithmetic! While encouraging progress has been made with methods of online estimation of blood propofol concentrations from measurement of exhaled gas concentrations of propofol metabolites, [12-16] and with point of care plasma propofol measurements,[17] these systems, even though since recently commercially available, require further refinement and development before they can become a useful pharmacological addition to the anaesthetists' clinical decision tools.

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Target-controlled infusions

Definition

A target-controlled infusion is an infusion where the intent is to achieve a user-defined drug concentration in a body compartment or tissue of interest. An anaesthetist using a TCI system to administer an anaesthetic agent is thus able to set a desired concentration (usually referred to as the "target concentration"), and to change the target concentration based on the observed responses to the set target concentration. TCI systems are programmed to use multi-compartmental pharmacokinetic models, and accompanying poly-exponential equations, to calculate the infusion rates required to achieve the target concentration (see below).

Theoretically, a TCI system can control the concentration in any compartment or tissue in the body. The pharmacokinetic models used are derived from previously performed population pharmacokinetic studies. By convention the central compartment in a pharmacokinetic model is referred to as Vc or V1, and this compartment includes the vascular compartment. Thus when the target is a user-defined concentration in the central compartment (which includes the vascular compartment), the infusion is referred to as a plasma targeted TCI. When the target concentration is a concentration at the site of action of the drug, the infusion is referred to as an effect-site targeted TCI.

Development of TCI systems

A brief description of the history of the development of TCI systems follows (this topic was reviewed in greater detail recently[18]). In 1968 Kruger-Thiemer described a theoretical approach to maintaining and achieving a steady state plasma concentration of a drug whose pharmacokinetics can be described by a

two-compartment model.[19] Vaughan and Tucker [20 21] developed the concept further, as did Schwilden who also developed the first clinical application of this theory, the CATIA system (computer-assisted total intravenous anaesthesia system).[22] The schemes developed by these pioneers for drugs whose pharmacokinetics can be described by a two-compartment model became known as BET (**B**olus, **E**limination, **T**ransfer) schemes. They were called this because they comprised an initial bolus to fill the central compartment, followed by two superimposed infusions, one to replace drug removed from the central compartment by elimination and one to replace drug that has been distributed to the peripheral compartment. A fixed proportion of the total amount of drug in the central compartment is eliminated each unit of time. Thus when the plasma concentration of a drug is constant the amount of drug eliminated each unit of time is constant, so that drug lost by elimination can be replaced by a constant rate infusion. In contrast the amount of drug distributed to peripheral tissues declines exponentially as the gradient between the central compartment and the peripheral compartment decreases. Thus an infusion at an exponentially declining rate is required to replace drug removed from the central compartment by distribution. The sum of these two infusions is naturally an infusion at a decreasing rate.

Since then it has been recognised that the pharmacokinetics of most anaesthetic agents conform best to three compartment models. Numerous algorithms, appropriate for a three compartment model, for targeting plasma concentrations [23-27] and for targeting effect-site concentrations [28 29] have been published, and several groups of investigators have developed model-driven automated systems capable of delivering steady state drug concentrations. Since the early 1990s the experimental target-controlled infusion software programs developed in Stanford (Stanpump), Stellenbosch (Stelpump), Erlangen (CATIA and IV FEED), Alabama (CACI), Leiden (Leiden TCI System), Brussels (Toolbox), Santiago (AnestFusor), and Gent (RUGLOOP) have been used to study the pharmacology of existing and new drugs and to investigate the advantages of TCI. Several other pharmacokinetic simulation programs have also been developed (see recent review [30]).

Initially different groups used different terminology to describe their systems.[22 31-34] Eventually a consensus was reached among the leading groups, who published a letter in Anesthesiology suggesting that the term TCI should be adopted.[35] The group also suggested standard nomenclature for plasma and effect-site concentrations (C_p and C_e respectively, with the added subscripts T to indicate that the concentration being discussed is the "target" concentration, CALC to indicate that the concentration is the calculated plasma or effect-site

concentration, and MEAS to indicate that the plasma or effect-site concentration is a measured concentration).

The first commercially available TCI system was the Diprifusor®, a microprocessor that was embedded in intravenous infusion pumps sold by several manufacturers from 1996 onwards (in numerous countries around the world, but not in the USA). The development of the Diprifusor® has been described in detail.[18 36 37] TCI pumps controlled by it can only administer target-controlled infusions of propofol, and only if the microprocessor is able to detect the presence of single-use pre-filled glass syringes of 1 or 2% propofol purchased from AstraZeneca. These syringes contain a programmable metallic strip in the flange that is detected by a sophisticated process called programmed magnetic resonance. When the syringe is almost empty the strip is "de-programmed" so that it cannot be re-used.

A few years after the release of the first generation of TCI systems, the patent for propofol expired, resulting in significantly cheaper generic forms of propofol becoming available. This prompted the development and launch of second generation of TCI systems, the so-called "Open TCI" systems. These systems allow the use of a variety of drugs, administered from a variety of syringes and sizes. Numerous second generation systems are now available.[30]

Components of a TCI system

The basic components of a TCI system are a user interface, a computer or one or more microprocessors and an infusion device. The microprocessor controls the appearance of the user interface, implements the pharmacokinetic model, accepts data input and instructions from the user, performs the necessary mathematical calculations, controls and monitors the infusion device, and implements warning systems to alert the user of any problems (e.g. mains disconnection, syringe almost empty).

Audible and visible warning systems are an essential feature, and TCI devices should be programmed to respond appropriately to all possible fault conditions. Should a serious fault occur, then alarms should sound and the system should shut down or stop infusing, depending on the fault. The first generation TCI pumps contained two microprocessors. A 16-bit microprocessor implemented the algorithm to calculate the infusion rates required for the target concentration, and controlled the syringe driver motor speed accordingly. In parallel, an 8-bit processor monitored the number of rotations of the driving motor and used a simpler mathematical process (involving Euler approximations) to

calculate the estimated plasma concentration based on the amount of propofol delivered. If the target and estimated plasma concentrations differed significantly, the system shut down. As this was a very rare occurrence and faster microprocessors had been developed, the dual processor technique has not been implemented in the new generation pumps.

The user interface prompts and allows the user to enter the patient data such as age, weight, gender and height and of course the target drug concentration, whilst displaying useful numeric and/or graphic information (such as the current infusion rate, and the trend of the calculated plasma and effect-site drug concentrations). Typical TCI systems incorporate infusion devices that are capable of infusion rates up to 1200 ml/hr, with a precision of at least 0.1 ml/hr.

Plasma concentration targeted TCI

HOW DO PLASMA-TARGETED TCI SYSTEMS DELIVER STEADY STATE PLASMA CONCENTRATIONS?

TCI systems are programmed with pharmacokinetic models that mathematically describe the processes of drug distribution and elimination (see Figure 2 and also the later section on pharmacokinetic models). Although different TCI systems might use slightly different mathematical techniques, the practical end result remains a variation of a BET scheme.

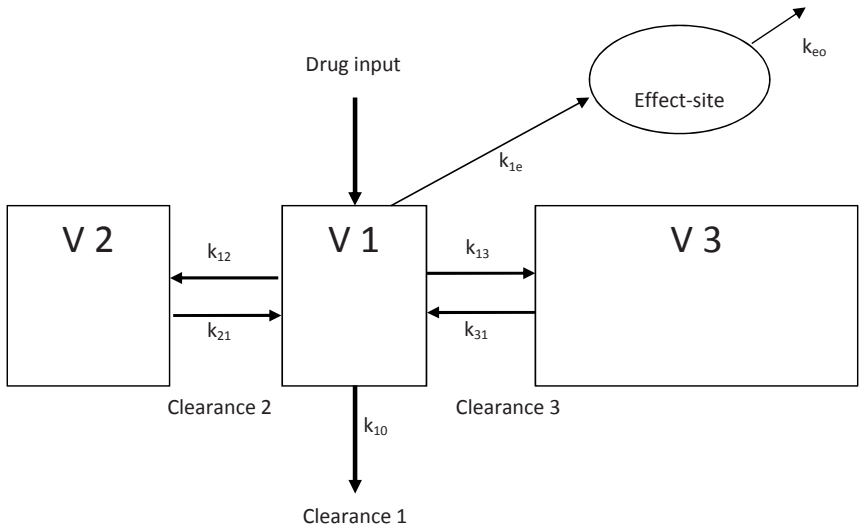

Figure 2: The three compartment pharmacokinetic model enlarged with an effect compartment. The concentration in this compartment is called “effect-site concentration”.

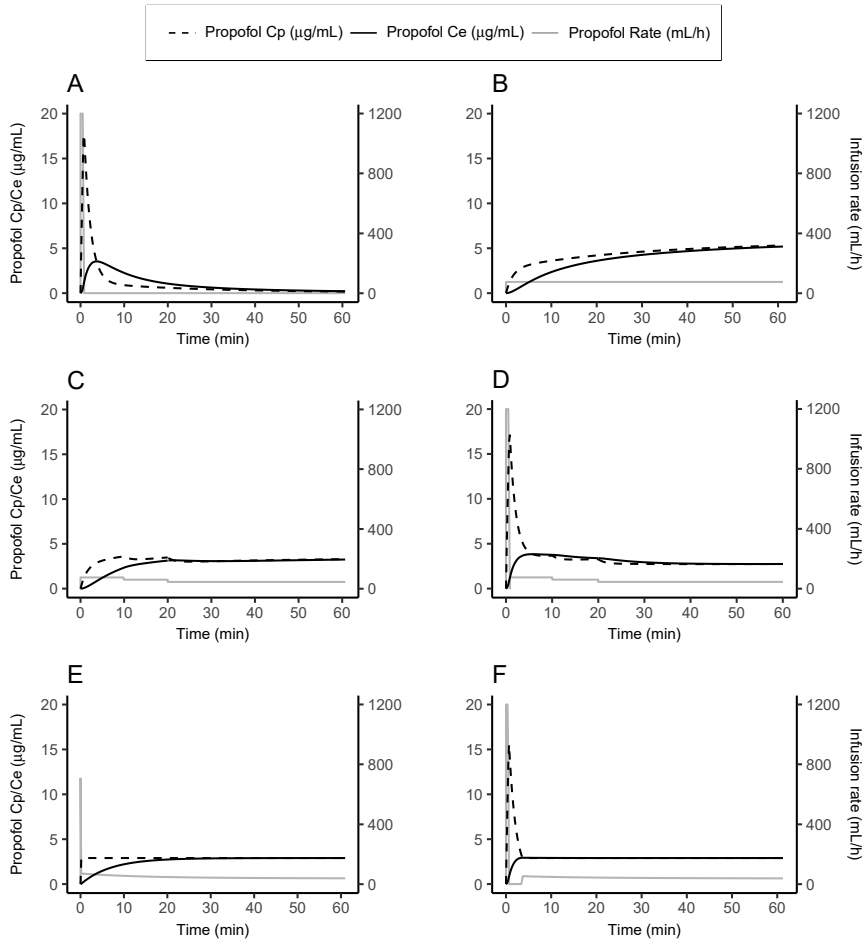

Figure 3: Propofol plasma and effect-site concentrations of various propofol infusion schemes predicted by the Eleveld model. A: bolus 2 mg/mg at 1200 ml/h; B: continuous infusion at 10 mg/kg/h; C: Continuous infusion of 10 – 8 – 6 mg/kg/h (10 minute intervals between decrements) ; D: bolus 2 mg/kg, followed by a 10 – 8 – 6 mg/kg/h continuous infusion (10 minute intervals between decrements) ; E: plasma targeted TCI at 2.89 µg/ml ; effect-site targeted TCI at 2.89 µg/ml. Patient is male, 170 cm, 75 kg, 45 years.

The general method is illustrated in Figure 3. When the anaesthetist increases the target concentration the system administers a rapid infusion (bolus) to quickly fill the central compartment thereby giving an almost step-wise increase in plasma concentration. The amount infused is calculated according to the estimated central compartment plasma volume and the difference between the current calculated concentration and the target concentrations. When the system calculates that the plasma concentration has reached its new target, it stops

the rapid infusion, and commences an infusion at a lower rate. For practical reasons, current TCI systems repeat the calculations, and alter the infusion rate, at discrete intervals (typically every 10 sec). Thus, although the amount of drug removed from the central compartment changes continuously, the infusion rate changes in a "step-wise decreasing" manner. If a three compartment model is in use, three superimposed infusions are required. While the target concentration is constant, a constant rate infusion is required to replace drug removed by elimination. Two first-order infusions – at exponentially decreasing infusion rates – are required to match the net movement of drug from the central to the other two compartments. The net result is a slowly decreasing infusion rate over time (until total steady-state is reached, which requires an infusion lasting > 24 hours). This is shown in figure 3, panel E.

When the anaesthetist decreases the target concentration the system stops the infusion, and waits until it estimates that the plasma concentration has reached the target concentration. The rate at which the plasma concentration falls depends on the rate of elimination, and on the gradient between the concentrations in the central and other compartments. Thus if the concentration in the central compartment is greater than that in another compartment, the plasma concentration will fall more rapidly, whereas if the reverse is true, the return of drug from the peripheral compartment will reduce the rate of decline in the plasma concentration. Once the system estimates the plasma concentration has reached the target, it will re-start the infusion at a lower rate, once again calculating the changing infusion rates required to maintain the plasma concentration at the target concentration.

TCI VS MANUAL INFUSIONS

Although pharmacological models exists for all drugs, in most areas of medical practice doctors tend to use manually controlled infusions, usually at a fixed rate. Target-controlled infusion systems automatically take into account drug accumulation over time (without the user having to adapt the infusion rate manually) and this gives the clinician more precise control of plasma and effect-site concentrations. Certainly in anaesthesia, where it is important for the clinician to be able to exert fine, rapid control over specific drug concentrations, TCI offers benefits.

With most drugs administered by a fixed rate infusion, the plasma concentrations take a long time to reach a plateau or steady state. This is illustrated for propofol in Figure 3, panel B, which shows that after 60 minutes, the plasma concentration is still rising. In fact, plasma concentrations will continue rising for >12 hours, since it takes >24 hours for the drug to equilibrate throughout all

the tissues in the body. For drugs such as fentanyl, morphine and midazolam, the time taken for equilibration and steady state is even longer.

For the latter drugs and also for propofol large changes to an infusion rate will not lead to significant changes in plasma concentration for some time (see Figure 3, panel C – at 10 minutes the infusion rate from 10 to 8 mg/kg/hr, and after another 10 minutes to 6 mg/kg/hr, but despite these sizeable changes, the plasma propofol concentration undergoes a proportionally far smaller change. The time delay before there is a significant change in effect-site concentration, and thus in clinical effect, will be even longer.

When a rapid increase in the drug concentration is needed then this is best achieved by administration of a bolus, but it is difficult to judge the size of bolus appropriate for the patient and the desired change in plasma or effect-site concentration (see Figure 3, panel D). Similarly, to decrease the concentration as rapidly as possible, it is best to switch off the infusion temporarily, but in the busy theatre environment there is a real risk the anaesthetist may forget to re-start the infusion. With TCI systems, these changes are made automatically, enabling precise and rapid control of the plasma concentration.

It is not surprising that TCI systems are popular with anaesthetists, who have assessed them as easy to use, and providing a high level of predictability of anaesthetic effect.[38] In a study comparing manual infusion with TCI propofol by anaesthetists unfamiliar with propofol infusion anaesthesia, it was found that anaesthetists quickly became familiar with both techniques, but expressed a clear preference for the TCI system.[39] A multicentre study found that the control of anaesthesia was easier in subjects anaesthetised with target-controlled than with manually controlled propofol infusions.[40]

How does the quality of clinical control compare between TCI and manually controlled infusions? Although many of the early target-controlled infusion systems were used for infusions of opiates, most of the evidence comes from studies comparing TCI with manually controlled propofol infusions. Quality of anaesthesia is difficult to measure, but studies have used simple categorical measures where the anaesthetist rates the quality as good, adequate or poor as well as other numerical methods such as a quality of anaesthesia score.[41] In studies comparing TCI with manual propofol infusion regimens the quality of induction and maintenance of anaesthesia the incidence and severity of haemodynamic effects, and the recovery times were either similar or better with TCI administration.[39 42-47] Despite this, there is no strong evidence that TCI administration is associated with better outcomes than manual administration.[48]

Effect-site concentration targeted TCI

The first generation TCI systems incorporated the Diprifusor microprocessor which is programmed to target the plasma concentration. Although some systems displayed the estimated effect-site concentration, they did not allow effect-site targeting. The disadvantage of targeting the plasma concentration is that when the target concentration is changed there is a temporal delay before the plasma and effect-site concentrations equilibrate. This is clearly illustrated in Figure 3 panel E. As the clinical effect of a drug depends on the concentration at the effect-site, there is an hysteresis in clinical effect when the target plasma concentration of the agent is increased or decreased. In fact it was, in part, the observation made by anaesthetists using early propofol TCI systems that patients lost and regained consciousness at different estimated plasma concentrations that lead to the realisation that plasma-effect-site equilibration is not instantaneous; and that when plasma concentrations were changing it was the effect-site and not the plasma concentration that determined the clinical effect.

The rate of equilibration between plasma 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 cardiac output and cerebral blood flow), the plasma-effect-site concentration gradient, and the pharmacological properties of the drug that determine the rate of transfer of the drug across the blood-brain barrier (lipid solubility, degree of ionisation etc). The time course of plasma-effect-site equilibration can be mathematically described by a rate constant typically referred to as the k_{eo}. Strictly speaking k_{eo} should be used to describe the rate of removal of drug from the effect-site out of the body, but the effect-site is usually regarded as a volume-less additional compartment, so that there is no need for separate constants describing the rate constants for movement into *and out of* the effect compartment.

Naturally the concentration at the effect-site cannot be directly measured, and most of the time the plasma concentration is not known either. However, the time-course of the changes in the effect-site concentration can be estimated from measures of clinical effect such as spontaneous or evoked EEG parameters. When plasma concentrations and clinical effect are measured concurrently, the k_{eo} can be estimated using mathematical modelling [49 50] and incorporated in a combined pharmacokinetic-pharmacodynamic model may be applicable to a similar population.

When pharmacokinetic and pharmacodynamic data are not available from the same subject group then it is recommended that the time to peak effect (TTPE), a model-independent parameter, is used to estimate the k_{eo} for a

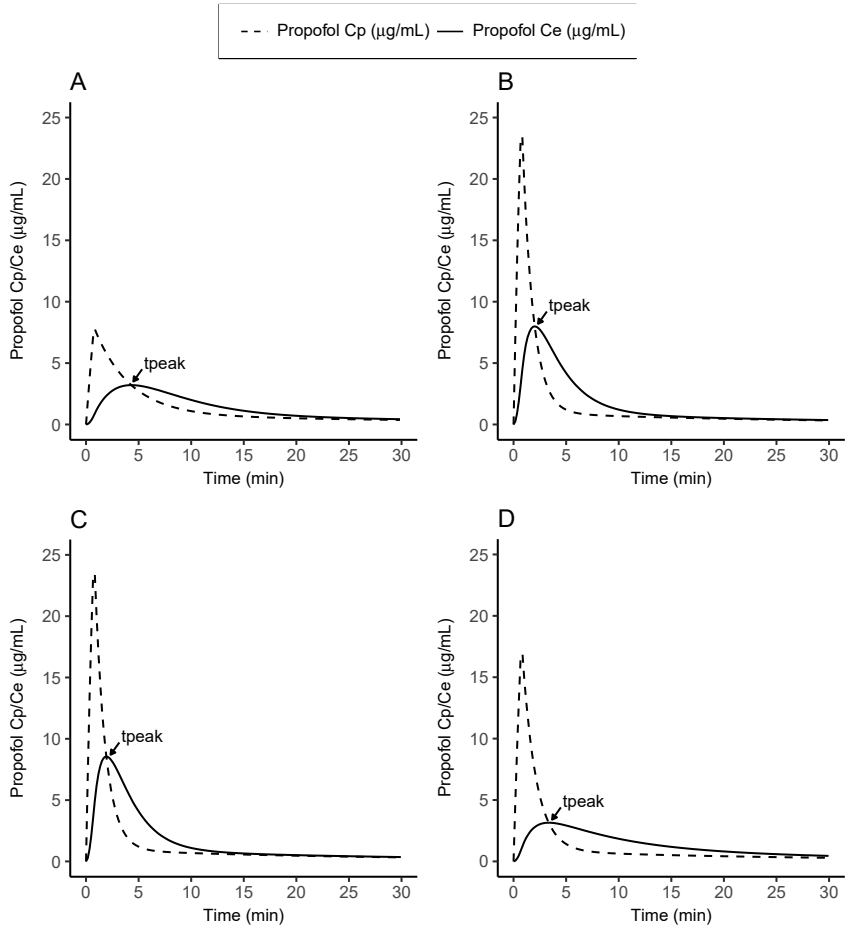

Figure 4: Predicted plasma and effect-site concentration of a propofol (10 mg/ml) bolus 2 mg/kg using the Marsh model, Schnider model with fixed ke0, Schnider model using fixed tpeak, and the Eleveld model. The tpeak is indicated for every model. Patient is male, 170 cm, 75 kg, 45 years.

pharmacokinetic model and patient group.[51] For a given patient, and a given drug, bolus administration of a drug will result in a rapid increase in plasma concentration, followed by a bi- or tri-exponential decline, the rate of which is determined by the pharmacokinetic characteristics of the drug. When the plasma concentration is greater than the concentration in the effect-site, the effect-site concentration rises, and vice versa. After a bolus the maximum effect-site drug concentration occurs at the point when the plasma and effect-site concentration curves cross (see Figure 4). As the clinical effect is determined by the effect-site concentration, the time delay between a bolus injection and the

time at which the plasma and effect-site concentration curves cross or intersect, is referred to as the "time to peak effect" (TTPE). It is important to remember that in general, the time to peak effect of a given drug in a given patient is independent of the size of the bolus dose.

After a standard bolus dose calculated on a mg/kg basis, a simple model such as the Marsh model,[52] in which all volumes and clearances scale linearly with weight, will predict the same peak plasma concentration, and the same time-course of plasma drug concentration, for all patients, regardless of their age, weight, gender or height. In this case, the same TTPE will generate the same k_{eo} for all patients. More complex multivariate models also include height, weight and gender as co-variates (e.g. Schnider,[53 54] Minto[55 56] or Eleveld[57]). For the same dose calculated on a mg/kg basis, complex models will predict different peaks and/or time-courses of plasma concentrations for patients with different gender, height or weight. In this case, if the TTPE for that drug and population is known, then that TTPE can be used to calculate a unique k_{eo} for each patient.[58]

When a combined pharmacokinetic-dynamic model is available it is possible to "target" the effect-site rather than the plasma concentration. With effect-site targeting the system manipulates the plasma concentration to bring about the target (effect-site) concentration as rapidly as possible without an overshoot of the effect-site concentration. This is illustrated in Figure 3, panel F. A more detailed example is shown in Figure 5.

When the target effect-site concentration is increased the system calculates an optimal peak plasma concentration that will cause a gradient sufficient to cause the most rapid increase in effect-site concentration but without an overshoot of the effect-site concentration. Once the system estimates that this calculated plasma concentration has been reached the infusion is switched off. If the peak was calculated correctly the (declining) plasma and (increasing) effect-site concentrations will reach the target simultaneously. The system will then restart the infusion to maintain the plasma (and effect-site) concentrations at the target concentration.

If the target effect-site concentration is decreased the system switches off the infusion, and allows the plasma concentration to fall below the target level, thereby creating a gradient driving drug out of the effect-site. This causes the most rapid possible decline in effect-site concentration. As soon as the effect-site concentration reaches the target, the infusion is re-started. A bolus is given to bring the plasma concentration back up to the target concentration and an infusion is then started to maintain the plasma and effect-site concentrations at the target concentration.