Principles of intravenous drug infusion

David J Chambers

Abstract

Intravenous infusions are required when a drug has a short half-life or a narrow therapeutic window. Pharmacokinetic models are employed to calculate the infusion rate for a particular target plasma concentration. While the one-compartment model is based on relatively simple mathematics, it is of little practical use. Multi-compartment models involve complex mathematics: a bolus-infusion regimen requires a variable-infusion rate. In clinical practice, this means incorporating the pharmacokinetic models into specially designed target-controlled infusion pumps. The physicochemical properties of different drugs result in very different behaviours, especially following cessation of intravenous infusion.

Keywords Anaesthesia; delayed emergence from anaesthesia; infusion pumps; infusions; intravenous; intravenous anaesthesia

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- explain why some drugs must be given by intravenous infusion
- draw schematics for one- and multi-compartment pharmacokinetic models
- describe why intravenous infusions are often bolus primed
- state the difference between plasma- and effect-site targeting
- explain why the recovery from the intravenous infusion of certain drugs takes a prolonged time period

When we administer drugs to patients, our aim is that the drug reaches the target tissue in the desired concentration for the right amount of time to exert its effects while minimizing any side-effects. The plasma drug concentration following drug administration to a patient is determined by the pharmacokinetic effects of absorption, distribution, redistribution, metabolism and excretion.

When a clinical situation requires a therapeutic concentration of a particular drug for an extended period of time, the options are intermittent dosing, e.g. via oral or intravenous routes, or continuous administration, e.g. via the transdermal route or by intravenous infusion (Figure 1). Intravenous infusion is chosen when:

- The half-life ($t_{½}$) of the drug is short, so that intermittent dosing becomes unacceptably frequent. For example, the $t_{½}$ of noradrenaline is 2 minutes.
- The drug has a narrow therapeutic range, e.g. heparin. That is, wide fluctuations in plasma concentration (as occurs with the intermittent bolus regimen in Figure 1) may result in toxicity.

If we know the therapeutic plasma drug concentration, we can use pharmacodynamic models to calculate the intravenous infusion rate. The aim of this article is to give an overview of that process, as it applies to anaesthesia.

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Conflict of interest: none declared.

Pharmacokinetic models

Pharmacokinetic models are mathematical models which have been developed to explain what happens to a drug once it has been administered. The pharmacokinetic model is then used to plan a drug dosing regimen for an individual patient. The compartment model divides the body into a number of 'compartments'. Although these compartments do not actually correspond to anatomical structures, they can be thought of as similar tissues grouped together, e.g. highly perfused tissue. The simplest model has one compartment, but few drugs behave in this way. Most intravenous infusions used within anaesthesia follow a three-compartment model.

One-compartment model

In this model, the whole body is considered as a single compartment of a fixed volume (the volume of distribution, V_1). As a drug is added to the compartment (Figure 2a), it immediately diffuses across all tissue types. An analogy for this model is water filling a bath.

Constant rate infusion

Before the infusion starts, there is no drug present in the compartment – the initial plasma drug concentration (C_0) is zero. As the drug is added, it distributes throughout the compartment. But rather than the plasma drug concentration (C_p) increasing in a linear fashion, it follows a negative exponential pattern, initially rising rapidly before reaching a plateau (Figure 2b). The reason for this is drug elimination – the drug is being removed from the compartment at the same time as it is being infused, rather like filling a bath with the plug removed. Elimination is a term that describes any process that removes a drug from the body, encompassing metabolism (chemical conversion of the drug to a metabolite) and excretion of unchanged drug from the body (via the kidneys, biliary tract and, in the case of volatile drugs, the lungs). For most drugs, the rate of drug elimination is proportional to the drug concentration. Mathematically, the rate of elimination, k_{10} = clearance × C_p. After a period of time, a point is reached where the rate of drug infusion equals the rate of drug elimination – at this plateau, the drug concentration is termed the 'steady state concentration' (C_{ss}). C_{ss} is therefore influenced by the drug infusion rate and clearance – the infusion rate may be altered to increase or decrease C_{ss} as required.

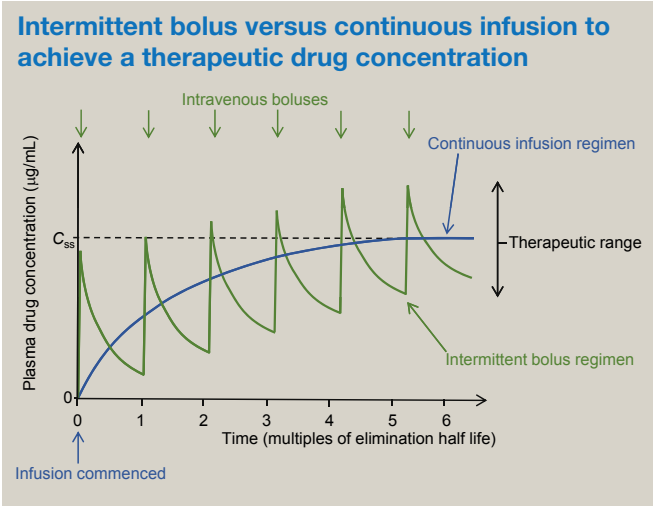
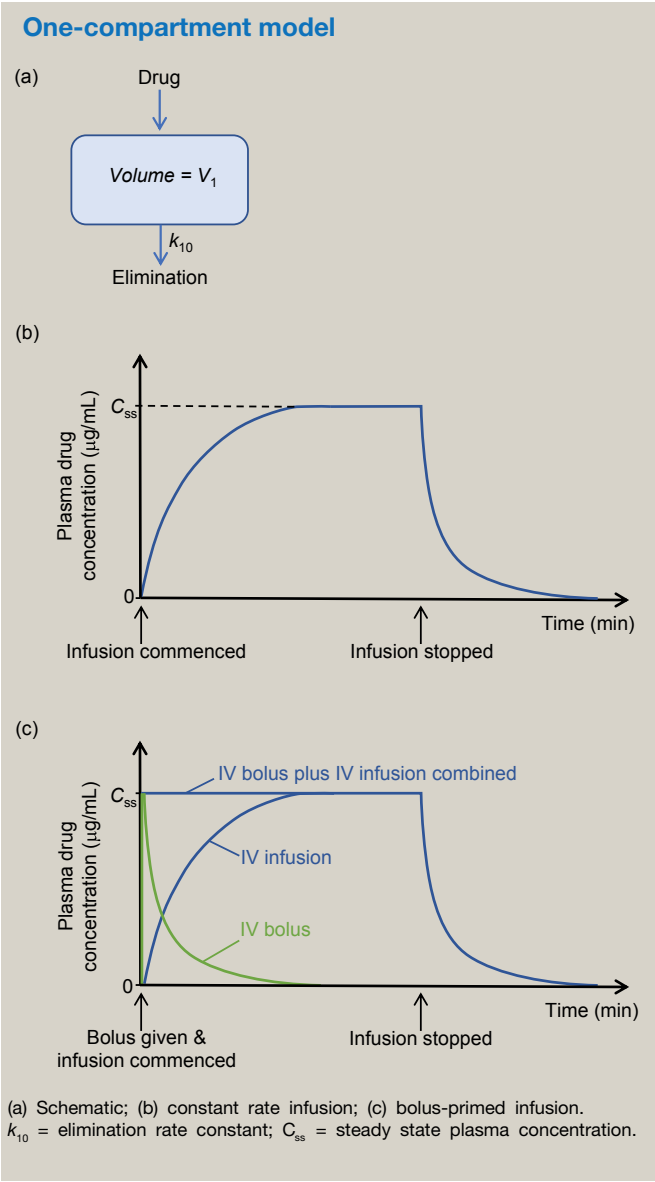


Figure 1



(a) Schematic; (b) constant rate infusion; (c) bolus-primed infusion. k_{10} = elimination rate constant; C_{ss} = steady state plasma concentration.

Figure 2

Bolus-primed infusion

The main problem with the constant rate infusion described above is the length of time taken to reach C_{ss}, roughly five drug half-lives. Many clinical situations (e.g., anticoagulation with heparin) require that therapeutic plasma drug concentration is reached sooner. This is achieved by giving the patient an initial intravenous drug bolus before commencing the intravenous infusion. The plasma drug concentration due to the bolus then decreases exponentially as the concentration of the drug due to the infusion increases exponentially, with the overall effect of a constant C_p (Figure 2c). The size of the drug bolus depends on the desired C_{ss} and the volume of distribution — in the case of the one-compartment model, this is simply calculated as C_{ss}/V_1.

Stopping the infusion

Once the infusion is stopped, elimination continues; C_p decreases in an exponential fashion. The curve is the same for both bolus-primed and continuous infusion (Figures 2b and 2c), even if the infusion is stopped before steady state is reached, and is independent of duration of infusion. Mathematically, this exponential decay is described by the equation $C_p = C_o\, e^{-k_{10}t}$, where C_o is the plasma concentration when the infusion is stopped (i.e. C_{ss} if the infusion is stopped after steady state is reached), k_{10} is the elimination rate constant and t is time. The half-life of a drug obeying the one-compartment model is the time taken for the plasma concentration to halve, which is described mathematically as $t_{½} = \frac{0.693}{k_{10}}$.

Multi-compartment models

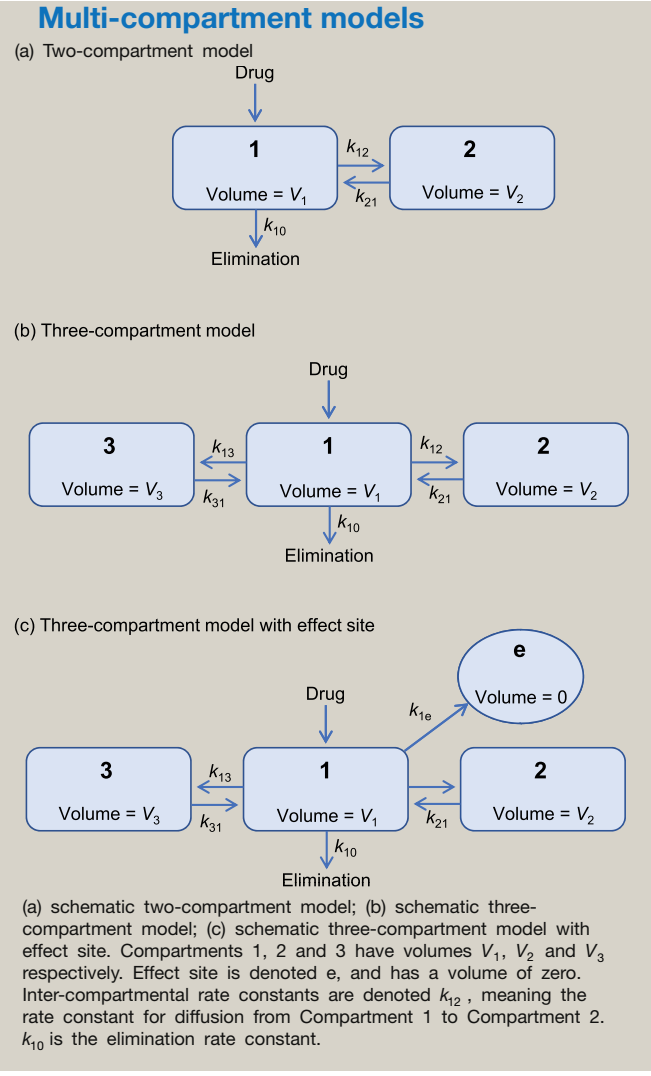
The pharmacokinetic behaviour of most drugs is more complex than the simple one-compartment model; a two- or three-compartment model is required (Figure 3).

Two-compartment model

In the two-compartment model (Figure 3a), the body is divided into a central compartment (which can be thought of as containing highly perfused tissue such as heart, lungs, brain, liver and kidneys) and a peripheral compartment (containing poorly perfused tissues such as muscle, fat and skin). Drugs that are permanently positively charged, e.g. rocuronium, approximate to a two-compartment model.

The drug is injected into the central compartment, but it may also diffuse from the central compartment into the peripheral compartment — this is termed 'distribution'. The rate of distribution depends on the concentration gradient between the two compartments and a rate constant, k_{12}. Distribution of the drug from the central compartment is only temporary — when the drug concentration in the central compartment falls below that of the peripheral compartment, the drug may diffuse back ('redistribute') into the central compartment. The rate of redistribution is dependent on the intercompartmental concentration gradients and a rate constant, k_{21}. Thus the peripheral compartment can be thought of as a drug reservoir, initially storing drug which is later returned.

Like the one-compartment model, elimination removes the drug from the central compartment at a rate proportional to the drug concentration. Thus two simultaneous processes are responsible for removing the drug from the central compartment



(a) schematic two-compartment model; (b) schematic three-compartment model; (c) schematic three-compartment model with effect site. Compartments 1, 2 and 3 have volumes V_1, V_2 and V_3 respectively. Effect site is denoted e, and has a volume of zero. Inter-compartmental rate constants are denoted k_{12} , meaning the rate constant for diffusion from Compartment 1 to Compartment 2. k_{10} is the elimination rate constant.

Figure 3

following an intravenous drug bolus: distribution (temporary) and elimination (permanent).

Three-compartment model

This model comprises a central compartment and two peripheral compartments (Figure 3b). The central compartment can be thought of predominantly as plasma, whereas compartment 2 represents vessel-rich tissue (e.g. muscle) and compartment 3 represents vessel-poor, lipid-rich tissue. Many of the drugs commonly used by anaesthetists (e.g. propofol) behave according to the three-compartment model. The relative volumes of each compartment are dependent on the physicochemical properties of the drug (e.g. its lipid solubility) and the patient (e.g. tissue binding). A highly lipophilic drug, such as fentanyl, may have a much larger volume of compartment 3 (V_3) than the central compartment (V_1) – this has implications following a prolonged infusion (see below).

When a bolus of drug is injected into the central compartment, it may distribute into either peripheral compartment (dependent on the relative concentration gradients and the rate constants k_{12} and k_{13}), or be removed through elimination (according to the elimination rate constant k_{10}). When the concentration of a drug in the central compartment falls, the drug may re-enter the central compartment from the peripheral compartments through redistribution, according to the concentration gradients and rate constants k_{21} and k_{31}. All these processes follow an exponential pattern, and the underlying mathematics becomes sufficiently complicated to warrant computer modelling.

Intravenous infusion

A constant rate infusion would result in a very similar-looking plasma drug concentration–time graph to that of the one-compartment model (Figure 2), i.e. an initial rapid increase in C_p before reaching a plateau at C_{ss}. However, the mathematics underlying this process is more complicated, as the drug is removed from the central compartment by three exponential processes; distribution to the two peripheral compartments and elimination from the central compartment.

In the one-compartment model above, clinical situations which require rapid onset of drug action use a bolus-primed infusion, comprising a 'loading' drug bolus followed by a constant drug infusion. When the same principle is applied to a multi-compartment model, the situation again becomes more complex. To achieve a desired 'target' plasma concentration (C_{pt}), the loading dose must be followed by a variable rate of infusion, which aims to maintain the plasma concentration at the target C_{pt} until equilibrium is reached.

This problem is overcome by using a target-controlled infusion (TCI) pump, which uses a microprocessor to adjust the drug infusion rate according to the pharmacokinetic model. The TCI pharmacokinetic models use inputted patient data such as age, sex, weight and height, to refine the relative compartment volumes and inter-compartment rate constants. Following the loading dose, the TCI pump adjusts the drug infusion rate to compensate for the rapid and slow distribution to compartments 2 and 3, respectively (rate constants k_{12} and k_{13}), and drug elimination from the central compartment (rate constant k_{10}). Later, as the drug concentration between the central and peripheral compartments reaches equilibrium, the TCI pump reduces the rate of infusion to match the rate of elimination, k_{10}. Effectively, the TCI pump delivers three superimposed infusion rates, to match the rates of the three processes by which drug is being removed from the central compartment.

If the anaesthetist decides to increase the C_{pt}, the pump will deliver another small bolus of the drug, and recalculate the rate of infusion. Likewise, if the anaesthetist decides to decrease the C_{pt}, the pump stops temporarily, which allows the plasma concentration to decay to C_{pt}, then restarts the drug infusion at a lower rate.

Plasma-site versus effect-site targeting

The clinical effect of anaesthetic drugs such as propofol are exerted on the brain, yet so far the discussion has referred to the concentration of drug in the central compartment. When C_{pt} is used, there is a lag between achieving the desired plasma drug concentration and its clinical effect while the drug diffuses from the plasma into the 'effect site'. This time lag is influenced by the concentration gradient between the plasma and the effect site,

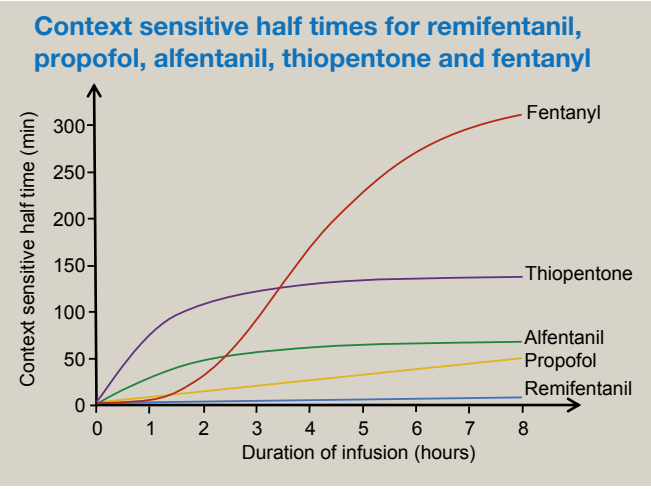


Figure 4

and the rate constant k_{1e}. The Marsh propofol model, which uses a three-compartment pharmacokinetic model in which C_{pt} is targeted, is subject to this time lag. In contrast, the Schnider propofol and the Minto remifentanil models utilize a fourth compartment, the effect site (Figure 3c), which allows the anaesthetist to target brain concentration (C_{et}). When C_{et} is targeted, the TCI pump delivers drug with the aim of reaching the effect site concentration as soon as possible. It does this by delivering a 'plasma overshoot' — a higher central compartment drug concentration — to generate a high concentration gradient between the central compartment and effect site. In the case of propofol, while the plasma overshoot achieves unconsciousness rapidly, it may also occasionally result in adverse haemodynamic consequences.

Stopping the infusion

In the one-compartment model above, stopping the intravenous infusion results in an exponential decrease in C_p solely due to elimination, with the drug half-life related to k_{10}. When the intravenous infusion is stopped in the multi-compartment model, C_p also decreases. However, the decrease in C_p is due to both distribution to peripheral compartments and elimination. The decay in C_p follows a curve that is characterized by the sum of several exponentials, and the concept of half-life no longer applies. The duration of infusion is important:

- After a very short infusion, little drug will have diffused into the peripheral compartments: the drug concentration gradient between the central and peripheral compartments will be high. C_p will decrease rapidly due to the effects of both distribution to the peripheral compartments and elimination.
- After a prolonged infusion, a greater quantity of drug will have entered the peripheral compartments: the concentration gradient between the central and peripheral compartments will be reduced. C_p will therefore decrease more slowly, with the initial decay predominantly due to elimination. Later, as C_p decreases below the peripheral compartment drug concentration, the drug will diffuse back to the central compartment through redistribution. Thus the peripheral compartments act as a reservoir of drug, which further prolongs the decay of C_p.

Context-sensitive half time

The time taken for C_p to halve is known as the 'context sensitive half time' (CSHT). Continuous infusions of the drugs propofol, fentanyl, remifentanil, alfentanil and thiopentone are used in anaesthesia and critical care. These drugs have very different CSHTs following a prolonged infusion (Figure 4), which can be explained by their pharmacokinetic models. For example, fentanyl has very long duration of action following prolonged infusion because of a large relative size of V_3, whereas remifentanil is effectively context-insensitive due to its very high rate of elimination (ester hydrolysis) and small compartment volumes.

Although CSHT predicts time taken for the plasma drug concentration to decrease by 50%, it does not necessarily relate to 'wake-up time'. TCI pumps will frequently display a 'decrement time', which is an estimate of the time it will take for the patient to wake if one were to stop the infusion at that point.

TCI educational resources

Tivatrainer is an online pharmacokinetic educational resource produced by EuroSIVA which develops the concepts in this article, and is available at http://www.eurosiva.eu/tivatrainer/TTweb/TTinfo.html. ◆

FURTHER READING

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