Pharmacokinetics of drug infusions

SA Hill MA PhD FRCA

Key points

The i.v. route provides the most predictable plasma concentrations.

Pharmacodynamic effects of a drug are related to plasma concentration.

Both plasma and effect compartments can be targeted.

The context of a context-sensitive half-time is the duration of infusion.

Propofol is suitable for long-duration infusions but fentanyl is not.

In clinical practice, drugs are given by continuous infusion to maintain a predictable pharmacodynamic action. In anaesthesia, the most common route is by continuous i.v. infusion, but the extradural, subarachnoid and subcutaneous routes are also regularly used. The effective use of drug infusions requires an understanding of both the pharmacokinetic and pharmacodynamic characteristics of the drug used. Pharmacokinetics describe how the plasma concentration of a drug changes over time, with the assumption that plasma will equilibrate with an effect compartment to produce pharmacodynamic activity. This article will describe, rather than derive equations to explain, the pharmacokinetics of i.v. infusions and a basic understanding of simple models of pharmacokinetics and the relationships between parameters is assumed.

Pharmacokinetic terms

For an i.v. infusion, plasma concentrations are influenced by distribution, redistribution, metabolism and excretion. For other routes of administration, absorption must also be considered. Elimination is a non-specific term describing any process that removes drug from plasma. There are several processes contributing to elimination: distribution describes elimination attributable to a drug temporarily being taken up by tissue other than plasma; redistribution is the release of such temporary stores back to plasma; and excretion the processes that permanently removes a drug from the plasma. Excretion is therefore a combination of metabolism (producing metabolites) and excretion of unchanged drug (e.g. from the kidneys or lungs). Metabolism to active products may prolong duration of action, thus altering the relationship between plasma concentration of a drug and pharmacodynamic activity.

The central volume of distribution (V_1) describes an apparent volume in a model that assumes that some tissues behave the same as plasma. Volume of distribution at steady-state (V_d^{ss}) describes the apparent volume into which a drug will disperse during a prolonged infusion; it is the sum of all the compartment volumes in the model describing a drug's kinetic behaviour (V_1, V_2 and V_3 in the three-compartment model shown in Fig. 1). Movement of drug between different compartments (distribution/redistribution) is determined by the concentration gradient between compartments and the inter-compartmental clearance. Clearance attributable to excretion describes removal of drug from the body. Rate of elimination from one compartment to another is the product of concentration in the compartment from which drug is being eliminated, and inter-compartmental clearance. Rate of excretion is the product of central compartment concentration and clearance. The relative importance of distribution and excretion in removing a drug from, and redistribution returning a drug to, plasma is central to our understanding of how plasma concentration changes during and after infusion. These changes will then be reflected in the effect compartment, but with a time-lag. Modelling is a mathematical tool used to predict the way in which plasma concentration varies over time. Each drug requires its own model as it is fitted to observed drug behaviour. The three-compartment model for propofol will not be the same as that for fentanyl or remifentanil.

It is assumed for modelling purposes that the link between pharmacokinetics and pharmacodynamics is through the concentration of drug at the effector site. The effect compartment is not included in the model, as it does not remove a significant amount of drug from the plasma. However, there is a half-life for equilibration ($t_{1/2}\ k_{eo}$) resulting in a time-lag before concentration changes in plasma are reflected in the effect compartment. This produces a delay in both onset and offset of pharmacodynamic effect when infusion rates are changed.

All pharmacokinetic parameters take constant values only for a given patient under a given set of clinical circumstances; as soon as pathological processes affect the body, these

SA Hill MA PhD FRCA
Consultant Anaesthetist
Shackleton Department of Anaesthesia
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD
Tel: 02380 796135
Fax: 02380 794348
E-mail: sahneuro@aol.com

Continuing Education in Anaesthesia, Critical Care & Pain | Volume 4 Number 3 2004 DOI 10.1093/bjaceaccp/mkh021

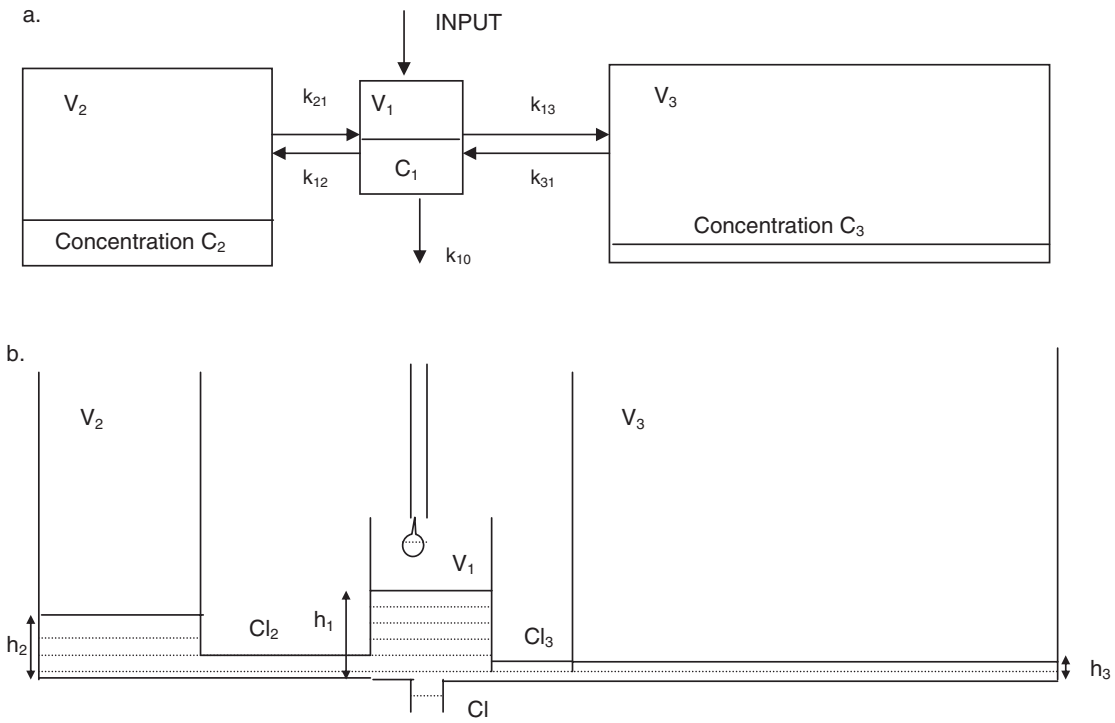


Fig. 1 (a) A three compartment model. The central compartment has a volume V_1 and the peripheral compartments volumes V_2 and V_3. The sizes of these vary from drug to drug and are influenced by physichochemical properties of the drug such as lipid solubilty. The rate constants for elimination from plasma: k_{10} represents excretion, and k_{12} and k_{13} represent distribution to compartments 2 and 3, respectively. In addition, k_{21} and k_{31} represent movement of a drug back into the central compartment once concentration gradients are reversed. Clearances: attributable to excretion ($V_1 \cdot k_{10}$) and inter-compartmental clearances between compartments 1 and 2 ($V_1 \cdot k_{12} = V_2 \cdot k_{21}$) and 1 and 3 ($V_1 \cdot k_{13} = V_3 \cdot k_{31}$). A drug may only enter and leave the model through the central compartment. (b) The hydraulic analogy of the three-compartment model. In the hydraulic analogy the height of water in the three chambers (h_1, h_2, h_3) represents the concentrations in those chambers; the volume of the chambers represents the volumes of distribution; the diameter of the connecting pipes represent the inter-compartmental clearances (Cl_2, Cl_3) and that of the exit pipe clearance due to excretion (Cl).

parameters will change. This is of particular relevance when considering the behaviour of drugs given by continuous infusion in critically ill patients.

One compartment model

Constant rate infusion

When an i.v. infusion is started at a constant rate of f mg min^{-1} in a simple one-compartment model, there is no drug present initially, so plasma concentration (C) is zero. As the infusion continues, C increases, initially quickly, but then more slowly, as the rate of excretion is initially slow but increases with increasing plasma concentration. Thus, plasma concentration increases in a negative exponential fashion. Equilibrium is reached when input = output. The input rate is f mg min^{-1} and output is the rate of excretion, giving $f = \text{Cl} \times C$ mg min^{-1}. Thus the concentration at equilibrium is determined by the ratio of the infusion rate to the clearance of the drug ($C = f/\text{Cl}$ mg ml^{-1}). The plasma concentration will remain unchanged as long as the infusion rate is held constant.

Bolus-primed continuous infusion

If an infusion is started at the rate needed to achieve the required plasma concentration it would take about three time constants (or five half-lives) to reach that concentration. This is usually too long for most circumstances where infusions are needed. Instead, a bolus dose of drug is given and the infusion started at our calculated rate. The size of the bolus dose should be enough to fill the volume of distribution; for the simple one-compartment model this would be C_e/V, where C_e is the required equilibrium concentration.

Stopping the infusion

If the infusion is stopped after reaching equilibrium, the decline in plasma concentration for this simple model will follow a simple single exponential curve. The time constant will be that for excretion. The decay curve will have the same time constant (and half-life) for both constant and bolus-primed infusions, even if the infusion is stopped before equilibrium is reached. This is because, in this simple model, the handling of drug by the body can be described as a single exponential process, and, independent of the

duration of infusion, it will always take the same time for the plasma concentration to halve.

Multi-compartment models

In practice, the simple model does not explain the pharmacokinetic behaviour of many drugs and either a two- or three-compartment model is required (Fig. 1). The central compartment models the changes in plasma concentration of the drug in question and the other compartments represent regions of the body that can temporarily remove drug from, and later release drug back into, the plasma. It should be remembered that a drug can only enter and leave such a model system through the central compartment.

The relative sizes of the compartments and their intercompartmental clearances depend upon physicochemical properties of the drug in question, particularly lipid solubility and patient factors (e.g. tissue binding). Drugs that are permanently charged have low volumes of distribution and are often described using a two-compartment model (e.g. pancuronium). Drugs that are highly lipid soluble, such as fentanyl and propofol, have a very large peripheral volume of distribution (V_3) compared with their central compartment volume (V_1) (Table 1). For example, intercompartmental clearance between central and third compartment is given by $V_1 \cdot k_{13} = V_3 \cdot k_{31}$ (see Fig. 1). If V_1 is much smaller than V_3 it implies that rapid distribution is associated with slow redistribution; however, slower distribution is associated with rapid redistribution. Clinically, this is particularly important after prolonged infusions. Predicting how plasma concentration changes with time in such a system requires computer simulation.

Fixed infusion rate

In this model, starting a fixed rate infusion will cause plasma concentrations to increase rapidly at first, but three processes will remove drug from plasma: distribution to compartments 2 and 3; and excretion. Initially, distribution (mainly to the second compartment) may contribute more to removal of drug from plasma than will excretion; an exception is remifentanil, where metabolism is extremely rapid and peripheral compartment volumes are small. The direction and speed of drug movement will depend on the concentration gradients between the plasma and peripheral compartments and the inter-compartmental clearances. As the infusion continues, movement of drug into the second compartment slows as the concentration within that compartment increases, but distribution to the third compartment continues. Plasma concentrations continue to increase, but more slowly, as the concentrations in the two compartments approach that of plasma. Excretion will contribute to elimination throughout, but becomes increasingly important as plasma concentration increases. Eventually, steady-state will be reached when there is no inter-compartmental movement of the drug. Input to the central compartment from infusion balances output from excretion and the concentration of drug is the same in each compartment. For drugs with very large V_d^{ss} and slow distribution it may take many hours before equilibrium is reached with a fixed infusion rate.

Target-controlled, variable infusions

In the one-compartment model, a bolus dose could be used to fill the volume of distribution and then a constant infusion rate calculated to maintain the plasma concentration needed. In the three-compartment model, the situation is more complex. A bolus dose can fill the initial volume of distribution (the central compartment), but then a *changing* rate of infusion is needed to maintain a constant central compartment concentration until steady-state is reached. This requires a method of *targeting* plasma concentration by varying the infusion rate to match the changes in contributions from distribution and excretion as the duration of the infusion increases. Target-controlled infusion (TCI) pumps are available for delivering propofol according to a three-compartment model. To maintain the operator-determined plasma concentration, patient weight and target concentration must be entered. It gives a small initial bolus dose followed by an infusion that is at first rapid, but which slows as peripheral compartments become saturated with the drug. If the target concentration is increased, the pump again delivers a small bolus dose to achieve the new target before it increases its infusion rate. If the target concentration is reduced, the pump stops temporarily, then resumes with a lower infusion rate once it has calculated that the plasma concentration has fallen to the required value. The *actual* plasma concentration will not exactly match the target concentration in most patients; the parameters used to control the pump are averaged from many patients.

One problem with using plasma concentration as the target is the time lag for effect concentration to equilibrate with plasma

Table 1 Pharmacokinetic parameters for drugs commonly used by continuous i.v. infusion. These data are averaged over a number of sources

	V_1 (litre)	V_2 (litre)	V_3 (litre)	I-Cl 2 (ml min^{-1})	I-Cl 3 (ml min^{-1})	Cl (ml min^{-1})	$t_{1/2}\,k_{eo}$ (min)
Propofol	16	35	250	1800	650	1900	2.6
Thiopental	6	34	150	2750	590	215	1.2
Remifentanil	5	10	6	2050	770	2600	1.2
Alfentanil	10	12	15	810	130	300	1.1
Fentanyl	15	35	250	3460	1650	1000	5.8

V_1, central compartment volume; V_2 and V_3, peripheral compartment volumes; I-Cl 2, inter-compartmental clearance between compartment 2 and the central compartment; I-Cl 3, inter-compartmental clearance between compartment 3 and the central compartment; Cl, clearance attributable to excretion; $t_{1/2}\,k_{eo}$, half-life for equilibration with effect compartment.

concentration. Pharmacodynamic effect will be delayed, particularly at onset of a targeted infusion. However, by targeting effect compartment concentration rather than plasma concentration, rapid onset can be achieved. The faster onset of action will necessarily be associated with higher initial plasma concentrations and this could produce unwanted side-effects. New infusion pumps are now available with options of targeting either plasma or effect compartment for both remifentanil and propofol.

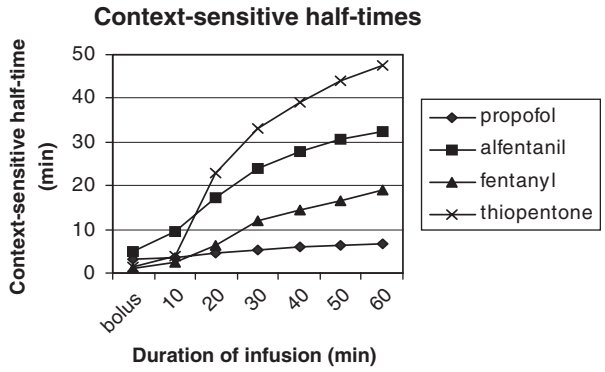
Stopping the infusion

Unlike the simple model, the decline in plasma concentration after stopping an infusion for complex models is characterized by a curve that is the sum of several exponentials. In particular, the rate of decline of the plasma concentration/time curve changes according to the duration of the infusion.

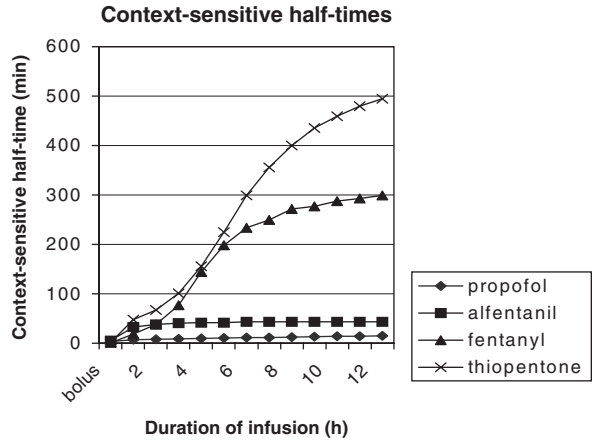
Context-sensitive half-time

On stopping an infusion, three possible processes contribute to a decline in plasma concentration: distribution to the second and third compartments, and excretion. The relative contributions of these to the initial decline in plasma concentration vary according to the duration of the infusion. The longer the infusion, the lower the concentration gradients between plasma (central compartment) and compartments 2 and 3, so the lower the contribution of distribution to elimination. After a very short infusion, plasma concentration will fall to half the initial concentration in a very short time, due to the combined effects of distribution and excretion. If the infusion runs to equilibrium, there is no contribution from distribution and elimination occurs only by excretion, which is opposed by re-distribution from peripheral compartments. Thus, the longest time for plasma concentrations to halve will occur following equilibrium when, with some drugs such as fentanyl (see below), it may come close to terminal elimination half-life. For infusions of intermediate duration, the time for the plasma concentration to halve will be between these two extreme values. This 'halving time' is known as the context-sensitive half-time where the 'context' is the duration of the infusion. Note that, unlike in the simple model, the time for plasma concentration to halve again (i.e. from a half to a quarter of the concentration on stopping the infusion) is longer than the context-sensitive half-time, so these are not half-*lives* (which are constants) but half-*times*. The extent of the variation in context-sensitive half-time for a given drug depends on the relative magnitude of clearance attributable to excretion compared with inter-compartmental clearance. The time to reach maximum context-sensitive half-time depends largely on V_d^{ss} and rate constant for re-distribution; it is shortest for drugs with a low V_d^{ss} and low rate constant for redistribution (e.g. remifentanil) and longest for large V_d^{ss} and high rate constant for redistribution (e.g. fentanyl).

Continuous infusions of propofol, alfentanil, fentanyl and remifentanil are used commonly in anaesthesia. Not only do they have very different context-sensitive half-times, but they



(a) short infusions



(b) infusions up to 12 hours

Fig. 2 Context-sensitive half-times. (a) Context-sensitive half-times after targeted infusions lasting up to 60 min. (b) Context-sensitive half-times after infusions lasting up to 12 h. Context-sensitive half-times calculated using Tivatrainer™.

also show very different patterns of changes in context-sensitive half-time as infusion time increases (Fig. 2). Propofol has a context-sensitive half-time that varies between 3 min for a very short infusion to about 18 min after a 12-h infusion. This relatively small variation in context-sensitive half-time, despite a large V_3, occurs because excretion is rapid compared with redistribution. For weak acids and bases, the degree of ionization influences pharmacokinetics. The lower pK_a of alfentanil (6.4) compared with fentanyl (8.5) means that the concentration of the un-ionized, diffusible form of alfentanil is 100 times greater than that of fentanyl. This accounts for its rapid onset-time and short $t_{1/2}\,k_{eo}$. For modelling purposes, alfentanil has a smaller central compartment volume, a very much lower V_d^{ss} and a lower clearance than fentanyl. As a result of these differences, fentanyl has a shorter context-sensitive half-time than alfentanil for short infusions (<2 h). However, alfentanil reaches its maximum context-sensitive half-time after just 90 min, so has a very much shorter context-sensitive half-time than fentanyl after very long infusions. Fentanyl becomes a very long acting drug if given at high infusion

rates for many hours because it has a large V_3 and redistribution is rapid (in contrast with propofol); thus plasma concentrations are maintained despite rapid excretion. Remifentanil has a relatively constant context-sensitive half-time. This is because clearance attributable to excretion (ester hydrolysis) is very high and V_d^{ss} is much smaller than for other opioids.

Thiopental is less commonly given by continuous infusion but may be used for burst-suppression of the EEG when it is given for many hours or even days at high dosage. It takes an extremely long time for the effects to wear-off and there are several reasons for this. The metabolism of thiopental is normally a first-order process; however, once plasma concentrations exceed a certain value, the enzyme system becomes saturated and metabolism becomes a zero-order process (i.e. rate of elimination becomes constant rather than dependent upon plasma concentration). Thus, the usual pharmacokinetic models are inappropriate after prolonged infusion. It should also be remembered that thiopental is metabolized to pentobarbital, which is also a sedative and excreted slowly. Thus, the *clinical* effects reflect not only plasma concentration of thiopental but also that of its major metabolite.

Decrement times

For offset of drug action, we may need plasma concentration to decrease by a percentage other than 50% at the end of infusion. Such times are known as decrement times. A decrease to just 50% of the original concentration is the 50% decrement time, synonymous with context-sensitive half-time. In the Diprifusor, a 'decrement time' is displayed that is the calculated time it would take plasma propofol to fall to a predetermined concentration at which the patient should be awake. This is therefore a *variable* decrement time, dependent upon the 'wake-up' concentration, the target plasma concentration and the duration of the infusion. It should be remembered that many other factors will affect the time to awakening, such as the use of opioids; therefore, this time must be taken as guidance only.

Mean effect time

A different approach to offset of action after an infusion is discontinued is the probabilistic approach described by Bailey. This uses a logistic regression model to predict the time it would take drug effects to disappear in 50% of patients. It is perhaps a more useful clinical predictor, but unfortunately there are relatively few data available for commonly used drugs. The advantage of such an approach is that it is more pharmacodynamic than pharmacokinetic.

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Web resources

European Society for Intravenous Anaesthesia <www.eurosiva.org>

See multiple choice questions 55–57.