

Total Intravenous Anaesthesia III

The application of pharmacokinetic and pharmacodynamic information to clinical practice

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Clinical implications of context sensitive half-time

When administering drugs by intravenous infusion, the context sensitive half-time (CSHT) is a much better indicator of the expected decline in drug concentration on discontinuing the infusion than any of the other pharmacokinetic parameters (TIVA I).

The application of this knowledge to clinical practice can be demonstrated if we consider the handling of an alfentanil infusion following a short (ten minute) and a prolonged (three hour) infusion. It helps our understanding if we imagine the previously considered three-compartment pharmacokinetic model with three compartments (Figure 1), where drug is delivered into and eliminated from only the central compartment (C_1). The amount of drug in each compartment is indicated by shaded portion of the compartment. Drug can move between C_1 (plasma) and C_2 , and between C_1 and C_3 via interconnecting pipes. The speed of equilibration between these compartments depends on the size of the interconnecting pipes (clinically analogous to the clearance from that compartment). It can be observed that the pipe from C_1 - C_2 has a larger calibre than from C_1 - C_3 , hence equilibration between C_1 and C_2 takes place more quickly than between C_1 and C_3 .

Short duration infusion

During any infusion, drug will redistribute from C_1 to C_2 and C_3 until they all have the same concentration of drug at equilibrium (dotted line). It can be observed that redistribution occurs more quickly into C_2 than C_3 . Hence, if we discontinue a short infusion of drug before equilibrium has been reached, drug continues to move into C_2 and C_3 (redistribution). This *speeds-up* the decline of drug concentration in the plasma (C_1). Because the redistribution is much quicker than the elimination, the observed CSHT at this point is closer to the redistribution half-life (see Table 1).

Figure 1a dotted line Drug levels in compartments following a short infusion

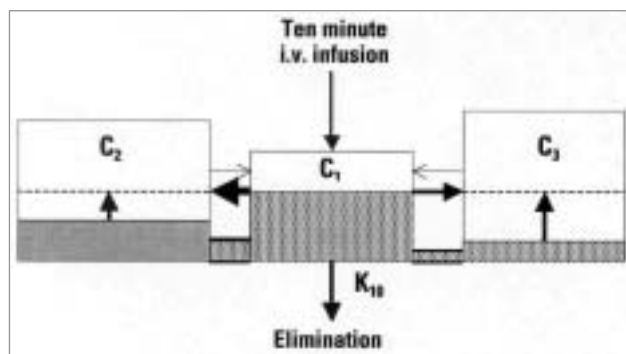
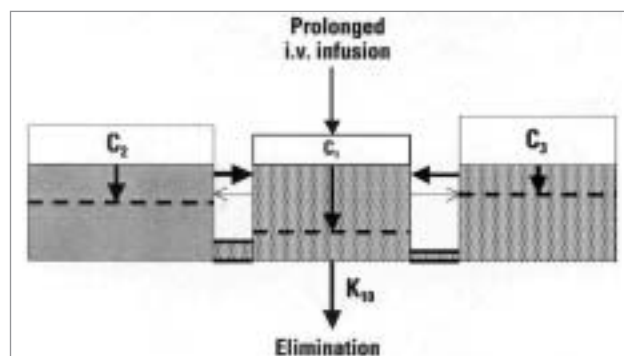


Figure 1b Drug levels in compartments following a prolonged infusion



Prolonged infusion

Following a prolonged infusion, the situation changes. There is more drug in the peripheral compartments, and at steady state the concentration in the three compartments will be the same (Figure 1b.). Hence, on discontinuing a prolonged infusion, instead of drug being removed from the plasma (C_1) by redistribution into C_2 and C_3 , it actually moves from C_2 and C_3 into C_1 , adding to the drug load to be eliminated. Therefore, the observed CSHT at this point is prolonged, and will be closer to the elimination half-life.

To look at this situation another way, we can consider the observed decline in alfentanil plasma concentration following the same short and prolonged infusions (Figure 2). This time we can see that the half-time is *four-times greater* for the three hour infusion.

If we infuse alfentanil to a constant plasma concentration for ten minutes and three hours respectively, and then measure the observed decline in plasma concentration from when the infusion is discontinued ($t=0$) we can see that the CSHT increases four-fold.

It is now clear that the effect of these peripheral compartments on the elimination of drug from C_1 is quite different after a short and prolonged infusion. This is the basis for understanding CSHT.

Figure 2 Effect of infusion duration on half-time

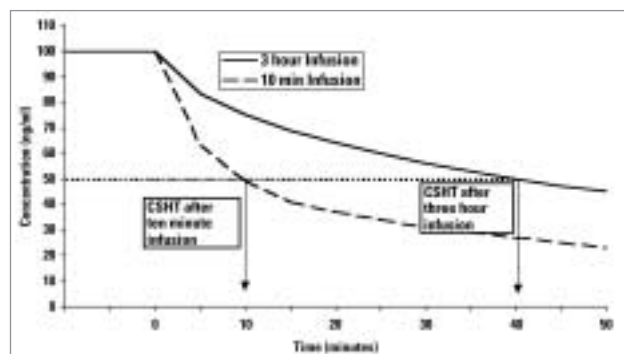


Table 1 Pharmacokinetic data

Drug	CSHT after ten minute/three hour infusion ⁶ (min)	Steady state Volume of Distribution ³ (l/kg)	Initial redistribution half-life ³ (min)	Elimination half-life ³ (min/hours)	Clearance ³ (ml/min/kg)
Opioids					
Remifentanyl	3/3	0.3–0.4	0.5–1.5	8–20 min	40–60
Alfentanil	10/40	0.25–0.75	1–3	60–120 min	3–8
Fentanyl	12/70	3–5	1–2	180–300 min	10–20
Hypnotics					
Propofol	5/9	2–10	1–4	4–7 h	20–30
Thiopentone	4/85	1.5–3.5	2–7	5–18h	3–4
Parameter predicts:	Describes the <i>clinically observed</i> half-time after an infusion of a certain duration	↑ Vd reflects increased peripheral drug stores	This is an inaccurate estimate of CSHT after a bolus dose	This is an inaccurate estimate of CSHT after prolonged infusion	Rate of removal of drug from plasma (C ₁₀)

Remember that: $t_{1/2} \propto Vd / Cl$

Published pharmacokinetics and CSHT

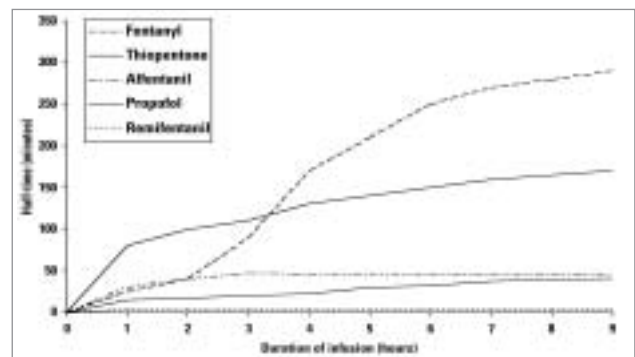
If we compare published redistribution and elimination half-lives with CSHT after a ten minute and three hour infusion (Table 1), we find that neither half life predicts the observed drug handling (CSHT). Whereas the pharmacokinetic parameters may be of great use to pharmacologists in constructing pharmacokinetic simulations, they are of limited use to clinicians. They can however give some clues as to the expected observed time course of clinical effects.

The closer a particular drug infusion is to steady state, the more closely the observed drug handling will resemble the situation in Figure 1b. If we plot CSHT against time, it generally increases, until it eventually plateaus at steady state (Figure 3). At this point, it will remain steady irrespective of the infusion duration, and is no longer context sensitive. Individual drugs reach this point after infusions of varying duration. In general, the larger the volume of distribution (Vd: volume of C₁ + C₂ + C₃) the longer it will take to reach steady state. For instance, remifentanyl reaches steady state after three to four minutes, alfentanil after three hours and fentanyl after 16 hours. The observed CSHT at steady state depends on speed of clearance from C₁, but also the size of the peripheral stores of drug and how quickly they can move back into the central compartment from the peripheral compartments (the rate limiting step for this is clearance from C₃-C₁).

For example, although fentanyl has a greater clearance from C₁ than alfentanil, its CSHT is longer. This is because there are vast peripheral stores of fentanyl (Vd of 70kg man =200–350l), and high clearance from C₃-C₁ (three times the Clearance of C₁₀). Hence, the peripheral stores of fentanyl effectively replace drug almost as fast as it is eliminated from C₁, prolonging CSHT.

Figure 3 Context sensitive half-time (CSHT)

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



CSHT and drug choice

All hypnotic drugs and all opioids (with the exception of remifentanyl) demonstrate this phenomenon. This does not mean they cannot be used for infusion, but merely that for prolonged operations, recovery may be delayed. Remifentanyl is unique because it is metabolised by tissue and plasma esterases (in effect eliminated from all three compartments), not just removed from the plasma.

A much easier way to predict drug disposition following infusions is to use a target controlled infusion. This can also calculate the expected time that it will take the current plasma concentration to fall to a certain level on discontinuing the infusion (decrement time). Unfortunately, TCI is currently only commercially available for propofol (Diprifuor).

Choosing the hypnotic

The usefulness of etomidate and ketamine infusions is limited by inhibition of adrenal steroid synthesis and psycho-mimetic side effects respectively. There are currently sparse data on s-ketamine infusions; hence, the only current choice for hypnotic infusions is between propofol and thiopentone. As can be seen from Table 1 and Figure 3, over the course of a three-hour infusion the CSHT for thiopentone increases **21 fold**, in contrast to propofol, which increases only **1.8 fold**. Quite clearly, propofol is the most suitable intravenous hypnotic currently available for intravenous infusion.

Why use propofol TIVA?

Currently the main alternative to intravenous propofol hypnosis is inhaled volatile anaesthesia. There are some benefits of propofol compared to volatile anaesthesia, but also some drawbacks: these are summarised in Tables 2a and 2b.

Which opioid

There is little to choose between the commonly used opioids remifentanyl, alfentanil and fentanyl with respect to their clinical effects. They are all full agonists and produce the same effects but at different plasma concentrations (reflecting their different potencies).

It has been shown that by increasing the blood concentration of opioid less hypnotic can be used (as demonstrated by the reduced $C_{p_{95}}$ of propofol). This confers haemodynamic stability and predictable anaesthesia. This technique has been used extensively in cardiac anaesthesia. However, high concentrations of alfentanil and fentanyl are associated with prolonged recovery. In contrast, the rapid elimination of remifentanyl (even following prolonged high rate infusions) allows an opioid-based technique to be used with predictable rapid recovery. The main limitation of this technique is that alternative analgesia should be instituted before discontinuing the remifentanyl infusion.

A practical example:

Following a three hour infusion, the CSHT of alfentanil was stabilised at four-times the baseline. The CSHT of fentanyl however has increased six-fold, and continues to rise being **17-times** longer at six hours, and stabilising after 16 hours at **23-times** the CSHT of a ten minute infusion. In contrast, the CSHT of remifentanyl remains unchanged throughout at three to five minutes (Figure 3). This prolongation of CSHT with prolonged infusions (especially for fentanyl) should be taken into account when planning recovery from anaesthesia. Unfortunately, this can be clinically quite difficult to judge without the aid of target-controlled infusions (which are not commercially available for either of these drugs). It can be seen that if prolonged postoperative opioid analgesia is desirable then alfentanil and fentanyl may be reasonable drugs to use. Conversely, if rapid recovery is desirable, especially after prolonged opioid infusion then **remifentanyl** makes a more logical choice.

Titration drugs

As previously explained (TIVA II) the clinical effects of drugs with respect to their plasma concentration (C_p) are less predictable during rapidly changing plasma concentrations e.g. at induction, emergence and while titrating dose. This can be demonstrated by the delay in equilibration of effect-site concentration (C_e) with C_p . **The larger the difference between these, the more unpredictable the clinical effect.**

Table 2a Advantages of TIVA with Propofol

Advantages of TIVA with Propofol	Comment
Safe in malignant hyperthermia	No reports of MH with propofol.
Rapid and predictable recovery	Discharge of day-case patients and their return to normal function is rapid. This has financial implications.
Anti-emetic	At least equivalent effect to the 5HT ₃ antagonists such as ondansetron. Improves quality of recovery.
Airway manipulation is facilitated	Instrumentation of the airway is possible without neuromuscular blockade.
Predictable anaesthesia with shared airway	TIVA does not rely on anaesthetic control of the airway to maintain anaesthesia (though obviously oxygenation must be maintained by some other means).
Reduced intracranial pressure	The cerebral metabolic rate for oxygen ($CMRO_2$) is reduced. Cerebral vasoconstriction, with a reduction in cerebral blood flow in proportion to the reduced $CMRO_2$, over all it reduces ICP.
Reduced atmospheric pollution	Maximum levels of volatile anaesthetics and nitrous oxide are set by the Committee of Substances Hazardous to Health (COSHH), and are enforceable by law.
Superior oxygenation reported with one-lung anaesthesia	Preservation of Hypoxic Pulmonary Vasoconstriction (HPVC) has been shown experimentally. This is in contrast to the volatile anaesthetics, which uncouple HPVC thus worsening V/Q matching, even at clinical levels. The clinical benefit of this is controversial.

Table 2b Limitations of TIVA with Propofol

	Comments
Still not standard practice	Not all hospitals have TIVA practitioners, so there is a need for specialised training. This has been addressed by courses run by enthusiasts. These are to be recommended.
Requires reliable i.v. access	Few would give inhalational anaesthesia without reliable i.v. access.
Administered drug cannot be recovered (exhaled)	The drug cannot be retrieved or 'blown off' as with inhalational anaesthesia, thus lightening of anaesthetic depth relies on redistribution and elimination of the drug.
Increased expense of specialised equipment and drugs.	The quality and speed of recovery, reduced requirement for expensive anti-emetic drugs, and reduced duration of post-operative stay allow a higher throughput of patients reducing staffing and ancillary costs. In addition in a gas free operating theatre scavenging equipment costs could be saved. These factors offset the apparent increased drug cost.
No direct objective measure of <i>individual's</i> plasma concentration (cf. end tidal monitoring)	Validation of the precision and bias of TCI systems has revealed a similar degree of difference between calculated and measured Cp (MDAPE) as between end tidal and arterial anaesthetic partial pressure (20–25%).
Awareness possible when used with neuromuscular blockers	The incidence of awareness with neuromuscular blockers used with TIVA appears to be the same as with inhalational anaesthesia at 0.2%. There has not been a randomised controlled trial to date, which compares the incidence of awareness between inhalational anaesthesia and TIVA.
Seizures: these have been reported at low concentrations	There continue to be case reports of convulsions with the use of propofol. Conversely, the anti-convulsant properties of propofol are becoming clear. It has clearly been shown to raise the convulsive threshold, and reduce seizure activity when used for electroconvulsive therapy. Furthermore, propofol is gaining popularity as a treatment for status epilepticus.
Pain on injection:	Reduced by adding lignocaine.

If we consider a patient having propofol plasma concentration titrated slowly and quickly (Figures 4a and 4b) we can observe that slower titration minimises the difference between Cp and Ce. This minimises the unpredictability of the clinical effect.

Figure 4a Large increments

If the target concentration is titrated in large ($2 \mu\text{g}\cdot\text{ml}^{-1}$) increments, the difference between the plasma and effect site concentration (solid arrow) is greater.

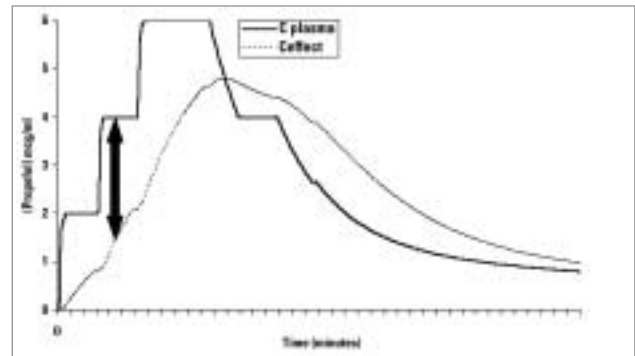
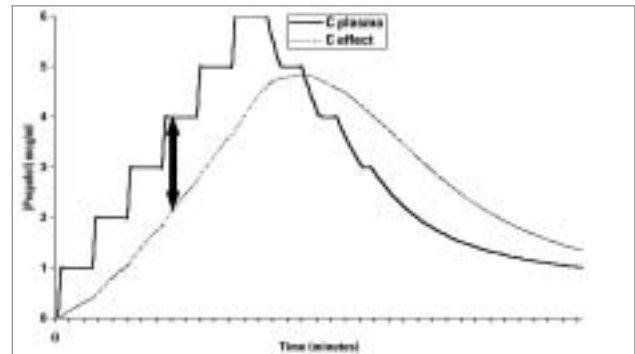


Figure 4b Small increments

If the target concentration is titrated in small ($1 \mu\text{g}\cdot\text{ml}^{-1}$) increments then the difference between plasma and effect site concentration (solid arrow) is smaller.



Further reading

- 1 Anaesthesia 1998;53(supplement 1):1–86.
- 2 Glass PSA. Intravenous infusion techniques: how to do it and why we should do it. Can J Anaesth 1998;45:R117–127.
- 3 Miller RD. Anesthesia. Churchill Livingstone; ISBN 0-4430-7988-9. Chapters 8–11.
- 4 Padfield NL. Total Intravenous Anaesthesia. Butterworth-Heinemann. ISBN 0-7506-4171-1.
- 5 Sear JW. Recent advances and developments in the clinical use of i.v. opioids during the perioperative period. Brit J Anaes 1998;81:38–50.
- 6 TIVA trainer pharmacokinetic computer programme is available from www.eurosiva.org (demo version is free).