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# Principles of total intravenous anaesthesia: basic pharmacokinetics and model descriptions

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## Key points

- Competency in total i.v. anaesthesia (TIVA) allows safe management of general anaesthesia in patients with malignant hyperthermia risk.

- Poor understanding of the pharmacokinetics of target-controlled infusion (TCI)/TIVA practice has contributed to accidental anaesthetic awareness as reported by NAP5.

- There is no defined 'ideal' TIVA technique, but co-administration of propofol and remifentanil by TCIs approaches this goal.

- A variety of pharmacokinetic models for propofol and remifentanil have been described, but only a few have been implemented in commercial infusion devices.

- All models incorporate assumptions and elements of inaccuracy in the prediction of plasma and effect-site targets. However, inter-individual variability in pharmacodynamic response represents a more challenging aspect of using TIVA.

Total i.v. anaesthesia (TIVA) describes the maintenance of general anaesthesia without inhaled hypnotics. Some indications for TIVA are given in Table 1. Competency in TIVA is vital for safe management of patients with malignant hyperthermia risk who require general anaesthesia.

Any combination of hypnotics (with or without analgesics) can be used to achieve a desired clinical endpoint. This heterogeneity confounds the interpretation of TIVA outcome data as no technique defines 'ideal' TIVA. Suboptimal techniques are often included in outcome analyses, but the results are generalised to all methodologies.[1–3] Poor understanding of the pharmacokinetics underlying TIVA has caused accidental awareness as documented in the Fifth National Audit Project on accidental awareness during general anaesthesia (NAP5) report.[3]

## Choice of agents

Drugs with fast onset and offset times are most useful for balancing adequate hypnosis/analgesia with rapid recovery. The decline in the plasma concentration of most i.v. agents slows as the duration of infusion increases ('context-sensitive half-time'—CSHT) and impairs recovery. Propofol and remifentanil demonstrate short or minimal CSHT unlike other i.v. agents. For this article, 'ideal' TIVA constitutes the co-administration of these agents by target-controlled infusion (TCI). This approach exploits their known synergy in obtunding responses to noxious stimuli.[4]

## The three-compartment model

After an i.v. bolus, the plasma concentration of a typical drug follows an exponential decline in three distinct phases (Fig. 1). These observations are explained by distribution of drug between a central compartment ($V_1$, principally plasma) and two compartments which equilibrate rapidly ($V_2$, well-perfused tissue like muscle) and slowly ($V_3$, mainly fatty tissue) (Fig. 2).

- Malignant hyperthermia risk
- Long QT Syndrome (QTc≥500 ms)
- History of severe PONV
- 'Tubeless' ENT and thoracic surgery
- Patients with anticipated difficult intubation/extubation
- Neurosurgery—to limit intracranial volume
- Surgery requiring neurophysiological monitoring
- Myasthenia gravis/neuromuscular disorders to avoid NMBs
- Anaesthesia in non-theatre environments
- Transfer of anaesthetised patient between environments
- Day-case surgery
- Trainee teaching
- Patient choice
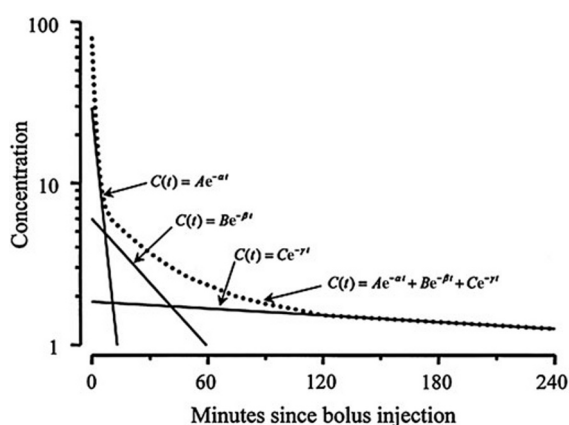


**Fig 1** Plasma concentration *vs* time curve demonstrating tri-exponential decline after a bolus injection. In conventional pharmacokinetic terminology, these are phases A–C. The plasma concentration at time $t(Ct)$ may be derived from $C(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$, where $t$ is time since i.v. bolus. $C$, concentration after a bolus dose. A–C represent the phase coefficients which sum to the plasma concentration after an i.v. bolus. $\alpha$, $\beta$, and $\gamma$ represent phase rate constants. e, natural logarithm.

Mathematical analysis allows the compartment volumes and rate constants for drug transfer between them to be calculated.[5] Detailed discussion of the modelling process has been published in this journal.[6,7]

## Target-controlled infusions

Adequacy of TIVA depends on the maintenance of brain propofol and remifentanil concentrations which are clinically appropriate and in equilibrium with levels in the plasma. The best way to achieve this state is by TCI from dedicated pharmacokinetic pumps. These devices solve the complex equations which describe the distribution of agents between compartments and allow for rapid adjustments in targets to achieve the desired clinical effect. Manual infusion regimes are prone to errors in the calculation and implementation of the required changes in infusion rate as reported by NAP5.[3]

## Principles of TCI

A bolus/elimination/transfer (BET) principle is used to approximate a constant plasma level of drug (however, the algorithms

in pharmacokinetic pumps use more exacting analytical solutions). Once compartment $V_1$ is filled by the bolus, the subsequent infusion rate compensates for rapid and slow transfer of drug to $V_2$ and $V_3$, and drug elimination from $V_1$ as described by the rate constant $K_{10}$ (rate constant for drug elimination from the central compartment in a pharmacokinetic model). When the three compartments reach steady-state concentration (>20 h for propofol), the infusion rate slows to match elimination only. Without an appropriate bolus, a constant propofol infusion at 10 mg kg$^{-1}$ h$^{-1}$ requires 40–90 min (dependent upon which kinetic model is used for calculation) to achieve a clinically useful plasma concentration of 4 μg ml$^{-1}$ in an 85 kg adult male. It is likely that an inadequate clinical effect would be observed in the interim as was reported by NAP5.[3]

## The TCI system

The key components are:

- User interface
- Microprocessor(s) with pharmacokinetic software
- Infusion pump which delivers up to 1200 ml h$^{-1}$
- Visual and audible safety systems and alarms

A typical system calculates the bolus dose and speed of subsequent infusion required to maintain the targeted plasma drug concentration (Cpt). Calculations are repeated every 10 s and the infusion rate adjusted until Cpt is achieved. Diffusion of drug from plasma to brain occurs exponentially with a first-order rate constant ($k_{e0}$, see below). The half-time ($T_{1/2}$) for the process is calculated as $T_{1/2} = [\ln (2)/k_{e0}]$ and equilibration occurs after 4–5 half-times.[8] If Cpt is subsequently increased, an additional bolus is given to fill $V_1$ and the infusion rate increases to match additional transfer and elimination at the higher concentration.

When Cpt is decreased, the infusion stops until the plasma concentration declines to the new target and is restarted at a lower rate. Diffusion of drug from the brain occurs with the same half-time.

## Common TCI models

The differences in published models for propofol and remifentanil result from methodological aspects and limitations of the original studies. Relatively few of these solutions are implemented in commercial infusion devices (Table 2). Currently, there is no evidence to support the use of one model in preference to another and all have proved reliable in clinical practice. All have similar performance in terms of the accuracy and stability of predicted plasma (Cp) and effect-site (Ce) concentrations.

### Propofol

The key pharmacokinetic parameters for the adult Marsh and Schnider plasma-targeting models are shown in Table 2. The major difference is the volume of $V_1$ (Marsh 19.4 litre *vs* Schnider 4.27 litre for an 85 kg individual), and therefore a bolus administered as mg kg$^{-1}$ causes a four-fold difference in calculated peak plasma concentrations (Fig. 3).

The Marsh model ignores age and scales the volumes of $V_{1-3}$ linearly to patient weight. An identical bolus dose is administered to all patients of a given body mass for any chosen Cpt. This delivery contrasts with non-TIVA practice where the anaesthetist usually adjusts dosage for patient age and likely pharmacodynamic response. Age is input to the TCI pump only to ensure
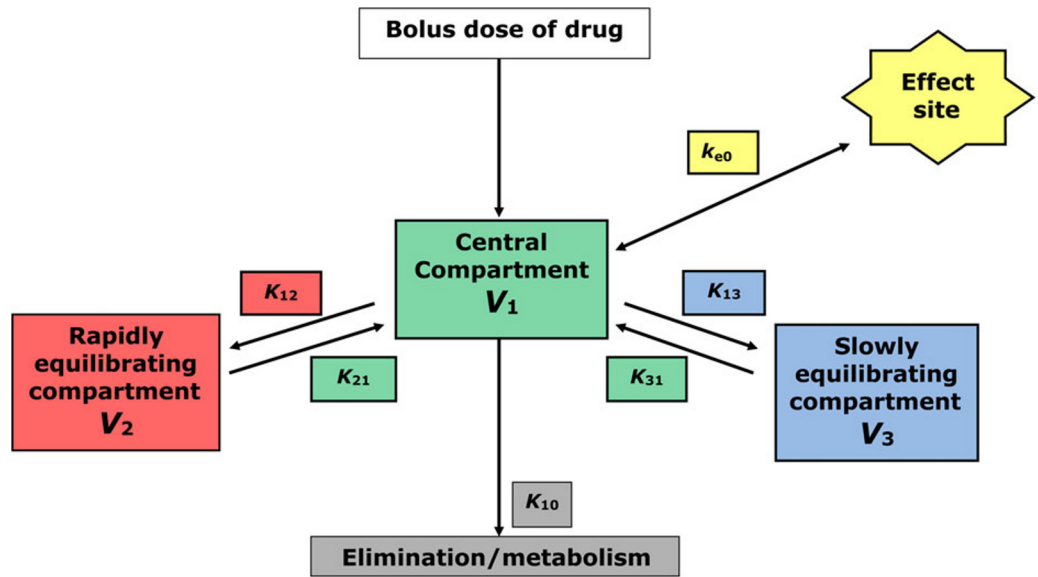
**Fig 2** Three-compartment model showing the various compartments and their associated rate constants. $V_{1-3}$ represents the compartment volumes. $K_{12}$ represents the rate constant between $V_1$ and $V_2$, $K_{21}$ between $V_2$ and $V_1$, etc. $K_{10}$ represents the rate constant for drug elimination from the central compartment. $k_{e0}$ is the rate constant for equilibration between plasma and effect-site concentrations.

**Table 2** Comparison of the pharmacokinetic parameters for the main TCI models implemented in commercial infusion devices. $V_1$, central compartment; $V_2$, rapidly equilibrating compartment; $V_3$, slowly equilibrating compartment; $K_{10}$, rate constant for drug elimination from the central compartment in a pharmacokinetic model; $K_{xy}$ and $K_{yx}$, rate constants for drug transfer from compartment $x$ to compartment $y$ or the reverse direction; LBM, lean body mass

| Model | Fixed parameters | Variable parameters | Parameter determined by |
|---|---|---|---|
| Marsh | All rate constants | $V_{1,2,3}$ | Weight |
| Schnider | $V_1 = 4.7$ litre | $V_2$ | Age |
| | $V_3, K_{13}, K_{31}$ | $K_{12}, K_{21}$ | Age |
| | | $K_{10}$ | Age, weight, LBM |
| Paedfusor | All rate constants except $K_{10}$ | $V_{1,2,3}$ | Weight |
| | | $K_{10}$ | Weight |
| Kataria | All rate constants | $V_{1,2,3}$ | Weight |
| Minto | $V_3 = 5.42$ litre | $V_1$ and $V_2$ and rate constants | Age, LBM |

that the patient is ≥16 yr and that the use of this model is appropriate. For less robust patients, it is better to start the pump at a lower Cpt and increase the target incrementally until a desired clinical effect is obtained.

Although the Schnider model adjusts some of the pharmacokinetic parameters for age (Table 2), this does not necessarily constrain the patient's pharmacodynamic response. A sex-specific lean body mass (LBM) is calculated and used to adjust the elimination rate constant $K_{10}$. Because a small fixed volume for $V_1$ is used, lower doses of propofol are required to achieve a given Cpt compared with Marsh (Table 3). In many instances, this bolus is inappropriately small and results in an inadequate

clinical effect. Consequently, the Schnider model can only be recommended for use in effect-site targeting mode (see below) as larger bolus doses are utilised.

Small differences between the Paedfusor and Kataria paediatric models are shown in Table 2. Both use weight as the key patient characteristic for scaling the volumes of $V_{1-3}$. The Kataria model is validated for use in patients aged 3–16 yr with a minimum weight of 15 kg. The Paedfusor model is a variant of the Marsh kinetics for patients 1–16 yr of age, and also uses weight to calculate the elimination constant $K_{10}$. It features non-linear scaling of $V_1$ volume as age exceeds 12 yr. Extrapolation of these models to patients outside of the described patient characteristics is not recommended due to increased pharmacokinetic differences, but is commonly practised.

A recently described allometric scaling model promises improved utility in propofol administration.[9] Allometry relates biological activity to proportional rather than absolute changes in body size. In the new model, 10 927 blood propofol concentrations were aggregated from 660 subjects (500 patients, 160 healthy volunteers) recruited to 21 separate studies. This contrasts with the limited data used to generate the Marsh and Schnider kinetics. Body composition in the new model is reflected in the calculation of the volumes of $V_2$ and $V_3$ which in turn are the primary determinants of their associated rate constants, not absolute body mass. This complex analysis allows the model to be used for patients aged 3 months to 88 yr and weighing 5–160 kg, but needs further clinical validation before it becomes commercially available.

### Remifentanil

The Minto model for remifentanil is popular because it is applicable to a wide range of patient characteristics. Age is used for calculation of pharmacokinetic parameters (Table 2) but in common with the Schnider model, this adjustment does not influence pharmacodynamic response. A sex-specific LBM is calculated and used to fine tune some of the parameters to the patient.
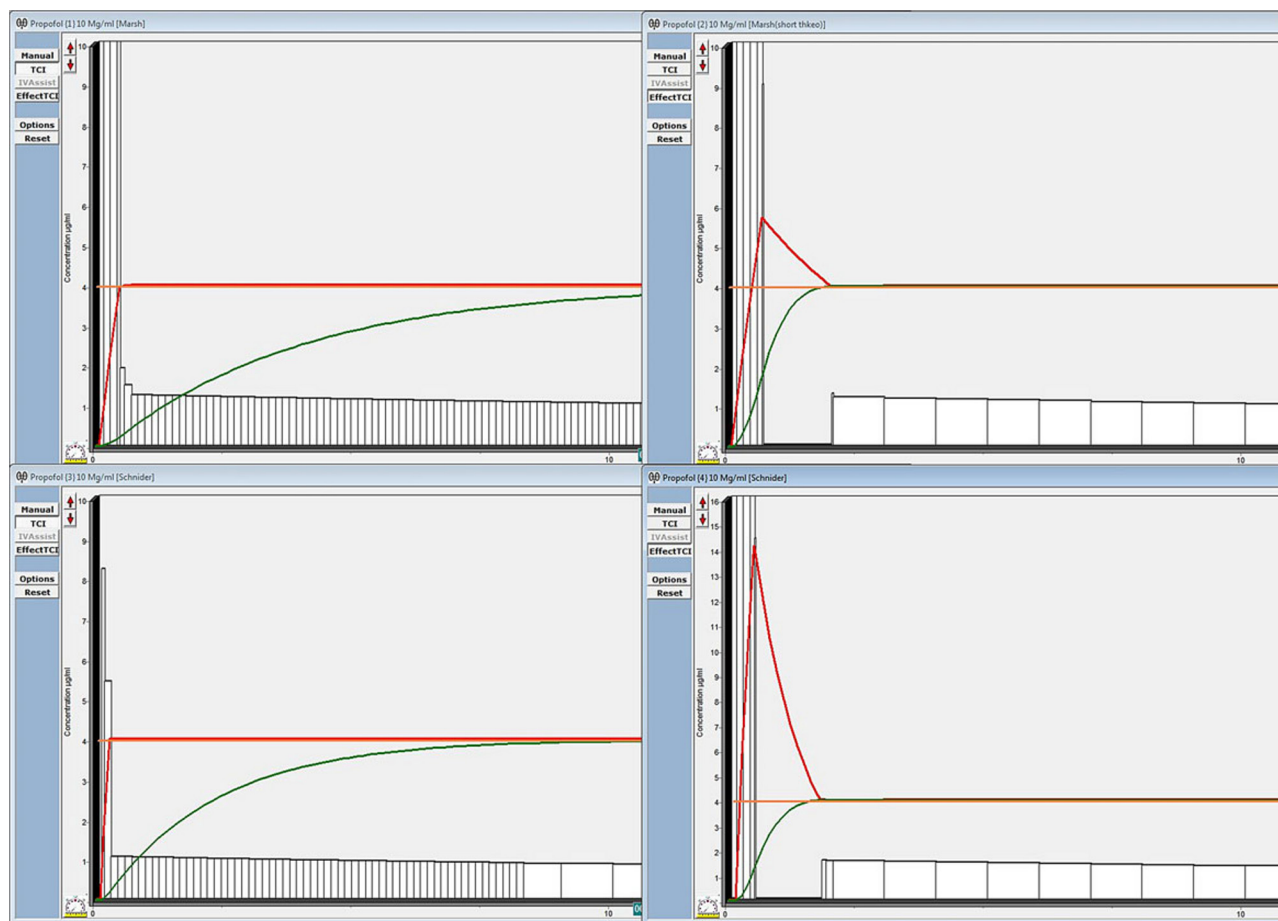
Fig 3 Comparison of propofol concentrations predicted for a 40-yr-old male, 178 cm tall, and weighing 85 kg by the Marsh (upper panels) and Schnider (lower panels) models using Tivatrainer 9 software (www.eurosiva.eu). Left-hand panels show plasma targeting (Cpt) mode; right-hand panels show effect-site targeting (Cet). The target was set at 4 μg ml$^{-1}$ and all diagrams have the same time scale in minutes on the x-axis. Note the major difference in plasma concentration predicted in Cet modes—this is largely due to the difference in the volume of the central compartment $V_1$ assumed by each model. Differences in the time to equilibration of the plasma and effect-site concentrations for the Marsh model are due to the different $k_{e0}$ utilised in each calculation. The $k_{e0}$s used in the effect-site models are based on a TTPE of 1.6 min after the bolus dose. Red line, plasma concentration; orange line, chosen target level; green line, effect-site concentration; vertical white lines represent the infusion rate of TCI pump.

# Effect-site targeting

## Propofol

Clinicians regularly but unintentionally use effect-site targeting in non-TIVA practice to rapidly achieve unconsciousness. The high plasma concentration generated by a large bolus of propofol causes fast diffusion of drug into the brain and rapid onset of the desired effect. However, propofol diffusion continues until the brain concentration has equilibrated with the diminishing plasma level (Fig. 3, right-hand panels). This occurs 1.6–3.9 min after injection irrespective of the size of the bolus dose[9] (the 'time to peak effect', TTPE, as predicted by the Schnider and Marsh models, respectively). Depending on the patient's idiosyncratic sensitivity to propofol, this peak brain level can cause unwanted cardiovascular instability (reflecting an effect-site overshoot). Effect-site targeting achieves unconsciousness rapidly without effect-site overshoot provided that the target effect-site drug concentration (Cet) is appropriate for the patient's physical status.

A peak blood concentration (called the plasma overshoot) generates the desired Cet at equilibrium (Fig. 3, right-hand panels) and can in theory be calculated from the rate constant for drug transfer into the brain. The bolus dose required to produce this plasma overshoot is governed by the volume of $V_1$ used in the calculation and hence the model chosen. Once the bolus is given, the TCI pump stops infusing until equilibration occurs at the relevant TTPE and then re-starts at a rate matching inter-compartmental transfer and elimination (also right-hand panels in Fig. 3).

However, brain propofol concentrations cannot be measured *in vivo* and the rate constant required for direct calculation of plasma overshoot is unknowable. Instead, drug concentration in a theoretical surrogate called the effect-site is used for mathematical analysis of effect and prediction of plasma overshoot.[10] This virtual compartment is assumed to have negligible volume compared with $V_1$ and causes little perturbation in plasma concentration at equilibrium. A rate constant called $k_{e0}$ (Fig. 2) describes equilibration of effect-site concentration with plasma propofol levels but has to be derived indirectly in experimental studies.

A measure of dynamic anaesthetic effect, typically a processed EEG signal, is recorded simultaneously with measured plasma propofol concentrations in volunteer subjects. A numeric value for $k_{e0}$ can then be derived to match the timing of the

Table 3 Comparison of the dose of propofol administered to a 40-yr-old male, 178 cm tall, and 85 kg in weight when a 4 µg ml$^{-1}$ target concentration is set. The table shows the initial bolus dose, the time to equilibration of plasma and effect-site concentrations, and the cumulative doses at two time points. Time to equilibration is equivalent to TTPE with effect-site targeting. Data derived from Tivatrainer 9 software (www.eurosiva.eu). Greyed areas show non-applicable data

**Comparison of adult propofol models**

| Model | Plasma targeting Cpt | | | | Effect-site targeting Cet | | | |
|---|---|---|---|---|---|---|---|---|
| | Initial bolus (mg) | Time to equilibrium (min) | Cumulative dose | | Initial bolus (mg) | Time to equilibrium (min) | Cumulative dose | |
| | | | At equilibrium (mg) | After 30 min of infusion (mg) | | | At equilibrium (mg) | After 30 min of infusion (mg) |
| Marsh | 86 | 16 | 360 | 570 | | | | |
| 'Modified Marsh' | | | | | 119 | 1.6 | 119 | 574 |
| Schnider | 18 | 9.8 | 142 | 414 | 73 | 1.6 | 73 | 444 |

calculated peak Ce to the observed maximum EEG effect. This $k_{e0}$ is linked to rate of decay of drug concentration in $V_1$ and hence to the specific pharmacokinetic model used to administer the agent. Once established, $k_{e0}$ allows manipulation of plasma overshoot to achieve a particular Cet.

For any given pharmacokinetic model, a large numeric value of $k_{e0}$ will predict a more rapid increase in Ce and allow a smaller initial bolus dose to be given. Similarly, the decline in Ce to a level representing recovery from anaesthesia will be predicted to occur more quickly.

Effect-site targeting is the only approach recommended for the Schnider model as larger bolus doses are required to achieve plasma overshoot (Table 3). Because this model incorporates more patient characteristics, it has been recommended for use in the elderly and less robust patient. However, it is always better to start at a low Cet in frail individuals and increase the target incrementally until the desired response is obtained.

The original description of the Schnider Cet model matched peak kinetic and dynamic parameters at a TTPE of 1.6 min and allowed for small variations in $k_{e0}$ between individuals based on their idiosyncratic pharmacokinetics.[10] It is also possible to use the 'average' $k_{e0}$ published in this study as a fixed parameter and allow small variations in TTPE between patients.[11] Pump manufacturers implement one particular approach in their equipment. Consequently, a clinician using different pump brands may observe some differences in the bolus dose administered for a desired Cet in similar individuals.[12] Care must be taken to ensure that the expected clinical response is actually obtained.

The original 'Diprifusor' Marsh Cpt model did not have a $k_{e0}$ and could not be used in the Cet mode. Subsequently, a $k_{e0}$ was assigned to allow calculation of Ce for information only, and the selected value predicts a TTPE of 3.9–4.5 min after a typical 2–3 mg kg$^{-1}$ bolus. This timing may seem lengthy, but the prediction of Ce by this model has been validated in a patient study.[13] Attempts have been made to find the 'best' $k_{e0}$ for enabling the Marsh model in the Cet mode, and a variety of solutions have been published. A method using a TTPE of 1.6 min to derive $k_{e0}$ has been implemented in some commercial TCI devices as the 'Modified Marsh' model.[14]

For both Marsh and Schnider models, larger bolus doses of propofol are used in the Cet mode at any given numeric target compared with the same model in the Cpt mode. Marsh always administers a larger bolus dose than Schnider in either mode principally due to the significant difference in the volume of $V_1$ used in calculations. However, the absolute mass of agent may seem small compared with that used in non-TIVA practice

(Table 3) where unwanted effect overshoot is common. The propofol TCI models described above prove highly effective in combination with remifentanil TCI.

## Remifentanil

The Minto model for remifentanil can be used in the Cet mode, but the $k_{e0}$ used is derived from studies of EEG parameters as a measure of effect. It must be remembered that an EEG parameter does not necessarily equate with the onset of analgesic action. The increased plasma remifentanil concentrations required in the Cet mode can be associated with a higher likelihood of chest wall rigidity and severe bradycardia via non-vagal mechanisms, so an incremental approach to remifentanil Cet may be a reasonable technique.

## Conclusion

Currently, there is no 'best' TCI model for propofol. The clinician should become familiar with the model which matches the patient characteristics of their usual patient population. All pharmacokinetic models have inherent assumptions which generate elements of inaccuracy in prediction. However, inter-individual variability in pharmacodynamic response represents a more challenging aspect of using TIVA. Close clinical monitoring of the patient remains an important part of the anaesthetist's role.

## Educational video

The European Society for Intravenous Anaesthesia (EuroSIVA) provides an educational video on the basic pharmacokinetics of a simple infusion at the following link: https://www.youtube.com/watch?v=6U_K-ToHRvs (accessed 1 May 2015).

## Declaration of interest

D.M. is a member of the Committee of SIVA, the UK Society for Intravenous Anaesthesia (www.siva.ac.uk) (accessed 1 May 2015).

## MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

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