

# Total Intravenous Anaesthesia (TIVA) II: Pharmacodynamics of intravenous anaesthetics

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**P**harmacokinetics describes the distribution and elimination of drugs by the body, in particular the relationships between drug concentration and time. The relationship between concentration and response is known as pharmacodynamics, and describes what the drug does to the body. For intravenous anaesthetics the plasma is not the site of drug effect.

## The relationship between plasma concentration and effect

It is apparent during induction and emergence from anaesthesia, that the plasma concentration ( $C_p$ ) does not always correlate, with the clinical effects of anaesthetic drugs (Figure 1).

For instance, during induction (at point A) the effect site concentration ( $C_e$ ) lags behind the plasma concentration, hence the plasma concentration is higher than the effect site concentration. Again during emergence (at point B) the effect site concentration lags behind the reduction in plasma concentration, however at this point the effect site concentration is higher than the plasma concentration. Since time is required for the blood and brain concentrations to equilibrate it has been suggested that when titrating the drug to effect, it would make more sense to consider the effect site concentration which is related to that clinical effect. The mathematics of the equilibration of anaesthetic drug plasma concentration and effect site concentration are described by the pharmacokinetic rate constant  $k_{e0}$ .

## Effect Site

The principal effects of i.v. agents in which anaesthetists are interested are the sedative and hypnotic effects. Thus the site at which the drug exerts these effects (termed the biophase or effect site) is the brain. Unfortunately it is impossible to measure the

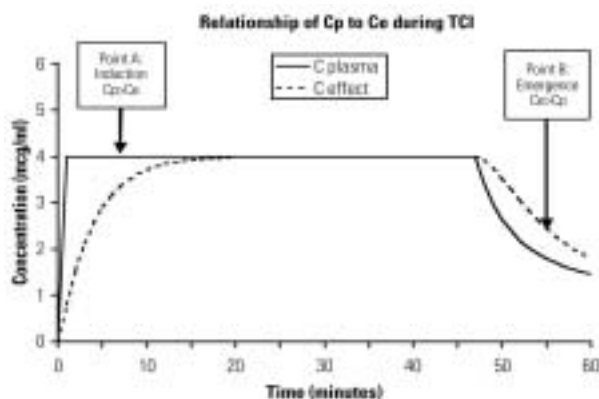
actual brain concentration of drug, the closest we have in animal models, is sampling from the cerebral venous system. Even if we could measure direct brain concentration, to relate concentration to effect properly, it would be necessary to know the exact regional concentrations or even receptor concentrations where the drug exerts its effect.

Therefore, we must rely on the clinical effects produced by the drug, to describe the relationship between the blood concentration and brain concentration or effect. The commonly used end points of clinical effect are loss of verbal contact or lack of response to surgical or noxious stimulus. Assessment of this is usually quantified by interval scales such as the Objective Observer's Assessment of Sedation Scale. Other more convenient measures of anaesthetic, or more specifically hypnotic effect have been used, predominantly measures of cortical activity. The most commonly used of these are processed EEG signals such as Bispectral Index (BIS) and 95% Spectral Edge Frequency (SEF95), or by Auditory Evoked Potentials (AEP). These monitors of 'anaesthetic depth' are useful **surrogate markers** of the effect site concentration. They make it easier to relate plasma concentration to effect because they are objective rather than subjective, and also they are measured on a continuous scale.

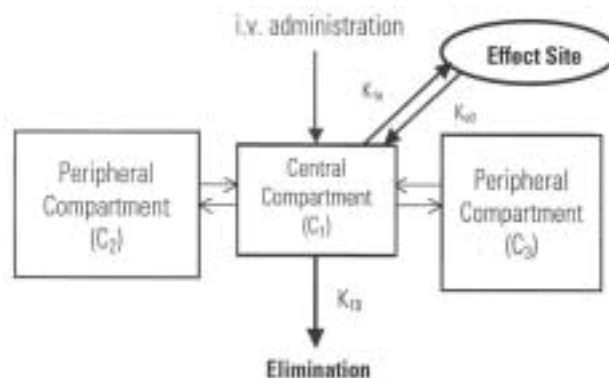
## Effect site model

If the clinical effects of the drug are measured with respect to the plasma concentration, then the apparent rate of drug flow into and out of the biophase can be mathematically modelled. Thus, by the addition of another (effect site) compartment to the three compartment pharmacodynamic model (Figure 2), the expected time course of the clinical effect for a plasma concentration can be calculated.

**Figure 1** The relationship of effect site to plasma propofol concentration during induction and emergence with TCI



**Figure 2** The three compartment pharmacokinetic model with added effect site compartment ( $C_e$ )



Movement of drug to and from the central compartment (plasma) is considered a first-order process, and the effect compartment is defined as being negligibly small in comparison to compartments  $C_1$ – $C_3$ . Therefore, the addition of this compartment has no effect on the concentration of the other compartments. For this reason some people consider movement from the effect site compartment to be drug eliminated from the model. Accordingly, the rate constants for delivery to and disposal from the effect site are called  $k_{1e}$  and  $k_{e0}$  respectively ( $k_{e0}$  is the time constant for elimination of drug from the model from any compartment named  $\chi$ ). Furthermore, since the effect compartment is negligibly small,  $k_{1e}$  is so much smaller than  $k_{e0}$  as to be disregarded. Therefore,  $k_{e0}$  characterises the equilibration of plasma concentration with drug effect. This allows calculation of the effect site concentration.

Numerous studies have calculated  $k_{e0}$  for various anaesthetic drugs, the value seems to depend on the patient population and the surrogate marker of effect used, e.g. BIS or AEP.

**$k_{e0}$ : Describing drug delivery to the effect site**

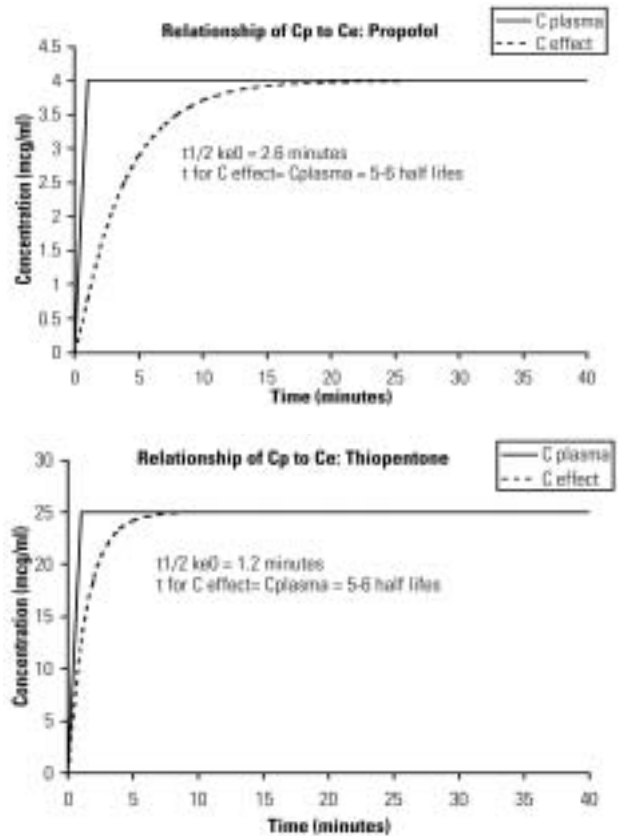
By definition,  $k_{e0}$  is the pharmacokinetic rate constant (for the Michaelis Menton equation), which describes the rate of equilibration between the plasma concentration and effect site. Perhaps a conceptually easier term is the  $t_{1/2k_{e0}}$ . That is the time it takes for half of the equilibration to take place between the plasma concentration ( $C_p$ ) and the effect site concentration ( $C_e$ ). Importantly, the concept has been incorporated into the Diprifusor package, which now can calculate and display effect site concentration also. This helps illustrate to practicing anaesthetists the difficulty in relating calculated  $C_p$ , or indeed measured  $C_p$  to effect. It can be seen from the relationship of  $C_p$  to  $C_e$  that the same calculated plasma concentration could be associated with greatly different effect site concentrations. It becomes obvious that the clinical effects depend on how long the blood and effector site have been allowed to equilibrate.

The value of this new knowledge can be illustrated if we compare drug disposition and effect following induction of anaesthesia with  $2\text{mg}\cdot\text{kg}^{-1}$  of propofol with  $5\text{mg}\cdot\text{kg}^{-1}$  of thiopentone. Simply by observation, we know that the onset of anaesthesia is slower with propofol than with thiopentone. Computer pharmacokinetic simulation confirms this, predicting the peak effect site concentration of the thiopentone bolus at 1.4 minutes and the propofol bolus at four minutes. Firstly, if we consider the effect of the  $t_{1/2k_{e0}}$ , we can see that for a constant plasma concentration of thiopentone that the effect site will equilibrate more quickly than propofol (Figure 3). The  $t_{1/2k_{e0}}$  of propofol is slower at 2.6 minutes compared to 1.2 minutes for thiopentone.

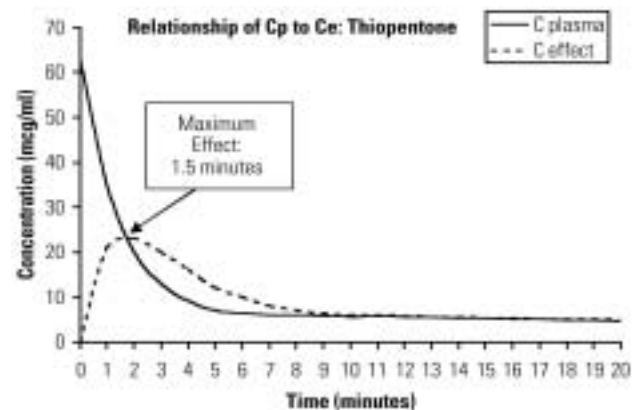
However, in real life, drug redistribution and elimination is also taking place concurrently as the plasma effect sites equilibrate. Since thiopentone is initially redistributed more quickly than propofol ( $t_{1/2}$  immediately bolus dose is one minute ten seconds for

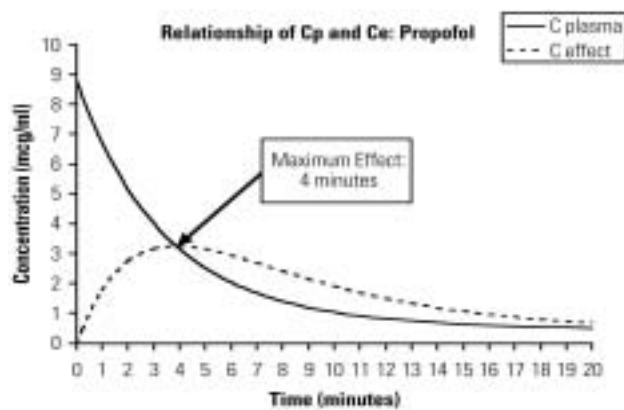
thiopentone and two minutes 30 seconds for propofol respectively), the concentration gradient for equilibration of plasma thiopentone with the effect site is continually reducing faster. Hence if we plot the plasma concentration and the effect site concentration of the bolus doses, then the peak effects are at the point when the falling plasma concentration crosses the rising effect site concentration (Figure 4).

**Figure 3** The effect that  $t_{1/2k_{e0}}$  has on time to equilibrate the effect site with a constant plasma concentration of thiopentone and propofol respectively



**Figure 4** The relationship of plasma concentration and effect site concentration following a  $2\text{mg}\cdot\text{kg}^{-1}$  bolus of propofol and a  $5\text{mg}\cdot\text{kg}^{-1}$  bolus of thiopentone





This is because drug will always move down its concentration gradient, that is from plasma to brain when the plasma concentration is greater than the brain concentration. When plasma concentration falls below brain concentration, drug movement reverses.

### Population pharmacodynamics

#### MAC and Cp50

Most anaesthetists are familiar with the term MAC (minimal alveolar concentration of an inhalational anaesthetic which prevents gross purposeful motor response in 50% of unpremedicated patients to skin incision). A similar concept has been developed for intravenous agents, and is referred to as the effective concentration 50 (EC<sub>50</sub> or Cp<sub>50</sub>). This is the plasma concentration (Cp) that prevents gross purposeful motor response in 50% of unpremedicated patients to skin incision. It is a preferred term to effective dose 50 (ED<sub>50</sub>), which relates to the dose of drug that prevents gross movement in 50% of the population to skin incision. In a population, for the same dose of drug, there will be variation in the blood concentration achieved owing to pharmacokinetic variation. This introduces a further level of uncertainty not present when relating plasma concentration to effect. Both Cp<sub>50</sub> and MAC are useful for comparing the potencies of anaesthetic agents within their respective class, but by definition only provide adequate anaesthesia for 50% of the population. A more useful concept clinically is Cp<sub>95</sub>, which is the effective concentration for 95% of the population. It is likely that expressing Cp<sub>50</sub> and Cp<sub>95</sub> in terms of calculated effect site concentration (Ce<sub>50</sub> and Ce<sub>95</sub>) will give even more clinically useful information (Table 1). From this data, dose-response curves for propofol plasma and effect site concentration can be constructed (Figure 5).

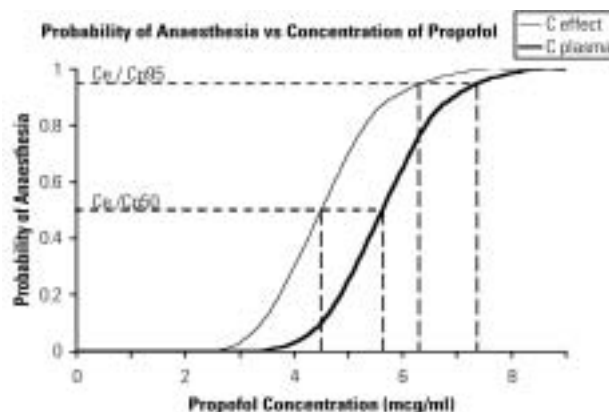
#### Pharmacodynamic interactions

Similar to the effect on MAC of volatile anaesthetics, concomitant administration of sedative premedication, benzodiazepines, opioids, nitrous oxide or indeed α<sub>2</sub> adrenoceptor agonists such as clonidine all reduce the Cp<sub>50</sub> for intravenous agents. This effect exhibits a dose response, for example, by increasing the concentration of opioid the MAC and Cp<sub>50</sub> are reduced further (Figure 6).

**Table 1** Relationship between Target and Effect site CP50 and CP95 of propofol for clinical end points. This is without any other sedative or opioid medication. (From Irwin MG et al. Anaesthesia 2002;57:242–248).

Clinical endpoint	CP <sub>50</sub> (µg·ml <sup>-1</sup> )		CP <sub>95</sub> (µg·ml <sup>-1</sup> )	
	Effect	Target	Effect	Target
Loss of Verbal Contact	2.7	3.9	3.8	5.4
Loss of purposeful response to surgical stimulus	4.5	5.6	6.4	7.4

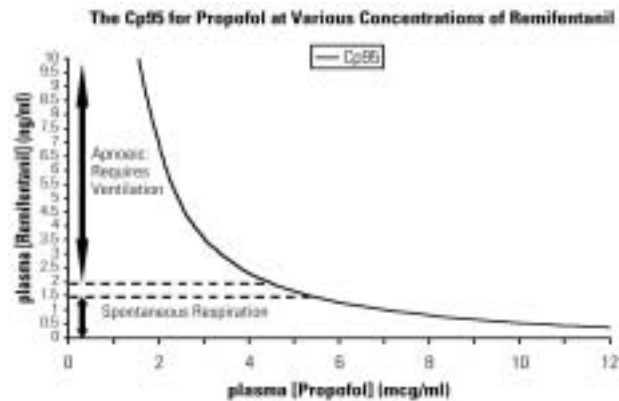
**Figure 5** The dose response curve for probability of anaesthesia (lack of response to noxious stimulus) versus calculated effect site and plasma concentrations of propofol. (Adapted from data by Irwin MG et al. Anaesthesia 2002;57:242–248)



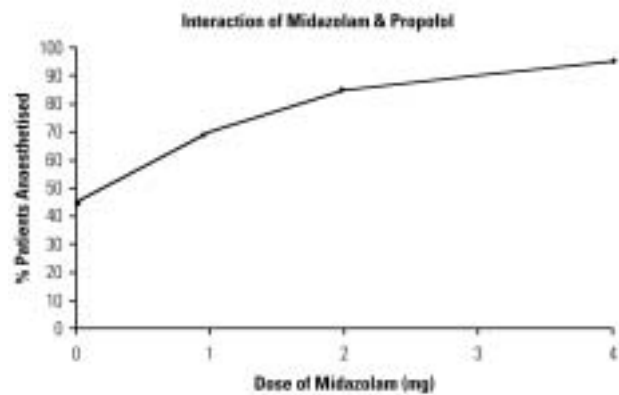
Similarly increasing the dose of midazolam given prior to induction of anaesthesia with propofol has been shown to reduce the ED<sub>50</sub>, and increase the proportion of patients successfully anaesthetised with a fixed calculated blood concentration (Figure 7).

Interestingly for opioids it is becoming clear that there is a ceiling to their effect on Cp<sub>50</sub> and Cp<sub>95</sub>, and no matter how high the opioid concentration, some hypnotic is necessary to prevent movement to surgical incision (Figure 6). Therefore, it can be surmised that opioids may reduce the magnitude of the surgical stimulus but do not provide hypnosis. It should be noted that although propofol concentration can be reduced in the presence of remifentanyl, if the plasma concentration of remifentanyl is greater than around 1.5 ng·ml<sup>-1</sup>, then the patient is likely to become apnoeic and require artificial ventilation (Figure 6). The interaction between opioids and propofol for total intravenous anaesthesia has been studied extensively. Computer pharmacokinetic simulations have been performed to calculate the optimum combination that provides adequate anaesthesia with minimal time to return of consciousness when the infusions are ended. The optimum combination changes depending on how long the infusions have been running (the context sensitive half-time) and the opioids used.

**Figure 6** The plasma remifentanyl versus plasma propofol concentration associated with no movement to surgical stimulus in 95% of patients ( $Cp_{95}$ ). Superimposed is the level of remifentanyl at which patients may be expected to breath spontaneously (from Mertens MJ. PhD Thesis. ISBN 9090156410. Chapter6)



**Figure 7** Clinical interaction of midazolam and propofol. The proportion of patients losing verbal contact with a fixed target controlled infusion of propofol at 3 mg·ml<sup>-1</sup> after varying doses of midazolam (Tzabar Anaesthesia 1996;51:536–538)



**Pharmacodynamic variability**

**Age**

Increasing age has been shown to reduce the  $Ce_{50}$  for propofol, showing increased sensitivity of the elderly to the effects of propofol. Importantly they exhibit greater haemodynamic effects also. Interestingly the  $ke_0$ , hence plasma effect site equilibration has been reported not to be changed by age. In contrast the time to the maximal haemodynamic effect can be delayed.

Similarly for remifentanyl the  $Cp_{50}$  is reduced with age, however the  $t_{1/2} k_{e0}$  is prolonged, reflecting that equilibration between plasma and effect site is slower in the elderly.

These properties suggest that induction in elderly patients should be achieved with lower plasma concentrations than in younger adults, however it should also be titrated more slowly to avoid side effects.

**Systemic disease**

In contrast to the well characterised effects of systemic disease, especially renal and hepatic disease, on the pharmacokinetics of intravenous hypnotics and opioids, there has been surprisingly very little work performed to examine their relative potency in patients with systemic disease. It has often been assumed that patients with significant disease would require less anaesthetic. This variation could be as a result of increased central nervous system sensitivity to the drug (pharmacodynamic), or an increased free fraction of drug secondary to reduced plasma protein binding (subtle pharmacokinetic changes). An increased clinical effect for a defined blood concentration has not been shown in disease states. In fact, patients with hepatic cirrhosis have been shown to waken at the same plasma concentration of propofol as healthy controls. Furthermore surprisingly little difference in plasma protein binding of propofol has been found in patients with hepatic and renal disease.

**Titration anaesthesia to stimulus**

Despite the fact that variation in  $Cp_{50}$  for intravenous anaesthetics has not clearly been shown to change with disease there is significant patient variability to the pharmacodynamic effects of intravenous anaesthetics in health, and due to aging. Obviously, the likelihood of response will depend on the depth of anaesthesia, effect site concentration and the degree of surgical stimulation. So in practice the depth of anaesthesia will need to be titrated to the surgical stimulation. To complicate matters further the requirements differ with the effect considered. For example the opioid concentration necessary for intubation is higher than for incision. It becomes obvious that, just as for inhalational anaesthesia, the anaesthetic depth should be individualised by titrating the different components of TIVA to the individual patient and the surgical stimulus at that moment. A sound knowledge of the pharmacokinetic and pharmacodynamic principles of intravenous anaesthetic agents will make appropriate drug selection and administration possible.

**Further reading**

Anaesthesia 1998;53 (supplement 1):1–86.  
 Padfield NL. Total Intravenous Anaesthesia. Butterworth-Heinmann. ISBN 0-7506-4171-1.  
 Glass PSA. Intravenous infusion techniques: How to do it and why we should do it. Canadian Journal of Anaesthesia 1998;45:R117–127.  
 Irwin MG et al. Anaesthesia 2002;57:242–248.  
 Schnider TW et al. Anesthesiology 1999;90:1502–1516.  
 TIVA trainer pharmacokinetic computer programme is available from [www.eurosiva.org](http://www.eurosiva.org) (demo version is free).