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Effect-compartment equilibrium rate constant (k_{eo}) for propofol during induction of anesthesia with a target-controlled infusion device

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Abstract The effect-compartment concentration (C_e) of a drug at a specific pharmacodynamic endpoint should be independent of the rate of drug injection. We used this assumption to derive an effect-compartment equilibrium rate constant (k_{eo}) for propofol during induction of anesthesia, using a target controlled infusion device (Diprifusor). Eighteen unpremedicated patients were induced with a target blood propofol concentration of 5 μg·ml^{-1} (group 1), while another 18 were induced with a target concentration of 6 μg·ml^{-1} (group 2). The time at loss of the eyelash reflex was recorded. Computer simulation was used to derive the rate constant (k_{eo}) that resulted in the mean C_e at loss of the eyelash reflex in group 1 being equal to that in group 2. Using this population technique, we found the k_{eo} to be 0.57 min^{-1}. The mean (SD) effect compartment concentration at loss of the eyelash reflex was 2.39 (0.70) μg·ml^{-1}. This means that to achieve a desired C_e within 3 min of induction, the initial target blood concentration should be set at 1.67 times that of the desired C_e for 1 min, after which it should revert to the desired concentration.

Key words Anesthetics · Intravenous · Propofol · Pharmacokinetics · Effect-compartment equilibrium rate constant

The effect-compartment concentration (C_e) is often used to predict the amount of pharmacological effect expected of a drug. As C_e cannot be directly measured, a predicted value is used. This prediction requires the use of an effect-compartment equilibrium rate constant (k_{eo}), which describes the transfer of drug from the blood or central compartment to the effect compartment.

However, drug delivery to the effect compartment may be affected by the depression of other organ systems. Early sustained elevated blood concentration of a drug such as propofol may lead to a depression of drug delivery to other tissues. This situation occurs when a target controlled infusion of propofol is set at concentrations beyond what is normally required for sleep. It is therefore possible that the k_{eo} derived from studies using constant rate infusions may not be suitable for target controlled infusions.

The C_e at a specific pharmacodynamic endpoint should be a constant and should be independent of the rate of drug injection. An earlier study made use of this assumption to derive the k_{eo} for propofol given by bolus and infusion [1]. Adopting the same methodology, this study aimed to derive the k_{eo} when using a target controlled infusion device.

The study was approved by the local clinical research ethics committee. Thirty-six patients, American Society of Anesthesiologists physical class 1 or 2, scheduled for elective surgical operations, gave informed consent for the study. Patients with a body weight above 80 kg, and patients with evidence of cardiovascular disease or a history of sensitivity to propofol were excluded.

No sedative premedication was given. On arrival in the operation theater, routine monitoring was set up and an intravenous cannula was inserted into a forearm vein for the infusion of drugs and fluid. Anesthesia was induced with propofol, using a target-controlled infusion device (Diprifusor; Graseby, Watford, UK).

Patients were randomized to one of two groups: group 1, infusion pump set at a target concentration of 5 μg·ml^{-1}, and group 2, infusion pump set at a target concentration of 6 μg·ml^{-1}.

The eyelash reflex was tested every 2.5 s, and the time at which the reflex was lost was recorded. After induction of anesthesia was successfully achieved, patients were maintained using a standard anesthetic technique.

Central compartment concentrations of propofol were initially predicted using the model reported by Marsh et al. [2]. Effect-compartment concentrations were then calculated numerically. The k_{eo} was defined

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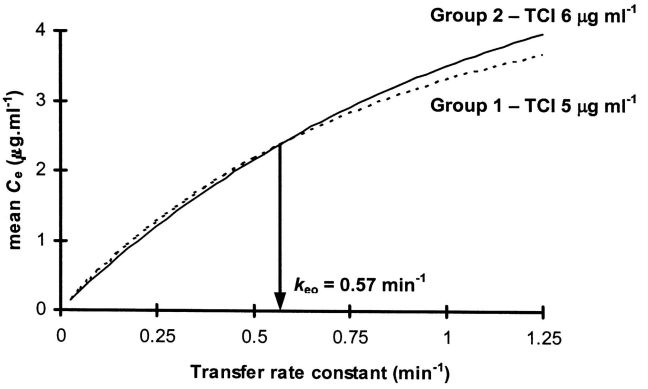

Fig. 1. Relationship between effect-compartment equilibrium rate constant (k_{eo}) and mean predicted effect-compartment concentration of propofol at loss of the eyelash reflex. *TCI*, Target-controlled infusion; C_e, effect-compartment concentration

as the rate constant that resulted in the mean C_e at loss of the eyelash reflex in group 1 being equal to that in group 2. This technique has been previously described [1,3].

Differences between the two treatment groups were tested using Student's *t*-test and the χ^2 test as appropriate. A value of $P < 0.05$ was considered significant.

The mean (SD) ages of patients in groups 1 and 2 were 35.9 (13.3) years and 37.1 (11.5) years respectively. The mean (SD) weight was 57.6 (9.8) kg and 57.1 (12.8) kg, respectively. Mean (range) time to loss of the eyelash reflex was 1.44 (0.83–4.00) min in group 1 and 1.14 (0.71–1.75) min in group 2. There was no statistically significant difference between groups with respect to age, weight, sex distribution, and time to loss of eyelash reflex.

Figure 1 shows the relationship between the K_{eo} and the C_e at loss of the eyelash reflex. A k_{eo} value of $0.57\,min^{-1}$ resulted in no difference in mean C_e between the two groups. The mean (SD) C_e was 2.39 (0.70) $\mu g \cdot ml^{-1}$.

The computer simulation used in this study relies on a compartmental pharmacokinetic model, which, unfortunately, does not deal well with the rapid changes in blood concentrations when a drug is infused at a high rate. Furthermore, the model assumes that the pharmacokinetic parameters remain constant during the induction of anesthesia. In spite of this, it is generally accepted that a single set of pharmacokinetic parameters is sufficient for predicting blood propofol concentrations during a target-controlled infusion. The Diprifusor is one such target-controlled infusion system that is considered acceptable for clinical purposes [4].

While the Diprifusor has a function that enables the user to check the C_e, the infusion algorithm itself has not been designed to target the concentration at the effect site. It may not be necessary to target the C_e during most of the anesthesia time, as the C_e will follow the plasma concentration. However, it is at the induction of anesthesia that targeting the C_e has distinct advantages.

The drug concentration in the effect compartment has a hysteresis-free relationship with the pharmacological effect. This means that specific pharmacodynamic endpoints can be reasonably predicted from the calculated effect-compartment concentration. From our study, we expect loss of the eyelash reflex to occur at around $2.4\,\mu g \cdot ml^{-1}$. Our results are comparable to those of previous studies, despite the fact that different pharmacokinetic parameter sets and k_{eo} values were used [1,5]. This suggests that when a parameter set appropriate for the drug administration regimen is used, the predicted C_e values obtained will be similar.

The k_{eo} derived in this study is appropriate for the induction of anesthesia using a Diprifusor. It is important to use the correct value for the k_{eo} when targeting the C_e at induction, in order to avoid overdosage or delayed induction. Other investigators have reported similar values for the k_{eo} at induction [6,7].

Using k_{eo} derived, we found that, to achieve a desired C_e within 3 min of induction, we would have to target a blood concentration 1.67 times that of the desired C_e for 1 min, and then turn the target concentration down to the desired C_e (Fig. 2). If a lower k_{eo} is used, a higher initial blood concentration may need to be targeted for a longer duration (middle graph in Fig. 2). This will lead to an overshoot of the C_e if the actual k_{eo} is higher than the value used in the calculations (shown as the broken line in the middle graph in Fig. 2). The opposite is seen when a higher k_{eo} is used. Although the C_e will eventually reach its desired value, it will take a longer time.

In the clinical setting, it is common practice to target a higher initial concentration in order to shorten the induction time. This is especially important when there is a need to rapidly secure the airway; for example, when performing a rapid sequence induction. Unfortunately, it is during these times that the anesthesiologist may be fully occupied with the patient and is unable to turn down the target concentration after the induction of anesthesia has been successfully achieved.

In this era of automation, the infusion algorithm can be designed such that, at the start of anesthesia in a new patient, the pump is made to target a higher concentration for a fixed duration of time, after which it would automatically revert to the set target concentration. This is where an accurate value for the k_{eo} at induction is required. As the intention is to target the effect compartment rather than the blood concentration, it would only be logical to program the infusion pump to automatically calculate the necessary infusion rates using the k_{eo}.

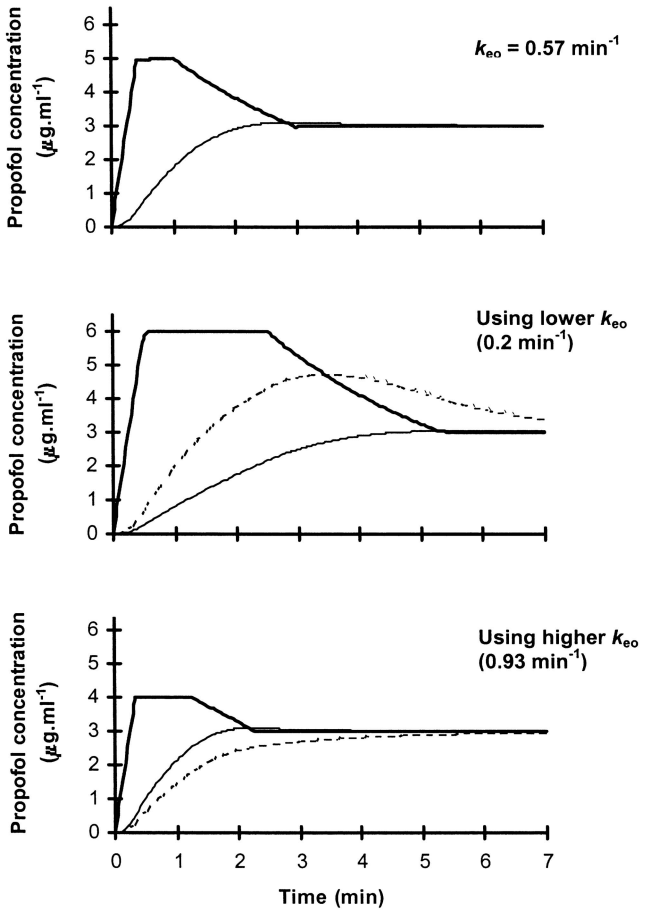

Fig. 2. Predicted concentration-time profiles when the effect-compartment concentration (C_e) was targeted to achieve and maintain a concentration of 3 μg·ml^{-1}. The *upper*, *middle*, and *lower* graphs show the profiles when k_{eo} values of 0.57, 0.2, and 0.93 min^{-1} were applied. *Thick continuous lines*, predicted blood concentration; *thin continuous lines*, predicted C_e; *broken lines*, predicted C_e if k_{eo} corrected to 0.57 min^{-1}

We show, in Fig. 2, an illustration of how the desired C_e can be quickly achieved at the induction of anesthesia using the k_{eo} value obtained in this study. This is supported by other investigators, who have demonstrated that targeting the effect-site concentration more accurately produced the desired time course of drug effect without causing undue complications [8].

In conclusion, this study used an alternative method of deriving the effect-compartment equilibrium rate constant during the induction of anesthesia using the Diprifusor. As this method uses data pooled from the entire sample, the k_{eo} derived is a population value. For propofol, the k_{eo} was found to be 0.57 min^{-1}.

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