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SHORT COMMUNICATIONS

A novel method of deriving the effect compartment equilibrium rate constant for propofol

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Background. Calculation of the effect compartment concentration (C_e) in non-steady-state conditions requires the equilibrium rate constant, k_{eo}. Most studies of propofol derive the k_{eo} using EEG measurements. This study investigated an alternative method. Starting from a predicted concentration–time profile, a k_{eo} value was included so that the predicted C_e at a specific pharmacodynamic end-point was the same when using three different methods of injection.

Methods. Seventy-five patients were given propofol for induction of anaesthesia. Twenty-five patients received a single bolus, 25 patients received an infusion, and 25 patients received a bolus followed by an infusion. Computer simulation was used to derive the central compartment concentration. The k_{eo} that brought about the same value for C_e at loss of the eyelash reflex using the three methods of injection was derived.

Results. K_{eo} was found to be 0.80 min^{-1}. Mean (SD) C_e at loss of the eyelash reflex was 2.27 (0.69) $\mu g\ ml^{-1}$.

Conclusions. The effect compartment equilibrium rate constant and concentration at loss of the eyelash reflex can be derived without the use of electronic central nervous system monitors.

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It has been shown previously that the predicted effect compartment concentration (C_e) of thiopental at loss of the eyelash reflex was independent of the method of injection.[1] While the use of thiopental is generally confined to induction of anaesthesia, propofol has established itself as an i.v. agent suitable for both induction and maintenance of anaesthesia.

A previous study demonstrated that plasma propofol concentrations after bolus injection are fairly well described by infusion pharmacokinetics, while the pharmacokinetics are linear during infusion.[2] These conditions are necessary if infusion algorithms are to accurately predict target concentrations.

Prediction of the concentration at the effect site requires an additional parameter, the effect compartment equilibrium rate constant (k_{eo}). This parameter is highly influenced by the pharmacokinetic model, making it unwise to mix the k_{eo} derived from one study with the pharmacokinetic data from a different study.[3]

Most studies derive the k_{eo} using EEG measurements taken either during an infusion, or after a bolus dose of the drug. The method used in this study differs from the methods used previously, as it does not require any EEG measurements. In addition, as the k_{eo} value was derived using a combination of infusion and bolus dosing, the value derived should be applicable to both methods of injection.

Methods and results

The study was approved by the local clinical research ethics committee. Seventy-five patients, ASA physical class I or II, undergoing elective surgical operations gave informed

Table 1 Patient data (mean (range or SD)), induction characteristics and predicted propofol concentrations at loss of the eyelash reflex (mean (range)). *P<0.05 when comparing between groups. †No significant difference between Groups 2 and 3.

	Group 1, single bolus	Group 2, infusion	Group 3, bolus and infusion
n	25	25	25
Age (yr) (range)	38.5 (22–58)	37.4 (18–60)	33.0 (18–54)
Weight (kg)	59.7 (9.5)	58.9 (11.1)	59.4 (11.5)
Gender (M/F)	8/17	5/20	9/16
Time to loss of the eyelash reflex (s)	20* (10–50)	160* (85–270)	80* (32.5–155)
Total dose of propofol (mg kg^{-1})	2.05* (1.91–2.13)	1.04* (0.63–2.04)	1.24*† (0.71 1.66)
Predicted blood propofol Concentration (μg ml^{-1})	7.97* (6.66–8.73)	3.63* (2.31–5.72)	3.93*† (2.87–5.46)
Effect compartment (C_e) Concentration (μg ml^{-1})	2.28 (1.48–4.19)	2.30 (0.96–4.22)	2.22 (1.02–3.01)

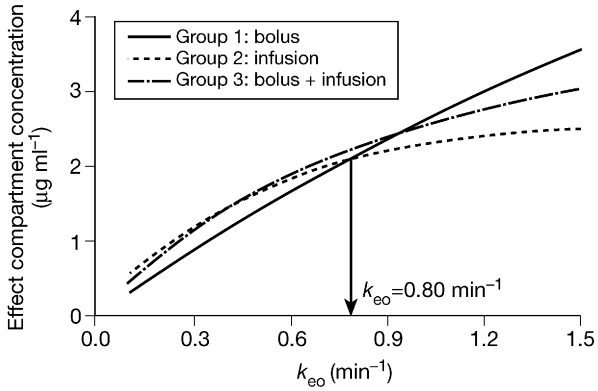

Fig 1 Relationship between effect compartment equilibrium rate constant (k_{eo}) and mean predicted effect compartment concentration of propofol at loss of the eyelash reflex.

consent for the study. Patients with a body weight above 80 kg, patients with evidence of cardiovascular disease, or a history of sensitivity to propofol were excluded. On arrival in the operation theatre, routine monitoring was set up and an i.v. cannula was inserted into a forearm vein for infusion of drugs and fluid. Patients did not receive premedication or any other sedative drug before induction of anaesthesia.

Patients were randomized to one of three groups:

1. Group 1. Patients received a single bolus dose of propofol 2 mg kg^{-1} injected over 10 s. If loss of the eyelash reflex was not achieved after 60 s, an additional dose of 0.5 mg kg^{-1} was given.
2. Group 2. Patients received a continuous infusion of propofol at 25 mg min^{-1} until loss of the eyelash reflex was demonstrated.
3. Group 3. Patients received a bolus of propofol (30, 40, or 50 mg), followed by a continuous infusion at 25 mg min^{-1}.

The eyelash reflex was tested every 2.5 s, and the time at which the reflex was lost was recorded (Table 1). After induction of anaesthesia was successfully achieved, patients were maintained using a standard anaesthetic technique.

Central compartment concentrations of propofol were initially predicted using the model reported in Marsh and colleagues.[4] C_es were then calculated numerically. This methodology has been described previously.[1]

For each group of patients, the mean C_e at loss of the eyelash reflex was calculated for any particular value of the k_{eo}. The sum of the squared differences of the mean effect compartment concentrations was then calculated using the formula:

$$\text{sum of squared differences} = (C_{e\ gp1\ -\ gp2})^2 + (C_{e\ gp2\ -\ gp3})^2 + (C_{e\ gp1\ -\ gp3})^2$$

where, $(C_{e\ gpx\ -\ gpy})^2$ is the squared difference between the mean effect compartment concentrations of groups x and y. Microsoft Excel Solver, which uses the Generalized Reduced Gradient non-linear optimization codesolver function, was used to derive the k_{eo} value that minimized the sum of the squared differences. This value was taken as the k_{eo} for propofol.

In order to determine the variability of the k_{eo}, each of the three treatment groups were divided into two sub-groups. Combinations of three sub-groups, each sub-group being from a different treatment group, were made. This gave a total of eight combinations. A k_{eo} value was then derived for each combination. The mean and SD of the k_{eo} obtained using this 'two-stage' method was calculated.

Differences between means were tested using ANOVA. A value of P<0.05 was considered significant.

A k_{eo} value of 0.80 min^{-1} gave the least difference between the mean predicted C_es of propofol at loss of the eyelash reflex using the three different methods of injection. Using the 'two-stage' method, the mean (SD) k_{eo} was 0.81 (0.25) min^{-1}.

C_e at loss of the eyelash reflex, calculated using the derived k_{eo} value, was not significantly different between groups (Table 1). After combining data from all three groups, mean (SD) C_e at loss of the eyelash reflex was 2.27 (0.69) μg ml^{-1}. Figure 1 shows the relationship between the k_{eo} and the C_e at loss of the eyelash reflex in the three groups.

Comment

The concentration at the effect compartment has a hysteresis-free relationship with the pharmacological effect. Estimation of the C_e usually requires some monitor of central nervous system electrical activity. This study illustrates a new method of estimating the C_e at a pharmacodynamic end-point without the use of such monitors. One advantage of this method is the reduction in cost. In addition, when different methods of analysis arrive at the same result, the confidence in such results is enhanced.

A wide range of k_{eo} values has been reported by previous investigators. Schnider and colleagues, using a value of 0.456 min^{-1}, reported a time to peak effect of 1.7 min after a bolus dose of propofol.[5] Struys and colleagues, using this time to peak C_e, calculated a k_{eo} of 1.21 min^{-1} when applied to the pharmacokinetic parameters reported by Marsh and colleagues.[6] Struys went on to show that this k_{eo} more accurately predicted the time of peak EEG effect. The value obtained in this study is between both these values, and is close to the value reported by Wakeling and colleagues.[7] Using the 'two-stage' method, the 95% confidence interval of the k_{eo} was found to be 0.32–1.30 min^{-1}. This wide confidence interval mirrors the range of previously reported k_{eo} values.

One way of assessing the accuracy of the derived k_{eo} value is to compare the predicted C_e with previous reports. The C_e reported in this study is similar to that reported in a previous study using a similar end-point.[8] In addition, the value derived is similar to the median pseudo-steady-state concentration at loss of eyelash reflex reported by other investigators.[9 10]

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 following a bolus dose. Furthermore, the model assumes that the pharmacokinetic parameters and the k_{eo} are not affected by the rate of drug administration. However, any inaccuracy caused by propofol affecting its own pharmacokinetics is likely to be much less than that introduced when a compartmental model is used to describe the concentration–time profile after a bolus dose. In spite of all this, it is generally accepted that a single set of pharmacokinetic parameters is sufficient for predicting blood propofol concentrations after a bolus injection and during infusion.

Most manual dosing regimens and target controlled infusion systems rely on a series of bolus injections and infusion rates to achieve a desired plasma or C_e. In the absence of real time estimation of the drug concentration, real time prediction of the concentration offers a reasonable alternative. The values of the parameters used for predicting such concentrations must be applicable equally well to bolus doses and infusions. The k_{eo} value derived in this study used both these methods of drug injection, and should be able to predict drug concentrations adequately in both situations.

In conclusion, this study reports a new method of deriving the effect compartment equilibrium rate constant. However, 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 0.80 min^{-1}.

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