PREDICTION OF INFUSION RATES: COMPUTER STUDY

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SUMMARY

The administration of two test doses in the ratio 1:0.5 has been shown to provide sufficient data (time intervals) to predict the infusion rate necessary to maintain the concentration of a drug at the therapeutic threshold in a two-compartment pharmacokinetic model. If the relationship between the durations of action of the test doses is linear, only one test dose may be needed to predict the infusion rate.

KEY WORDS
Pharmacokinetics: models.

Although many regimens have been described [1-4] for producing a steady concentration of a drug within its therapeutic range, they do not necessarily produce a predetermined pharmacological response. Noeldge, Hinsken and Buzello [5] used an approach based upon body weight in an attempt to produce an acceptable degree of neuromuscular block. The range of twitch tension achieved varied from 0% to 60% of control (mean 13 (SD 23)% ) when aiming for 90% neuromuscular block. This approach could not cope with the wide biological variation between patients.

A technique whereby the dosage of a drug may be tailored to the individual patient is thus desirable. The type of drug for which the technique may be used would be one with a clinically obvious effect, for example the onset and recovery of paralysis as measured by neuromuscular function. The present study was designed to investigate this possibility.

PHARMACOKINETIC CONSIDERATIONS

Figure 1 schematically demonstrates the drug concentration–time profile achieved with a drug regimen of three boluses (an induction dose and two test doses) administered to an open one-compartment pharmacokinetic model. It is possible to write two equations that relate the duration of action to drug concentration, volume of distribution and the elimination rate constant:

\[
(\text{CTT} + \frac{D_1}{V})e^{-k_1} = \text{CTT} \\
(\text{CTT} + \frac{D_2}{V})e^{-k_2} = \text{CTT}
\]

where CTT = concentration of the drug at the therapeutic threshold, that is where neuromuscular block is deemed inadequate; V = distribution volume; k = first-order elimination rate constant. D_1 and D_2 and t_1 and t_2 are the test doses and times from injection to return to CTT (duration of action), respectively.

CTT, k and V, which are common to both equations, determine the time intervals, t_1 and t_2 and the infusion rate required to maintain the concentration at CTT (CTT \times V \times k = CTT \times \text{clearance}). Thus it is possible to demonstrate

FIG. 1. Drug concentration profile following the administration of three bolus doses in the ratio 1:1:0.5.
graphically a direct relationship between the time intervals and the infusion rate. The same principle may be applied to drugs showing polyexponential disposition kinetics.

**METHOD**

The hypothesis was tested with a two-compartment pharmacokinetic model [6]. The program was modified so that the required dosage regimen could be given. After the pharmacokinetic parameters ($k_{10}$, $k_{12}$, $k_{21}$ and distribution volume) had been set, an infusion was administered to the model until a steady state had been reached. The concentration at which this occurred was recorded as the desired therapeutic threshold (CTT). The computer program was then reset, the same constants entered and a dose of drug was given to increase the concentration in the central compartment above that which was set to be the therapeutic threshold. When the concentration declined to CTT, the first of two test doses ($D_1$) was given; when the concentration again declined to the CTT the second test dose ($D_2$) was given, the second dose being 50% that of the first. The durations of action of these two test doses ($t_1$ and $t_2$) were recorded—that is, the time from injection of the bolus to the time at which the concentration in the central compartment decreased to CTT.

The parameters $k_{12}$ and $k_{21}$ were altered systematically, as were the infusion rate and the test doses that were administered to the model. $k_{12}$ was in the range 1–20: $k_{21}$ was 2–10. $k_{10}$ was held constant at 0.5 and the volume of distribution constant at 10 litre. The first test dose administered to the model was in the range 2–20 µg, the second test dose being 50% of these values. The infusion rates administered to the model were such that infusion rate/second test dose was 0.01–0.1, in increments of 0.01. The variation in the constants and the infusion rate produced different values for CTT. The data from the computer program were then used to produce a family of isopleths representing the relationship between time and infusion rate, the latter being designated as a fraction of the second dose per unit time.

Following the completion of this part of the study, one set of pharmacokinetic parameters, average values, describing the disposition of pancuronium [7] were entered into the model and further data points generated. The volume of distribution, nominally 7 litre, was changed to simulate patients of different sizes (2–10 litre), $k_{10} = 0.74$, $k_{12} = 3.2$ and $k_{21} = 4.2$. As described previously, the pharmacological end-point to which the test doses were timed (CTT) depended on the pharmacokinetic parameters used and the infusion rate.

**RESULTS**

Figure 2 demonstrates how the infusion rate may be determined from the duration effect of the two test doses. Each isopleth represents the infusion as a fraction of the second test dose per unit time. Figure 3 shows $t_1$ vs $t_2$ for different test doses (8, 6, 4, 2 and 1 mg) when the pharmacokinetic constants entered were those of an average patient given pancuronium. The relationship was...
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fig. 4. Graphical representation of the relationship between $D_2 \times t_2$ and the infusion rate in mg h$^{-1}$ for pancuronium, derived from figures 2 and 3. The isopleths are for different test doses as indicated.

represented by a straight line such that $t_2 = 1.04 t_1 - 8.4$.

Manipulation of the data from figures 2 and 3 enabled the construction of figure 4. For example, if the test doses of pancuronium were 4 mg and 2 mg, their respective durations of action could be 21 min and 12.5 min (fig. 3). If these values for $t_1$ and $t_2$ are applied to figure 2, they pinpoint the 0.03 isopleth. The infusion rate per minute is the product of the second dose and the isopleth value ($2 \times 0.03$), that is, 0.06 mg min$^{-1}$ or 3.6 mg h$^{-1}$. Referring to figure 4 confirms this relationship, $D_2 \times t_2 = 25$, which on the 2-mg isopleth is equivalent to a 3.6-mg h$^{-1}$ infusion rate.

DISCUSSION

The major assumption made in this study was that there was no displacement of effect vs time from concentration vs time.

Figure 2 may be considered part of a general solution to the problem determining infusion rate for drugs that exhibit linear kinetics. Some drugs have much longer time courses of action. Figure 4 is a form in which the solution appears for a particular drug and, in this case, from a single set of average pharmacokinetic parameters. This solution must be considered unproven until a clinical study has demonstrated the linear relationship between two test doses and thus the requirement for only a single test dose.

Wagner's [1] method for the achievement of a desirable concentration plateau is dependent upon a knowledge of the plasma clearance and half-life of the drug used. This is not normally known to the clinician for any individual patient. Hengstmann, Stoeckel and Schuttler [3] used Wagner's model and thus reduced the clinical usefulness of their technique. Vaughan and Tucker's method [2] for the achievement of the desired concentration is complex and requires a bolus dose, a constant infusion and an exponentially decreasing infusion. These techniques do not give a "personalized" infusion for the patient, and the clinical requirement is for a predetermined effect rather than concentration.

Jones, Laurence and Thornton [4] used a two-step infusion schedule to maintain anaesthesia using etomidate and fentanyl, but found that only 76% of the patients were provided with adequate anaesthesia. Noeldge, Hinsken and Buzello [5] observed a very wide range of effect when using a weight-related infusion regimen. They gave vecuronium 0.075 mg kg$^{-1}$ as a loading dose and 0.075 mg kg$^{-1}$ h$^{-1}$ as an infusion.

The conclusion of the present study is that it may be possible to determine a "personalized" infusion rate by the administration of two boluses of differing magnitudes of a drug, the effects of which are clinically obvious or measurable, and comparing the relationship between the durations of action of the two doses.

It is likely that it will be more difficult to maintain accurately the circulating concentration of a very short acting drug at the therapeutic threshold, because small errors in timing lead to large variation in the predicted infusion rate. Conversely, the longer acting the drug the more it should be possible to maintain accurately the plasma concentration at the therapeutic threshold. When dealing with a specific drug, where it has been shown clinically that the $t_1 : t_2$ relationship is linear, and inter-individual variation small, only one test dose may be required. This relationship needs clinical confirmation.

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REFERENCES

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