REVIEW

The Kinetics of Effect of Neuromuscular Blocking Drugs

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Abstract. In attempts to derive pharmacokinetic constants from effect data three methods were explored, using non-depolarizing neuromuscular blocking drugs as the paradigm for obtaining effect data. The first method, based on the simple assumption that following two doses, the drug concentrations at times of equal effect during recovery, were equal. Provided that recovery took place in the log-linear drug elimination phase, the elimination rate constant (β) could be calculated. This method proved rather inaccurate, a second method, again dependent on recovery in the log-linear phase yielded a constant which was the product of β and the exponent of the Hill equation (s). This method yielded results within 20% of values calculated from plasma drug assays, and it was demonstrated that the time — effect curve could be described from knowledge of this constant. The third method, using non-linear curve fitting technique, derived values for the rate constants of plasma redistribution (α) and elimination (β) as well as for the rate constant of elimination from an effect compartment (keo). If the values were derived from the effect of two doses of a drug, the intensity and duration of effect of a third dose could be predicted with reasonable accuracy. The dose dependent constants of the usual compartmental equations for the plasma concentration of a drug (A and B) could be derived in terms of the EC₅₀. The method can be applied to any drug whose effect can be measured and whose maximal effect can be defined. We believe that the method may be useful in rapidly and inexpensively estimating population kinetic parameters, and in screening drugs. (Keio J Med 43 (1): 27–30, March 1994)

Key words: pharmacokinetics, pharmacodynamics, non-depolarizing neuromuscular blockers, effect compartment

Orthodox pharmacokinetic studies usually deal with the changes of plasma or biophase drug concentration in time. That is, how the body absorbs, distributes, and eliminates a drug. The usual method involves administration of the test drug, sampling of blood and the determination of drug or metabolite concentrations in these samples. Non-linear curve fitting techniques are then used to fit these data to an adequate mathematical model, which then can be used for predictions, the design of dosage regimens or for comparisons between individuals, drugs or populations.

Our interest has been somewhat different. We have measured drug effect and then attempted to derive information from the effect data, alone similar to that usually derived from drug assays. The potential applications include drug screening and estimation of such things as population variability. In the final count, we clinicians are principally interested in the effect drugs have on our patients, therefore direct studies of the effect — time relation, such as these, are helpful in understanding and predicting responses.

We have performed these studies using non-depolarizing muscle relaxants for two reasons. First is that their effect is simple to measure and the second is that the maximal effect of these drugs, complete neuromuscular blockade, is easily defined. The methods, however, can be applied to other drugs, provided their effect can be measured, and the maximal effect defined. We have investigated three methods, but before I outline them, it may be appropriate to review the pharmacokinetic concept of the effect compartment.

An administered drug initially enters the plasma and is carried to all parts of the body. At the same time, drug elimination occurs by excretion and/or degradation. The

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most common models represent the pharmacological system as a central compartment with a variable number of compartments in communication with it. Drug transfer between compartments is assumed to be proportional to the concentration gradients. In these models, how many compartments are used to represent the body simply depends on the desired precision. Allowing for the errors inherent in drug assays, it is often sufficient to represent the body by one or two compartments, and rarely are more than three compartments warranted. Thus, after drug administration the plasma concentration is initially high, but falls rapidly as other tissues take up the drug. Once there is equilibration with the tissues, the fall in concentration becomes slower, now representing the elimination of the drug from the body. This two (or three) phase decay can be represented by equation 1, or equation 2, depending on whether the number of compartments used to represent the body are two or three. (1) \( C_p = A.e^{-\alpha t} + B.e^{-\beta t} \), (2) \( C_p = P.e^{-\gamma t} + A.e^{-\alpha t} + B.e^{-\beta t} \).

These equations describe adequately the changes in plasma drug concentration with time. Unfortunately, effect does not parallel these concentrations (see Fig 1)! Immediately after administration, when the plasma concentration is highest, the effect is usually negligible. In the case of the non-depolarizing relaxant drugs, maximum effect is achieved only after 6 or 8 minutes, when the plasma concentration is already much less than maximal. The simple model, which equates effect with plasma concentration fails, especially during onset of effect. We must therefore postulate a compartment to represent the site of action, (usually called an effect compartment or the biophase) to account for this discrepancy. We cannot directly measure concentration there, but we can assume that at all times, effect is proportional to effect compartment (biophase) concentration. The onset of effect parallels the initial increase in drug concentration, and decay of the effect, the elimination from this compartment. It is assumed that the effect compartment contains such a small mass of drug that the existence of this extra compartment does not affect plasma concentration. During recovery the plasma and biophase concentrations are generally close and more or less parallel.

Effect compartment models are defined in two ways and both share the assumption that the effect parallels the drug concentration in this hypothetical compartment. The model of Sheiner et al. assumes that there is a defined relation between effect compartment concentration and the effect, represented by the Hill equation (equation 3):

\[
\text{f} = \frac{\text{Effect}}{\text{MaxEffect}} = \frac{C^s}{C^s + \text{EC}_50^s}
\]

Where \( f \) is the fractional effect, \( C \) is the concentration, \( s \) is an exponent and \( \text{EC}_50 \) is the concentration for 50% effect. This equation is empirical but it works. The other models postulate that for equal effect during onset and recovery, there must be equal concentration of drug in the effect compartment. A third model is a refinement of the second, and defines the elimination rate constant of the effect compartment by minimising the hysteresis of the measured plasma concentration during onset and recovery.  

As stated above, our work has been devoted to trying to derive the commonly used pharmacokinetic rate constants from measurements of the effects of non-depolarizing neuromuscular blocking drugs. The first method we explored was suggested by our co-worker, Dr B Love. If two doses of a drug are administered and recovery takes place in the log-linear (\( \beta \)) elimination phase then if we chose two times during recovery following each of the doses, respectively, when the effects are equal, it can be assumed that the drug concentrations causing the equal effects are also equal. Thus, if the two doses are \( D_1 \) and \( D_2 \), and \( t_1 \) is the time between dose 1 and the first equal effect time and \( t_2 \) between dose 1 and the second equal effect and \( t_3 \) the interval between the second dose and the second equal effect, then: (4) \( D_1B.e^{-\beta t_1} = D_1B.e^{-\beta t_2} + D_2B.e^{-\beta t_3} \) and this equation can be solved for \( \beta \), but the method has proved not to be very accurate, probably because of measurement errors as well as the difference between biophase and plasma concentrations.

A more interesting method was then devised. As recovery from clinical doses of non-depolarizing relaxants occurs in the log-linear (\( \beta \)) elimination phase, we can approximate the concentration as: (5) \( C = B.e^{-\beta t} \). If we substitute this in the Hill equation (3) and divide through by \( B \), then (6) \( f = \frac{e^{-\beta t_s}}{e^{-\beta t_s} + \text{EC}_{50}^{-\beta t_{sw}}} \) where \( f \) is the
fractional effect, \( t \) is the elapsed time from administration of the drug, \( t_{50} \) is the time at 50% recovery and ‘s’ the exponent. Non-linear curve fitting techniques can be applied to the time course of the effect to derive a compound constant, \( \beta.s \), which can be used to describe the time – course of effect.

Equation 6 can be transformed, (7) \[
\frac{f}{1-f} = e^{-\beta.s.t} e^{-\beta.s.t_{50}}
\]
and in the logarithmic form: (8) \[
\ln \frac{f}{1-f} = \beta.s.t - \beta.s.t_{50} = \beta.s(t - t_{50})
\]
this function is linear. From this, \( \beta.s \) can be derived by linear regression.

In the elimination phase, \( \beta \) is the rate of decrease in drug concentration. \((\text{Ln} 2)/\beta \) or 0.693/\( \beta \) is the elimination half-life, the time during which concentration falls by half. Similarly 0.693/\( \beta.s \) is the half-life of CS during which CS changes by a factor of 2. If this is substituted into the Hill equation (Eq 3). The rate of change of effect can be described in terms of this constant as shown in Fig 2. Thus we can show that where the concentration – effect relation is expressed by the Hill equation (Eq 3) recovery from 3 to 6% and from 6 to 11 etc... take the same time⁷ and that the ‘recovery index’ (time for recovery from 75 to 25% effect) takes 3.17 effect half-lives. Table 1 compares the results obtained by this technique to results calculated from \( \beta \) obtained from plasma assay and \( s \) from concentration and effect data in 5 patients.

The final method which we are investigating at present involves the substitution of the effect compartment concentration algorithm (9) \[
C_e = \frac{A}{\alpha} \left( e^{-\alpha.t} - e^{-k_{eo}.t} \right) + \frac{B}{(\beta - k_{eo})} \left( e^{-\beta.t} - e^{-k_{eo}.t} \right) \]
where \( C_e \) is the effect compartment concentration and \( k_{eo} \) the rate constant of elimination of drug from the effect compartment, into the Hill equation. That is, (10) \[
f = \frac{C_e}{C_e + C_eE_{50}} \]
where \( C_eE_{50} \) is the effect compartment concentration at 50% effect.

Non-linear curve fitting of this equation to the time versus effect data will give values for \( \alpha, \beta, k_{eo} \) and \( s \). The dose dependent variables, \( A \) and \( B \) of the two compartment kinetic model are in units of the EC50 and cannot be determined in absolute values. A simple method of testing the accuracy of this method is to use effect data from three consecutive doses of relaxant.

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>( \beta.s ) by Assay</th>
<th>( \beta.s ) from Effect</th>
<th>% Error</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>2.76</td>
<td>3.24</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>3.75</td>
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</tr>
<tr>
<td>5</td>
<td>4.13</td>
<td>4.14</td>
<td>0</td>
</tr>
</tbody>
</table>

The % error is calculated as \(((\text{effect estimate} - \text{assay estimate})/\text{assay estimate}) \times 100\).

![Fig 2](image2.png)

**Fig 2** The effect half-life: The time course of effect in terms of the half-life of effect (\( \beta.s \) half-life). On the abscissa, 0 corresponds to 50% effect and the scale shows the effect at a given number of effect half-life before or after 50% effect showing how the \( \beta.s \) half-life describes the time – effect curve. The inset shows the percent effect corresponding to unit changes in the effect half-life.

![Fig 3](image3.png)

**Fig 3** The results of curve-fit estimates of the pharmacokinetic rate constants in a patient given 3.5 mg vecuronium, followed by 1 mg at 28 minutes and 2 mg at 44 minutes. The filled squares represent the recorded effect and the line the result of the curve fit. The fitting was done to the data from the first two doses and the figure shows how the parameters obtained predict the effect of the third dose.
The first two are used to derive the constants, and a prediction for the effect of the third dose is made on their basis. This can be compared to the actual effect of the third dose (Fig 3). We are at present working on this method and have not finished evaluating it.

In summary, in our present research we are using data from the effect of repeated doses of a non-depolarizing relaxant, to derive rate constants for redistribution, elimination, effect compartment elimination and the Hill exponent. These constants describe well the time course of effect of these drugs. The technique can be used for any drug whose effect can be measured and whose maximal effect can be defined. It may prove useful in estimating approximate pharmacokinetic and pharmacodynamic constants of drugs in individuals, in populations of for drug screening.

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References