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A NEW FOUR-PARAMETER THRESHOLD MODEL FOR THE PLASMA ATRACURIUM CONCENTRATION-RESPONSE RELATIONSHIP

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SUMMARY
The plasma concentration of atracurium and the electromyographic depression of the first response of the train-of-four (T1:TO) were measured during and after recovery from a 10-min infusion of atracurium 0.25 mg kg\(^{-1}\) in 14 patients anaesthetized with 66% nitrous oxide and 0.9% isoflurane (end-tidal) in oxygen. A standard pharmacodynamic model was fitted to the data; a small but consistent discrepancy was found between the time and rate of onset of depression of the ratio T1:TO and the predictions of the standard biophase model of best fit to the data. This discrepancy is reduced by the inclusion of a threshold term \(C_{PP0}\) in the model to represent the greatest steady state plasma concentration which would just fail to evoke an effect. The values of \(C_{PP0}\) correlated significantly with the values of \(C_{PP50}\) (r = +0.627; P < 0.02). The estimates of \(C_{PP50}\) and \(k_{ne}\) from the two models are very similar; the estimate of \(\Gamma\), the slope of the concentration–response curve, was less in the threshold model. The relationship of the present threshold model to existing knowledge of neuromuscular physiology is discussed.

KEY WORDS

Early attempts to relate the action of the nondepolarizing neuromuscular blocking drugs to their plasma concentration were frustrated by the fact that the relationship differs during onset and recovery; a given degree of twitch depression during onset is associated with a greater plasma drug concentration than that during recovery [1]. This discrepancy, which reflects the fact that the site of action is peripheral to the plasma, was overcome by the application of an effect compartment model by Hull and colleagues [2], and Sheiner and colleagues [3]. This model is characterized by three parameters: two define the position and slope of the concentration–response relationship at the site of action, generally denoted \(C_{PP50}\) and \(\Gamma\), respectively; the third parameter defines the rate of equilibration of drug in the plasma with the site of action, and is denoted \(k_{ne}\), the rate constant for exit of drug from the effect compartment.

The model has been applied widely to the nondepolarizing neuromuscular blocking drugs including atracurium [4–7], for which there arises the additional complication of possible degradation of drug close to its site of action, in addition to its return to the plasma. A similar scheme has been envisaged for other classes of drug, including the opioids [8] and propofol [9].

Despite the power and wide application of the model it remains a means whereby data obtained during the onset and recovery of drug action may be superimposed; it is not a summary of available knowledge of the neuromuscular junction. Furthermore, whereas Sheiner and colleagues offered a partial validation of the model by comparing the quality of its fit to the data with that of more restricted models [3], subsequent workers have not envisaged further alteration to the structure of the model.

We report a small but systematic discrepancy between the observed time and rate of onset of the action of atracurium and the predictions of the standard model of best fit to the data as a whole. We have shown that the discrepancy was greatly ameliorated by inclusion of a threshold in the effect compartment. The relationship of this modification of the model to the existing knowledge concerning the margin of safety of neuromuscular function is discussed. A preliminary report of this work has been presented elsewhere [10].

PATIENTS AND METHODS
We studied 14 healthy patients undergoing elective minor surgery requiring the use of neuromuscular block. The study was approved by the Ethics Committee of the Royal Liverpool Hospital and informed consent was obtained.

Premedication consisted of either promethazine 50 mg or diazepam 10 mg, orally on the night before surgery, or cyclizine 37.5–50 mg with morphine 7.5–10 mg i.m. 1 h before surgery. In those patients admitted to hospital on the day of surgery, premedication was omitted.

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THRESHOLD PHARMACODYNAMIC MODEL

At FIG. 1. The threshold pharmacodynamic model. The plasma compartment, denoted P, is connected to the site of action, compartment J, by a pathway in which drug moves at rates determined by rate constants $k_{JP}$ and $k_{PJ}$. Drug may leave compartment J without returning to the plasma at a rate determined by $k_{J0}$. The magnitude of drug effect is related to the amount of drug, $A_t$, greater than threshold in compartment J.

![Diagram of the threshold pharmacodynamic model](https://example.com/diagram.png)

**Fig. 1.** The threshold pharmacodynamic model. The plasma compartment, denoted P, is connected to the site of action, compartment J, by a pathway in which drug moves at rates determined by rate constants $k_{JP}$ and $k_{PJ}$. Drug may leave compartment J without returning to the plasma at a rate determined by $k_{J0}$. The magnitude of drug effect is related to the amount of drug, $A_t$, greater than threshold in compartment J.

Anaesthesia was induced with fentanyl 50–200 μg and thiopentone 250–500 mg and maintained with 0.9% isoflurane (end-tidal) and 66% nitrous oxide in oxygen. The end-tidal concentration of isoflurane was monitored using an infra-red analyser (Datex “Normac”). After induction of anaesthesia, electromyographic monitoring of the height of the surface compound action potential of the adductor pollicis of one hand in response to trains of four supramaximal stimuli to the ulnar nerve was commenced using the Medelec MS6 [11]. Recording of the electromyographic effect during profound block was facilitated by the fact that the amplifier gain could be altered according to signal size. In general, the height of the evoked electromyographic effect was quantified with a random error of not more than 1%.

A vein in the antecubital fossa of the arm used for electromyographic monitoring was cannulated for blood sampling. A vein in the opposite forearm was cannulated for administration of atracurium.

After 20 min, atracurium 0.25 mg kg$^{-1}$ was given by constant rate infusion over a period of 10 min. Ventilation was controlled and the trachea intubated when appropriate; end-tidal carbon dioxide tension was maintained in the range 4.0–5.3 kPa (Datex “Capnomac”).

Pharmacological antagonism of neuromuscular block was not used; neuromuscular monitoring was continued until both the ratios $T_1:T_0$ and $T_4:T_1$ were 80% or greater (in one patient monitoring was discontinued when $T_1:T_0$ recovered to 78.5%). After recovery from neuromuscular block and the end of surgery, anaesthesia was discontinued, spontaneous ventilation re-established and the trachea extubated.

Heparinized blood samples (2.5 ml) were taken before and at 1, 2, 4, 6, 8 and 10 min after the start of the infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75 and 90 min after the end of the infusion. The samples were immediately acidified and cooled, and plasma was separated promptly. The plasma was frozen rapidly in liquid nitrogen and stored at $-20^\circ$C until subsequent analysis of the atracurium concentration as described previously [11].

Data analysis

The threshold pharmacodynamic model is illustrated in figure 1 and described in the Appendix. It is defined by four parameters: three are directly comparable to those of the standard model ($C_{P^*}$, $k_{m}$). The fourth parameter, $C_{P^*0}$, is the steady state plasma concentration of atracurium which would just fail to evoke an effect.

For each patient, the standard and threshold pharmacodynamic models were fitted to the data for depression of the ratio $T_1:T_0$. A specific compartmental model of disposition was abandoned in favour of using numerical methods to define terms which relate the effect compartment concentration to the plasma concentration as measured (see Appendix). This freed the pharmacodynamic model from any potential mis-specification inherent in a compartmental pharmacokinetic model. The Gauss–Newton algorithm was used to find the least squares fit of the model to the data. No attempt was made to weight the data points.

The closeness of fit of the data and the model predictions were examined by consideration of residual error. The total sum of squared residual
errors was calculated; formal comparison of the residual errors in the two models was not undertaken using the $F$ test because the data formed a time series, and so successive residual errors were correlated. Residual error was examined using residual plots, and by calculation of the Durbin–Watson statistic [12], which evaluates the serial correlation of residual errors. The discrepancy between the model predictions and the data was examined further by comparison of the measured and predicted values of the time to 10% depression of $T_1: T_0$ and the change in $T_1: T_0$ which occurred during the 1 min thereafter.

**RESULTS**

Seven patients were male and seven were female; mean age was 36.4 (SD 15.8) yr (range 19—65 yr); mean weight was 63 (11.3) kg (range 48—89 kg).

The pharmacokinetic profile of these patients has been illustrated previously [11].

An example of the measured depression of $T_1: T_0$ during the first 15 min after the start of the atracurium infusion for patient No. 8, and the predictions of the standard model of best fit are shown in figure 2, together with the residual errors. The depression of $T_1: T_0$ began later, but then proceeded more rapidly than the depression predicted by the standard model of best fit. This discrepancy is reflected in the pattern of residual errors. The figure is entirely typical; a similar pattern of residual errors was found for all the patients studied.

The magnitude of residual error for the fit of both models to the data of each patient is shown in table I. It may be seen that the threshold term reduced the residual error in each patient, in many instances substantially.

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The degree of correlation of the residual errors, defined by the Durbin–Watson statistic also is shown for each patient in table I. In every patient, the serial correlation of residual errors was reduced by inclusion of the threshold term.

The time to 10% depression of $T_1: T_0$ predicted by both the standard and threshold models is plotted against the measured time in figure 3. It can be seen that, whereas the standard model underestimated the time to 10% depression in every case (by between 0.14 and 0.47 min), the threshold model made a more accurate prediction.

The standard model also underestimated the change during the 1 min after 10% depression in all

![Figure 3](http://bja.oxfordjournals.org/)

**FIG. 3.** Predicted time to 10% depression of $T_1: T_0$ plotted against measured time, in each patient, for both the standard (×) and threshold (○) pharmacodynamic models, together with the line of identity (--). The standard model consistently underestimates the time to 10% depression; the threshold model gives a better prediction in every patient.
14 patients (by from 2.6 to 14.4%). Although the threshold model overestimated the value in all but two of the patients, the absolute error was less than for the standard model in 11 of the 14 patients.

The logit depression of T1:T0 for patient No. 1 is plotted against the effect site concentration for the standard model in figure 4, which is typical of results from all patients studied. Whilst there was close approximation of data from onset and recovery, the relationship during onset was not linear; points during the early phase of onset were displaced to the right. This feature is inconsistent with the application of a logistic concentration–response relationship within the effect site of the standard model. The inclusion of a threshold at the effect site ameliorated the discrepancy.

The fitted values of the parameters are summarized in table II for both the standard and threshold models. The values of \( C_{P_{50}}^* \) and \( k_w \) were altered little by the choice of model; in no patient was \( C_{P_{50}}^* \) different by more than 1.5% between the two models, and for \( k_w \) the difference was in no case greater than 4% of the parameter value. The fitted values of \( f \) were substantially different between the two models; in every case the value of \( f \) was less in the threshold model than in the standard model.

The fitted values of the parameter \( C_{P_{50}}^* \) range from 81.8 to 225.1 ng ml\(^{-1}\). In every case a positive value was obtained. The values of \( C_{P_{50}}^* \) correlated positively with the values of \( C_{P_{50}}^\theta \) in the same patient (\( r = +0.627; 12 \) d.f.; \( P < 0.02 \)).

**DISCUSSION**

The effect compartment model was applied to the analysis of the effects of the non-depolarizing neuromuscular blocking drugs more than a decade ago [2,3], and it is still used widely [6,7]. It explicitly separates factors which affect disposition from those which affect drug response at the site of action, and it enables a maximum of information to be obtained from the study of each patient. The modification of this successful model should therefore not be undertaken without good reason, and the justification should proceed on both statistical and conceptual grounds. Furthermore, modifications should be parsimonious—that is, a small modification should be expected to produce a substantial enhancement of the explanatory power.

The statistical justification of the inclusion of the threshold parameter in the model is complicated by
the fact that the electromyographic data set comprises many closely spaced observations; each observation is similar to the preceding one. The residual errors from the fit of the (deterministic) model also form a time series with considerable serial correlation. This is borne out by the values of the Durbin–Watson statistic (table 1). Thus an assumption of the F test is violated and the test is not applicable. The problem is not that the F test does not find a "statistically significant" reduction in residual error, but that the significance is absurdly overstated, by a factor related to the correlation of the residual errors. This is illustrated by the results for patient No. 1, for whom $F_{1,179} = 587.5$.

The F test was used by Sheiner and colleagues [3] to compare the standard model with more restricted variants, and very highly significant values of $F$ were obtained. Because the statistical justification of the threshold model eludes a single test, reliance must be placed on other arguments.

First, an adequate model should reproduce accurately the pattern of the results, apart from random errors. In respect of the time and rate of onset of depression of $T_1:T_0$, it is clear both that the standard model fails to do so and that the threshold model represents a substantial improvement.

Second, the sign of the threshold parameter $C_{p^e_{as}}$ gives evidence for its justification; thus if $C_{p^e_{as}}$ were redundant, its fitted value should be close to zero, and its sign might be positive in some subjects and negative in others. In fact, the fitted value of $C_{p^e_{as}}$ was positive in all 14 subjects; this provides robust evidence that the threshold parameter is not redundant.

Third, the serial autocorrelation of residual errors is reduced in every patient by incorporation of the threshold parameter. This autocorrelation reflects the preponderance of systematic over random errors in the fit of the model to the data, and it is clear, therefore, that the systematic error in the model is reduced by the inclusion of the threshold term.

The formulation of an effect compartment model requires the synchronization of two separate data sets (for plasma concentration and electromyographic effect), and the question arises as to whether or not the error of the standard model in estimating the time to 10% depression of $T_1:T_0$ might be an artefact arising from errors in the timing of the data points. Whilst the time of the electromyographic data points is known to within 1–2 s, the timing of the blood samples is inevitably subject to greater errors. The design of this study included two factors which militated against the overstatement of the need to postulate a threshold. First, the use of venous rather than arterial blood samples, whilst giving a less accurate picture of the plasma concentration to which the arterial end of the muscle capillary is exposed, leads to the inclusion of a time delay in the plasma concentration data in the direction of underestimating the exposure of the muscle to drug during the early minutes of its administration. Second, the abandonment of a compartmental pharmacokinetic model in favour of fitting the dynamic model to the plasma concentration profile as measured avoids the possibility of a gross overestimate of the drug concentration to which the site of action is exposed during the early minutes of onset. Circulatory delays have been preserved in the data set used to fit the present models, and the drug concentration in the plasma close to the site of action has been estimated more accurately than it would have been by the concentration in the central compartment of a pharmacokinetic model (see Appendix).

The inclusion of the threshold term is robustly supported by the findings with respect to the change in block during the 1 min after the onset of 10% depression. This represents a rate of change of effect and is thus more immune to discrepancies in the synchronization of the data sets than is a single estimate of time.

Changes in the concentration of isoflurane at the neuromuscular junction during the onset of block might, conceivably, account for some of the discrepancy between the present findings and the predictions of the standard model. Whilst equilibration of isoflurane with the muscle was incomplete when the atracurium infusion was started [13], it is difficult to envisage that the concentration of isoflurane in the muscle could be changing sufficiently rapidly to affect the rate of onset of block as consistently as was found. Furthermore, a similar discrepancy has been noted in patients anaesthetized without the use of a volatile anaesthetic agent, some of the results from whom have been reported in preliminary form [14].

The discrepancy between the predicted and measured rate and time of onset of a non-depolarizing neuromuscular blocking drug noted in the present report may be discerned retrospectively in previous work. Thus measured and predicted effects have been plotted for a single individual given tubocurarine [15] for whom, upon close examination of figure 2, a discrepancy very similar to that noted here may be seen.

Whilst the concept of a threshold in the study of pharmacological effects was identified more than two decades ago [16], the presently postulated threshold term is also consistent with much evidence on the physiology of the neuromuscular junction. As early as 1956, the size of the normal end-plate potential was estimated to be about 45 mV [17], some three times greater than the threshold for initiation of an action potential. Thus there exists a margin of safety in the relative size of the end-plate potential and that needed to excite the muscle.

Knowledge of the margin of safety of neuromuscular transmission was advanced in 1967 by Paton and Waud [18]. They compared the doses of a non-depolarizing neuromuscular blocking drug required to block the effects of a humoral agonist injected intra-arterially, with the effect of neural stimulation. The response to neural stimulation was unaltered until about 76% of the postjunctional receptors were blocked.

The values of the threshold parameter, $C_{p_{as}}$, correlated with the values of $C_{p_{as}}$ in the same subject, and the ratio $C_{p_{as}}:C_{p_{as}}$ was about 40%. The magnitude of the margin of safety defined by Paton and Waud [18] might lead one to expect a somewhat greater value. The present model identi-
The site of action of a drug may be considered to be a single compartment, however, and the parameter $C_{P*J}$ is defined as that value of plasma concentration which just fails to evoke any depression of $T_1:T_0$. Thus $C_{P*J}$ is the margin of safety of the most sensitive end-plates, rather than the margin of safety of the muscle as a whole. The heterogeneity of the muscle militates against finding a greater value of $C_{P*J}$.

The present model, the first explicit demonstration of a margin of safety of neuromuscular transmission in the human, sheds light on an important clinical problem: the time to onset of action of the non-depolarizing neuromuscular blocking drugs. The existence of a threshold suggests that it may not be possible to achieve rapid onset of block with a non-depolarizing neuromuscular blocking drug.

**APPENDIX**

The equations which define the behaviour of the threshold model are derived below, in a manner similar to that given by Sheiner and others [3].

The threshold model is illustrated in figure 1. The observed effect on neuromuscular function is considered to be related to the amount of drug greater than the threshold concentration in compartment $J$, which is considered to be sufficiently small that the disposition of drug there has a negligible effect on the amount of drug in compartment $P$. The following definitions are given: $A_t = amount$ of drug in compartment $J$ at time $t$. $A_0 =$ amount of drug in compartment $J$ when the concentration there is at the threshold. $A_j = amount$ of drug in (plasma) compartment $P$. $C_P = drug$ concentration in the plasma compartment. $V_P = volume$ of the plasma compartment. $k_{P}$, $k_{P2}$, $k_{P0} =$ rate constants assigned in figure 1. Initially values are designated with superscript o, for example $A_j^o$. Laplace transforms are designated with a bar, for example $\bar{A}_j$. The Laplacian operator is designated $\mathcal{L}$.

Thus

\[
\mathcal{L} \{ A_t \} = \mathcal{L} \{ A_t - A_0 \} if \ A_t > A_0 \ otherwise.
\]

Considering entry and exit of drug to and from compartment $J$, we can write:

\[
\frac{dA_j}{dt} = A_{P} k_{P2} - A_{J} (k_{P1} + k_{P0})
\]

Taking the Laplace transform of this equation and rearranging, we have:

\[
\mathcal{L} \{ A_j (t + k_{P1} + k_{P0}) \} = \frac{A_{P} k_{P2}}{s} + \mathcal{L} \{ A_j \}
\]

Initially: $t = 0, A_j^0 = 0$. We denote the sum of rate constants for drug exit from compartment $J$ by $k_{m}$. That is:

\[
A_{jm} = k_{P1} + k_{P0}
\]

Thus:

\[
A_j = \frac{A_{P} k_{P2}}{s + k_{m}}
\]

To obtain the inverse transform of $A_j$ requires application of the convolution theorem. Thus an expression for $A_j$ at any time, $t$, may be written in terms of the time course of $A_{J}$ and the model parameters $A_{jm}$ and $k_{P2}$.

The amount of drug in compartment $J$ at any time ($t$) may be written:

\[
A_j (t) = k_{P2} \int_0^t A_{J} (T) e^{-k_{P1}T} dT
\]

so:

\[
A_j (t) = k_{P2} V_P e^{-k_{P1}T} \int_0^t C_P (T) e^{k_{P1}T} dT \]

As noted above, the effect on neuromuscular function ($E$) is considered to be exerted by the drug in compartment $J$ which is in excess of the threshold, $A_e$. An equation of the form used previously [3] is proposed:

\[
E = \begin{cases} 
- \frac{A_e}{A_t + A_e} & if \ A_t > A_e \\
0 & otherwise 
\end{cases}
\]

where: $E =$ observed effect on neuromuscular function; $g =$ slope of the relation between logit $E$ and log $A_e$; $A_e =$ value of $A_e$ when the effect is half maximal.

For any value of $A_J$ there is a value of $C_P$ which would produce that value of $A_J$ at steady state [3]. This value is denoted $C_{Pm}^-$. We may designate:

$C_{Pm}^-$ the value of $C_P$ which, if maintained at steady state, will produce a half maximal effect.

$C_{Pm}^+$ the value of $C_P$ which, if maintained at steady state, will produce $A_J = A_t$.

At steady state we may write:

In general:

\[
A_j k_m = A_j k_{P2}
\]

In particular:

\[
A_j = \frac{C_P^* k_{P2} V_P}{k_m}
\]

Thus equation (2) may be re-written:

\[
E = \frac{\left( C_{Pm}^- - C_{Pm}^+ \right) k_{P2} V_P}{k_m}
\]

if $C_{Pm}^- > C_{Pm}^+$, $E = 0$ otherwise.

This simplifies to:

\[
E = \frac{(C_P^* - C_{Pm}^-)^2}{(C_P^* - C_{Pm}^+)^2 + (C_{Pm}^- - C_{Pm}^+)^2}
\]

if $C_{Pm}^- > C_{Pm}^+$, $E = 0$ otherwise.

The expression for the amount of drug in compartment $J$ at any time ($A_J(t)$) given in equation (1) may now be rewritten in terms of the steady state plasma concentration which would produce that value of $A_J$ using equation (3).

Denote the steady state plasma concentration which will produce $A_J(t)$ by $C_{Pm}^- (t)$. Then:

\[
C_{Pm}^- (t) = \frac{k_{m} k_{P2}}{k_{P1} V_P} e^{-k_{P1}T} \int_0^T C_P (T) e^{k_{P1}T} dT
\]

This may be simplified:

\[
C_{Pm}^- (t) = k_{m} e^{-k_{P1}T} \int_0^T C_P (T) e^{k_{P1}T} dT
\]

The derivation of the present model differs from that given by Sheiner and others [3] in three important respects.

(1) The proposal of a threshold plasma concentration below which no effect is produced. It may be noted that the present model reduces to the standard model if $A_t$ is set to zero; for then $C_{Pm}^+$ is zero and the terms related to the threshold in equation (4) disappear.

(2) $k_m$ is explicitly the sum of all exit processes from compartment $J$. The model is thus entirely applicable to atracurium, for which the question of drug elimination at peripheral sites arises.

(3) No definite relationship is proposed with any pharmacokinetic model, and pharmacokinetic parameters were not obtained.
simultaneously with pharmacodynamic ones. This avoids the potential problem of mis-specification of the pharmacokinetic model affecting the interpretation of pharmacodynamic data, but dictates that equation (5) be handled numerically; this requires the estimation of the plasma atracurium concentration for each time point at which $C_P(t)$ is to be estimated, and hence interpolation between the measured concentrations.

The scheme of interpolation used the predictions of the two-compartment model of best fit to the plasma concentration data set at all times except the first 2 min after the start of the infusion and the 2 min after the end of the infusion, at which times simple linear interpolation between the measured plasma concentrations was used. This scheme is convenient, yet preserves the form of the measured plasma concentration profile at times when circulatory delays imply that the measured and predicted concentrations might differ most.

Other schemes of interpolation, including simple linear interpolation between the measured plasma concentrations, and spline methods based on a series of second order polynomials, have been used and found to give almost identical results [19].

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