A PHARMACODYNAMIC MODEL FOR PANCURONIUM

C. J. HULL, H. B. H. VAN BEEM, K. MCLEOD, A. SIBBALD AND M. J. WATSON

SUMMARY

It has been demonstrated that a simple two-compartment kinetic model may account for the changes in plasma concentration of pancuronium after i.v. administration. However, it can be shown that this simple model does not account satisfactorily for the observed changes in muscle twitch response. By the addition of a receptor (biophase) compartment, twitch response *can* be reconciled with model behaviour and the characteristics resemble those predicted by animal studies. The complete model is applied to the problem of total renal failure, and shows that patients with this condition are likely to be marginally resistant to small doses of pancuronium, with a normal rate of recovery. However, larger doses are likely to result in delayed recovery, the duration of effect increasing in a dose-dependent manner.

There is considerable variation in the human response to pancuronium. Recent studies (Miller, Stevens and Way, 1973; McLeod, Watson and Rawlins, 1976; Somogyi, Shanks and Triggs, 1976) have suggested that this may be largely a result of variation in distribution and elimination of the active drug. Agoston and colleagues (1977) have shown that, during the recovery phase, the plasma concentration of pancuronium correlates with the depression of muscle twitch response. Further analysis of their data suggests that twitch depression may vary with the logarithm of the plasma concentration, as was described for tubocurarine by Gibaldi, Levy and Hayton (1972). In both studies, measurements were limited to the recovery phase, and it is still not known if there is a pharmacodynamic model which will satisfy both plasma concentration and twitch depression throughout the time course of the drug.

It has been shown (McLeod, Watson and Rawlins, 1976) that plasma concentrations of pancuronium conform to the behaviour of the "central" compartment of a two-compartment open pharmacokinetic model. Thus, following an i.v. dose, plasma concentration ($C_1(t)$) declines according to a bi-exponential decay of the form:

$$C_1(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \qquad (1)$$

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where A, B, α, β are constants (Hull and McLeod, 1976) (fig. 1). $C_1(t)$ represents the concentration of pancuronium in compartment 1 (nmol litre^{-1}) at t min, and $\ln C_1(t)$ its natural logarithm.
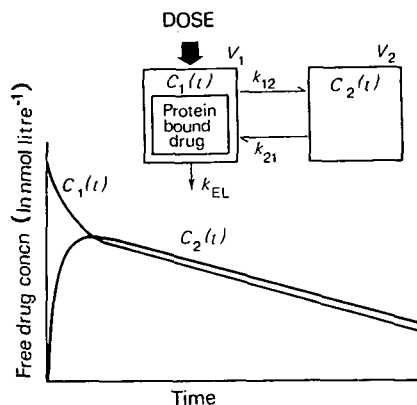

FIG. 1. The two-compartment open model. The two compartments have distribution volumes V_1 and V_2, and the drug moves between them along a simple concentration gradient according to rate constants k_{12} and k_{21}. Doses of drug are initially distributed in V_1. All the drug is assumed to leave the model via compartment 1, according to rate constant k_{EL}. Drug bound to plasma proteins is contained within compartment 1. After a single bolus dose, drug concentrations in the two compartments ($C_1(t)$ and $C_2(t)$) behave according to biexponential functions.

The present study was designed to investigate the applicability of $C_1(t)$ as a predictor of pharmacological activity, by the simultaneous measurement of adductor pollicis twitch response and plasma concentrations of pancuronium, following clinical doses of this agent.

METHOD

Informed consent was obtained from five healthy adult males undergoing inguinal herniorraphy. Each patient was premedicated with papaveretum 10 mg and hyoscine 0.2 mg, 1 h before anaesthesia, which was induced with fentanyl 100 μg i.v. and Althesin 2.5–4.5 ml i.v. and maintained with oxygen in nitrous oxide and increments of fentanyl or Althesin as required.

A Statham "Gold cell" force transducer, fitted with a tension load attachment, was coupled to the left thumb to measure isometric twitch tension in the adductor pollicis muscle (fig. 2). Subcutaneous needle electrodes were placed on each side of the ulnar nerve at the wrist, and connected to the stimulus isolation
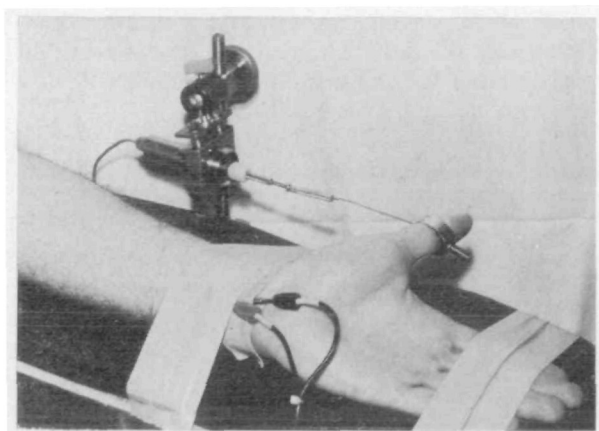

FIG. 2. Determination of muscle twitch response. The force transducer is mounted on a "pan and tilt" joint, to ensure correct alignment.

unit of a Grass S44 nerve stimulator. The ulnar nerve was stimulated supramaximally by 100-μs pulses at 0.08 Hz, and the resulting twitch tension recorded on a Devices MX2 recorder. Before recording, the twitch signal was conditioned by a "peak read and hold" circuit, in order to prevent damping errors (Van Beem et al., 1977).

When a consistent control tension was achieved, each patient was given pancuronium bromide 4 mg i.v., the trachea was intubated when muscle relaxation was adequate and the lungs ventilated mechanically with nitrous oxide in oxygen. Anaesthesia was supplemented as necessary with increments of fentanyl 25 μg, but no other agent was given. At frequent intervals, serial 5-ml blood samples were taken from the right antecubital vein as described in detail previously (McLeod, Watson and Rawlins, 1976).

At the end of the surgical procedure, recording was terminated, residual neuromuscular blockade was reversed with atropine 1.2 mg and neostigmine 2.5 mg and the patient allowed to recover. Venous sampling was continued for 6 h.

Blood samples were centrifuged, and the separated plasma stored at −10 °C until assay. Pancuronium concentrations were estimated by a development of the "rose bengal" technique (Kersten, Meijer and Agoston, 1973) described by Watson and McLeod (1977).

All results were corrected for plasma protein binding, which was assumed to be 80%, based on binding studies by Thompson (1976).

RESULTS

The time course for the concentration of free pancuronium in plasma was plotted for each patient, a bi-exponential function fitted by non-linear regression (Holland, 1976) and the parameters of the corresponding two-compartment open model determined. Figure 3 shows the results of this procedure for patient A. The results for all five patients are shown
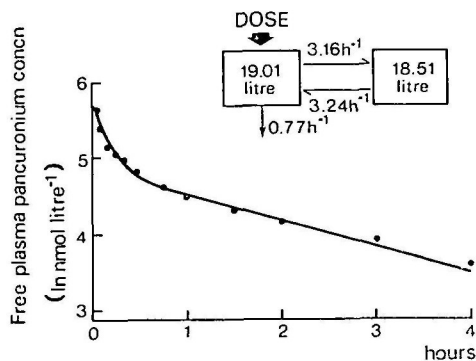

FIG. 3. Two-compartment analysis of data from patient A. An optimal bi-exponential function is fitted to the data points, and from the coefficients, the parameters of the corresponding two-compartmental model derived.

in table I. Since the distribution volumes are correlated poorly with body weight or calculated surface area, they are presented in absolute form.

Given the parameters of each model, it was possible to plot the concentrations of pancuronium in both compartments on the same time scale as the measured values of % twitch depression. Figure 4 shows the result for patient A. It should be noted that twitch depression increased to a maximum of 93% at 7.5 min, and then decayed more slowly to 50% recovery

TABLE I. *Results of two-compartment kinetic analysis*

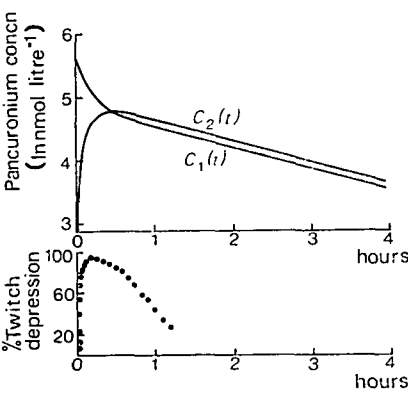| Subject	Age (yr)	Weight (kg)	V_1 (litre)	V_2 (litre)	k_{12} (h⁻¹)	k_{21} (h⁻¹)	k_{EL} (h⁻¹)	$\dot{V}p$ (litre h⁻¹)
Subject								
A	65	61.5	19.01	18.51	3.156	3.241	0.770	14.64
B	27	71.0	17.00	24.49	9.791	6.795	1.176	19.99
C	50	82.0	19.50	30.51	5.350	3.419	1.231	24.00
D	63	66.2	17.01	23.01	6.784	5.014	0.831	14.14
E	33	53.6	25.00	25.50	1.816	1.781	1.200	30.00
Mean	47.6	66.9	19.5	24.4	5.38	4.05	1.04	20.55
± SD	17.2	10.6	3.3	4.3	3.13	1.91	0.22	6.66

FIG. 4. Patient A. In the upper graph, figure 3 is developed further by the addition of drug concentrations in compartment two (computed and plotted by an electrical analog (Hull and McLeod, 1976)). In the lower graph, measured % twitch depression is plotted on the same time scale.

FIG. 5. Patient A. Data from figure 4 are re-plotted on *X–Y* ordinates, with indication of the time from administration. The "1-min" point for compartment 2 is not shown, as it is off-scale.

at 58 min. If the pancuronium log-concentration in either compartment were a direct predictor of twitch depression, a plot of % twitch depression against log concentration would show a hysteresis-free relationship. Figure 5 shows the data of figure 4 (patient A) replotted in this form. It is evident that no such simple relationship exists for either compartment 1 or compartment 2, since in each instance the plot exhibits gross hysteresis. The correlation coefficients are 0.13 and 0.39 respectively, and do not differ significantly from zero. Similarly, the coefficients for the other four patients are all indistinguishable from zero ($P > 0.1$).

However, in accordance with the results of Agoston and colleagues (1977), the log concentration in compartment 1 declines linearly against % twitch depression over a very limited range, corresponding to the late elimination phase. It is equally evident that the concentrations in compartment 2 follow a
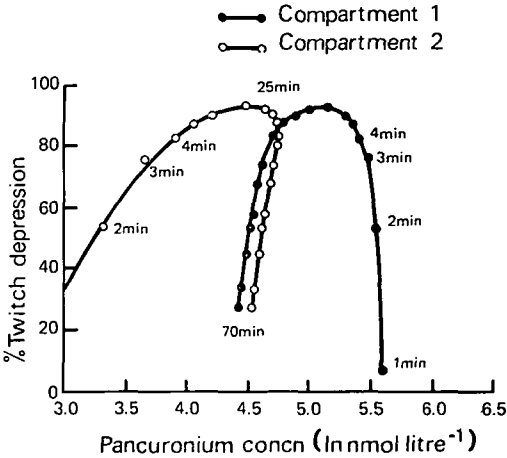
similar, parallel course over the same period. Since (fig. 4) both log concentrations decline at the same rate during this phase, this is hardly surprising. It is clear that, despite the linear relationship between log concentration and twitch depression during the late phase ($r = 0.996$ for the period 40–70 min), compartment 1 concentration is a very poor predictor of twitch depression during the earlier phase of redistribution and cannot be considered as a basis for a valid pharmacodynamic model.

HYPOTHESIS FOR A PHARMACODYNAMIC MODEL

That fraction of the pancuronium which is in equilibrium with end-plate receptors can be thought of as occupying a specific "biophase" pharmacokinetic compartment, as conceived by Furchgott (1955). Once present in the biophase, pancuronium has only to occupy its receptor sites to exert an immediate

pharmacological effect; so that, this process being very rapid, it can be assumed that any delay between dose and effect occurs during transit to the biophase (Waud, 1967). If we assume that the whole circulating plasma volume is in compartment 1, and that the drug reaches the biophase along a single concentration gradient, it is reasonable to assume also that drug concentration in the biophase will be related to plasma concentration by first-order kinetics. If the biophase rate constants could be determined, then the drug concentration in the biophase could be calculated. Since the drug in the biophase exerts an immediate effect, its concentration should relate at all times to the intensity of effect, according to the fundamental concentration/response characteristic of the neuro-muscular junction.

Since no direct information can be obtained on the likely volume of the biophase, it is impossible to consider it as a whole. It is possible, however, to consider an elemental *part* of the biophase volume which is by definition negligibly small (say 1 ml) and representative of the whole in concentration terms. Since the drug in the biophase exerts an immediate effect, it can be assumed that the same intensity of effect will be exerted by *increasing* drug concentrations in the onset phase as the same *decreasing* concentrations during recovery. To take a hypothetical example, 70% twitch depression might be found to occur twice in a single experiment—at 2 min during onset, and at 23 min during recovery. It follows that drug concentration in the biophase at 2 min *is identical with* that at 23 min. Given that the biophase is related to compartment 1 by first-order kinetics, it follows that there is a unique rate constant which can yield a biophase concentration curve with these characteristics.

With a known biophase rate constant, it is now possible to calculate drug *concentration* in the biophase, this being quite independent of volume. The quantity of drug in 1 ml elemental volume does not represent total biophase pancuronium, but simply that which is present in 1 ml of the biophase compartment. In mathematical terms, the model must be expanded to three compartments (see Appendix), so that plasma (compartment 1) concentration decays according to a tri-exponential function of the form:

$$C_1(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} + D \cdot e^{-\gamma t} \qquad (2)$$

and biophase concentration (compartment 3) behaves according to

$$C_3(t) = L \cdot e^{-\alpha t} + M \cdot e^{-\beta t} + N \cdot e^{-\gamma t} \qquad (3)$$

The overall function for $C_1(t)$ is, of course, virtually identical with the previous biexponential function (equation (1)) but the individual constants A, B, α, β may differ considerably, as a result of the introduction of the third term.

METHODS

Optimal biophase rate constants were determined for each model by re-iterative solution of equation (3) for progressively increasing values of k_{13}, at values of t (min) corresponding to the "70% response times" derived from the twitch record, until the two values of $C_3(t)$ were equal.

Having determined the rate constant, equation (3) was then solved for serial values of t, to yield the time course for drug concentration in the biophase.

RESULTS

The behaviour of each complete model can be displayed conveniently by an electrical analog, which performs continuous computations of the drug concentrations in all compartments (Hull and McLeod, 1976). Figure 6 shows a complete analog solution for patient A.
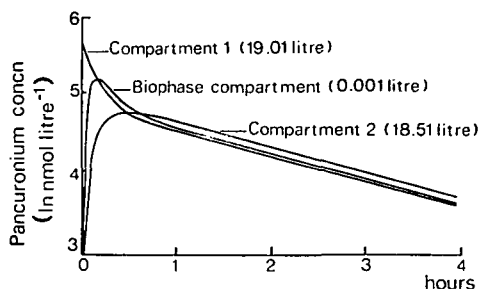

FIG. 6. Patient A. Three-compartment solution, plotted by the electrical analog. The biophase concentration curve has been added to the two-compartment solution in figure 4.

A log concentration biophase/response plot was drawn for each model (fig. 7).

It can be seen that, in each instance, a curve of sigmoid appearance is obtained, showing minimal hysteresis and an apparently linear response between 20 and 80% twitch depression. A linear regression line was determined for each group, taking those values of twitch depression lying between 20 and 80%. The regression coefficients vary considerably, and the extreme values differ significantly ($P < 0.01$). From each regression equation, drug log concentration for 50% twitch depression can be calculated.
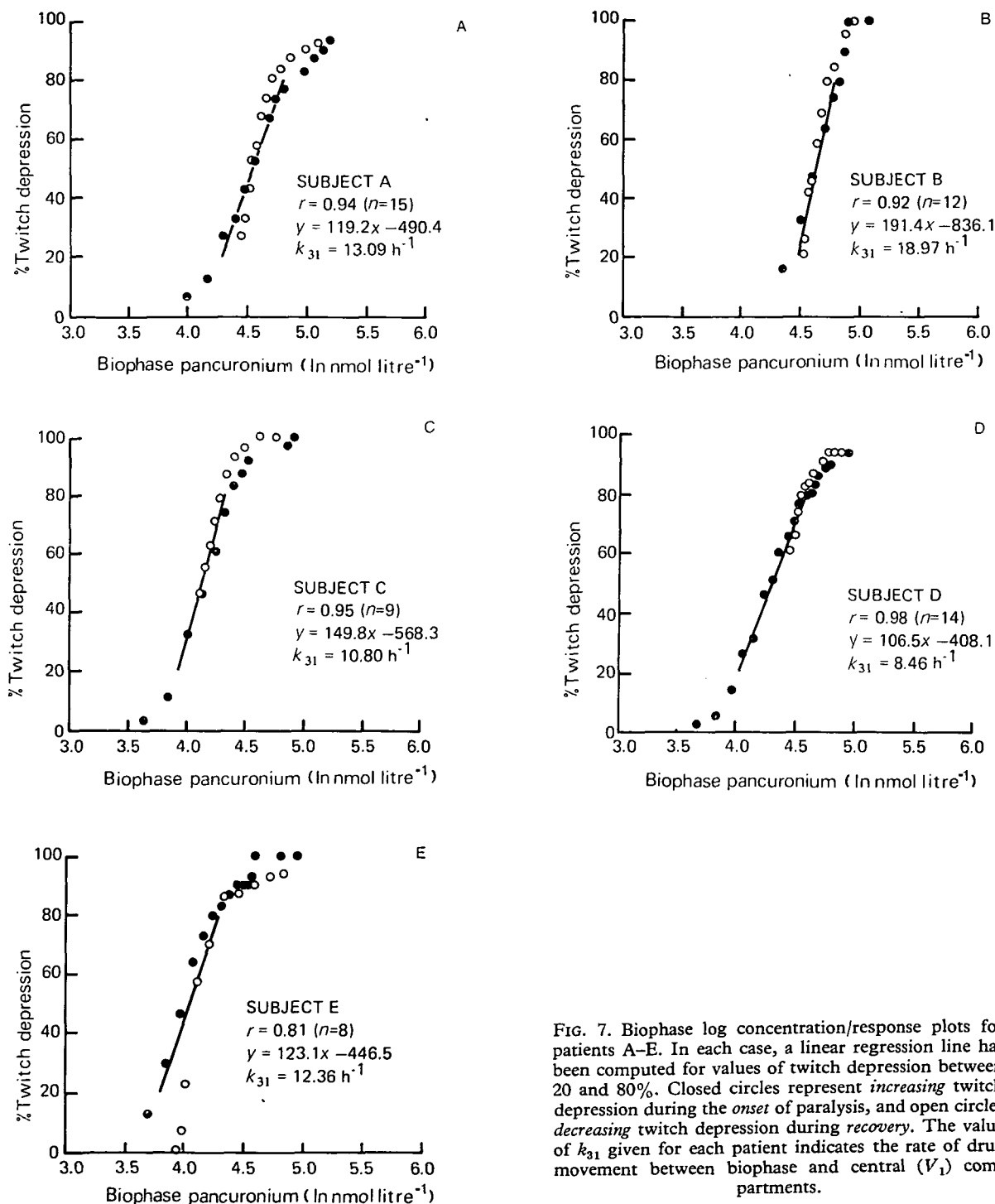
FIG. 7. Biophase log concentration/response plots for patients A–E. In each case, a linear regression line has been computed for values of twitch depression between 20 and 80%. Closed circles represent *increasing* twitch depression during the *onset* of paralysis, and open circles *decreasing* twitch depression during *recovery*. The value of k_{31} given for each patient indicates the rate of drug movement between biophase and central (V_1) compartments.

These values also show appreciable variation, with significant differences between the extreme values ($P<0.01$). The biophase rate constants varied widely, ranging between 8.46 and 18.97 h^{-1}. The variation in these parameters should, however, be considered in the context of the variation in observed twitch response. Recovery time to 50% twitch response varied between 26 and 82 min, and showed a higher coefficient of variation (0.38) than any of the pharmacokinetic parameters.

DISCUSSION

Drug log concentrations in both compartments were very poor correlates of twitch depression. On the other hand, drug log concentration in the derived biophase compartment appeared to correlate well up to 80% depression, above which the gradient diminished in all instances.

Should twitch depression be a "straight-line" function of log concentration? The relationship between drug concentration and mechanical response must be considered in two stages: the occlusion of acetylcholine receptors at the end-plate, and the effect of such occlusion on twitch response. It is accepted that in 1 : 1 competitive antagonism, as occurs with pancuronium, receptor occlusion (Y) is related to drug concentration $[D]$ by the expression:

$$Y = \frac{[D]}{[D]+K_B} \qquad (4)$$

where K_B is the drug/receptor dissociation constant (Waud, 1968; Waud, Cheng and Waud, 1973). Using a dose ratio technique, Waud, Cheng and

Waud (1973) estimated K_B for pancuronium in the guineapig lumbrical muscle to be 25.1 nmol litre^{-1}, and reported that an earlier study by Goldfine (1972) had yielded a value of 21.3 nmol litre^{-1}. In the absence of a reliable estimate for man, Waud's estimate of 25.1 nmol litre^{-1} will be assumed. (This value implies that at 50% receptor occlusion, the concentration of pancuronium in equilibrium with the receptors will be 25.1 nmol litre^{-1}, or in logarithmic terms, 3.22 ln nmol litre^{-1}.)

The relationship between receptor occlusion and twitch depression has been studied in the feline tibialis anterior muscle (Paton and Waud, 1967; Waud and Waud, 1971). Figure 8 shows data taken from these papers, with a linear regression line fitted to the points. It is evident from the confidence limits for the regression estimate that the gradient is uncertain. Clearly, however, there is a "margin of safety" (Paton and Waud, 1967), by which approximately 73% of receptors must be occluded before twitch depression can be demonstrated.

By taking the expression:

$$\ln [D] = \ln \frac{K_B \cdot Y}{1 - Y} \qquad (5)$$

which is simply a rearrangement of equation (4), all values of receptor occlusion (including regression data) can be transformed into drug log concentration terms, and re-plotted, as in figure 9. Were both the estimate for K_B obtained from the guineapig and the estimate for the "margin of safety" from the cat
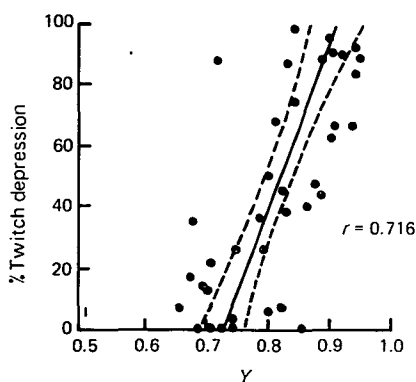

FIG. 8. The "margin of safety" for feline tibialis anterior, as determined by Paton and Waud (1967) and Waud and Waud (1971). A linear regression line has been fitted to the data, with a 95% confidence interval for the regression estimate. Y = receptor occlusion.
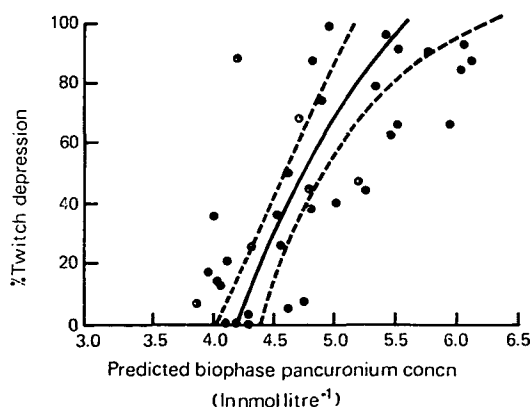

FIG. 9. Pancuronium concentration/response characteristics in the biophase. All values of receptor occlusion in figure 8 have been transformed into log concentration terms, using equation (5). The curved regression line and confidence limits are direct transforms of those shown in figure 8.

TABLE II. *Biophase characteristics for pancuronium*

Subject	k_{13} (h^{-1})	[PCB] for 50% recovery (ln nmol litre^{-1})	Concn/response regression coeff.	Time to 50% twitch recovery (min)
A	13.09	4.535 ± 0.014	119.2 ± 12.25	58
B	18.97	4.625 ± 0.012	191.4 ± 25.4	26
C	10.80	4.133 ± 0.013	149.8 ± 19.6	56.5
D	8.46	4.306 ± 0.010	106.5 ± 5.7	82
E	12.36	4.050 ± 0.031	123.1 ± 35.9	47
Mean	12.74	4.33	138.0	53.9
± SEM	± 1.96	± 0.25	± 33.8	± 10.12
Predicted	—	4.746	77.82	—
± 95%		4.609–4.897	57.75–117.85	

indicative of these parameters in man, then the curved regression line within the confidence interval shown in figure 9 should predict the concentration/response characteristic for pancuronium in the biophase.

Comparing this with the results of the present study (shown in figure 7), it is apparent that the theoretical relationship between log concentration and twitch depression is non-linear, so that the observed reductions in gradients for deep blockade in figure 7 are in accordance with the prediction. The important features of both predicted and measured concentration/response plots are summarized in table II.

Although all the measured regression coefficients were greater than predicted, the mean value is not significantly greater ($P > 0.05$). Similarly, in each instance the concentration for 50% response was lower than predicted, but the mean value is not significantly different ($P > 0.05$). Although there was no significant difference, it is necessary to consider the possible causes for the observed discrepancies.

The value of log concentration for 50% response is essentially dependent on two factors: K_B and the degree of protein binding assumed to occur in plasma. The effect of variation in K_B on the response curve is not great, so that to bring the experimental results to identity with the prediction would require a very large decrement from the estimate of 25.1 nmol litre^{-1} ($K_B < 6$ nmol litre^{-1}). Although there are species differences, such a decrement is unlikely. The estimate for protein binding does, however, have a marked effect on the "concentration for 50% response". The data in figure 7 are calculated on the basis of 80% plasma protein binding, that is, free plasma pancuronium is 20% of total plasma concentration. This estimate, based on studies by Thompson

(1976), is at variance with Waser (1973), who postulated 20% binding, and with Stovner, Theodorsen and Bjelke (1971) who considered significant binding to be unlikely. If we had assumed that 70% of plasma pancuronium was protein bound, then the mean value of "concentration at 50% response" would concur with the predicted 4.75 ln nmol litre^{-1}. Since there is such disparity in the available estimates, this problem must, for the present, remain unresolved, but it is fair to suggest that a value of 70% binding cannot be rejected.

The gradient of the log concentration/response curve (regression coefficient) is dependent upon both K_B and the gradient of the occlusion/response characteristic (fig. 8). Since neither has been measured in man, and considerable differences in the latter have been demonstrated, both between species (Waud and Waud, 1975) and between different muscle groups of the same species (Waud and Waud, 1972), the small differences between measured and predicted values (table II) cannot be considered decisive.

There are several possible sources of error in the present study.

(1) Venous blood samples do not reflect accurately "mean plasma concentration" until several complete circulations have ensured mixing. It is probable therefore that samples taken in the first minute after injection contain misleadingly low pancuronium concentrations. (Arterial samples would over-estimate mean plasma concentration for a similar period.)

(2) Plasma protein binding of the drug is assumed to occur very rapidly, and to a uniform degree. It is possible that the injected bolus of drug saturates locally available protein binding sites, so that for a

brief period the amount of free plasma pancuronium greatly exceeds our estimate.

(3) Measurement of muscle twitch tension over a wide dynamic range assumes a linear response to increments of muscle force. As a result of the problems associated with rigidly anchoring the intact hand, this assumption may not be wholly valid.

(4) The present biophase model assumes that transfer of drug from compartment 1 to the biophase is a linear, isotropic process, and that only a small proportion of biophase drug is sequestrated into either active or inactive binding sites. It is assumed also that the drug leaves the biophase only by the route of entry. In the case of pancuronium, this last assumption should be considered likely (Agoston et al., 1973), but the others may require confirmation.

Despite these possible sources of error, many of which are shared by models previously described, it is claimed that the biophase model (fig. 10) represents an advance over the simple two-compartment system assumed by Agoston and colleagues (1977).
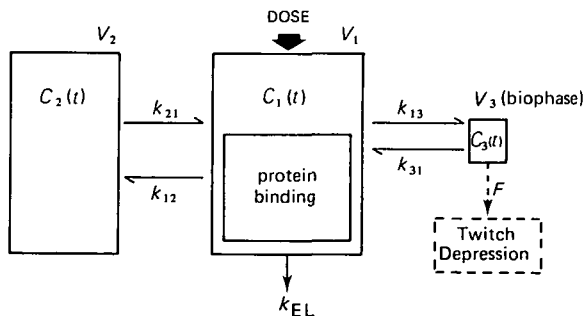
FIG. 10. The three-compartment biophase model. Function F is the transfer function from $C_3(t)$ to % twitch depression, and is characterized theoretically by figure 9.

PREDICTION

One of the purposes of a model is to estimate the probable behaviour of a system under unattainable experimental conditions.

We consider now the pharmacodynamic changes which would be likely if "patient A" were to develop total renal failure.

An optimal sigmoid curve was fitted to the biophase concentration/response data for patient A, so that values of twitch depression over the range 0–100% could be estimated. This was constructed by taking the linear function between 20 and 80% and extrapolating to both 0 and 100% respectively with simple exponential functions, which fitted well to the

data in figure 7A. The responses of the model to pancuronium 4, 5 and 6 mg were estimated first, and are shown in figure 11A.
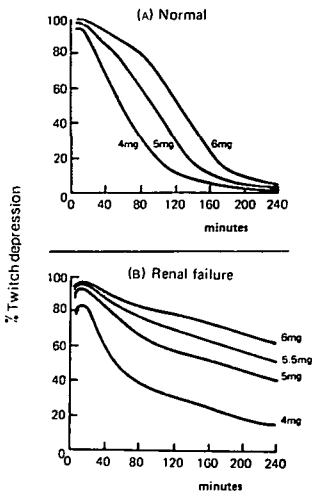
FIG. 11. Predicted responses of patient A to different doses of pancuronium, in "health" and in "renal failure".

The model was modified to simulate the likely effects of renal failure, according to the findings of McLeod, Watson and Rawlins (1976). These authors stated that renal failure was associated with the following average changes in pharmacokinetic parameters: $V_1 + 57.7\%$; $V_2 + 23.9\%$; $k_{12} - 48.7\%$; and $k_{EL} - 82.3\%$. In the absence of any reliable estimate, plasma protein binding was assumed to remain constant.

The responses of the model to pancuronium 4, 5, 5.5 and 6 mg were then estimated (fig. 11B). The principal changes in model behaviour are summarized in table III.

TABLE III. *Predicted effects of pancuronium on patient A*

Dose (mg)	Peak effect (%)	t (max %) (min)	Recovery to 80% effect (min)	Recovery to 50% effect (min)
Normal				
4	94.7	9	29	58
5	97.6	9	51	92
6	98.7	9	78	122
Renal failure				
4	83.9	12.5	20	51
5	92.6	12.5	42	168
5.5	94.7	12.5	61	248
6	96.1	12.5	100	322

(1) In renal failure, the peak pharmacological effect is delayed slightly, and is of reduced amplitude.

(2) In renal failure, the effect of pancuronium 4 mg decays to 50% recovery more rapidly than in the normal model, but the effect of larger doses is to prolong recovery to 50%.

Increasing the dose from 4 mg to 6 mg in the normal subject increases the duration (to 50% recovery) by 122%, while in renal failure the same increment in dose increases the duration (to 50%) by 531%.

If the renal failure model is given a dose (5.5 mg) equipotent with 4 mg to the normal model, the duration (to 50%) is increased by 328%.

It has been the authors' experience that patients in total renal failure exhibit resistance to pancuronium, while established blockade may recover very slowly, with some instances of "recurarization". This clinical impression has been reinforced recently by d'Hollander, Camu and Sanders (1978) who showed that twitch depression recovered more slowly in patients in renal failure, in a non-linear, dose-dependent fashion. The behaviour of the model provides a probable basis for these observations.

APPENDIX

THE THREE COMPARTMENT "OPEN" MODEL

List of symbols

Dose   Dose (nmol)
Z_n Mass of drug in compartment n (nmol)
V_n Volume of compartment n (litre)
k_{12} Rate constant from compartment 1 to compartment 2 (h^{-1})
k_{EL} Elimination rate constant (h^{-1})
$C_n(t)$ Concentration of drug in compartment n, at time t (nmol litre^{-1})
$C_n(0)$ Concentration of drug in compartment n, at time $t = 0$ (nmol litre^{-1})

The analysis of a mamillary two-compartment "open" model of drug distribution, described by Atkins (1969), can be extended to a three-compartment system (fig. 10), where distribution is defined by differential equations (1)–(3).

$$d(Z_1)/dt = Z_2 k_{21} + Z_3 k_{31} - Z_1(k_{12} + k_{13} + k_{EL}) \quad (1)$$

$$d(Z_2)/dt = Z_1 k_{12} - Z_2 k_{21} \quad (2)$$

$$d(Z_3)/dt = Z_1 k_{13} - Z_3 k_{31} \quad (3)$$

For a bolus dose into an empty model, these equations may be resolved by Laplacian transformation and simultaneous solution, using 3×3 matrices. Reverse transformation of the solutions yields the following equations, which define the concentration of drug in each compartment as functions of time:

$$C_1(t) = A.e^{-\alpha t} + B.e^{-\beta t} + D.e^{-\gamma t} \quad (4)$$

$$C_2(t) = P.e^{-\alpha t} + Q.e^{-\beta t} + R.e^{-\gamma t} \quad (5)$$

$$C_3(t) = L.e^{-\alpha t} + M.e^{-\beta t} + N.e^{-\gamma t} \quad (6)$$

Further inspection of the Laplacian expressions corresponding to equations (4)–(6) yields the following cubic function:

$$s^3 + (k_{31} + k_{21} + k_{12} + k_{13} + k_{EL})s^2 + (k_{21}k_{31} + k_{12}k_{31} + k_{13}k_{21} + k_{EL}k_{31} + k_{EL}k_{21})s + (k_{21}k_{31}k_{EL}) \quad (7)$$

of which the roots are $-\alpha$, $-\beta$ and $-\gamma$, and s is the Laplacian operator. The solution of cubic functions is described in detail by Hodgman (1957).

Given values for α, β and γ, the remaining constants in equations (4)–(6) can now be determined using the following equations, which are derived from the Laplacian forms of equations (4)–(6). $C_1(0)$ is the drug concentration in compartment 1 following a bolus dose into the empty model ($t = 0$):

$$A = \frac{C_1(0).(\alpha^2 - (k_{21} + k_{31})\alpha + k_{21}k_{31})}{(\alpha - \gamma)(\beta - \alpha)} \quad (8)$$

$$B = \frac{C_1(0).(\beta^2 - (k_{21} + k_{31})\beta + k_{21}k_{31})}{(\gamma - \beta)(\beta - \alpha)} \quad (9)$$

$$D = \frac{C_1(0).(\gamma^2 - (k_{21} + k_{31})\gamma + k_{21}k_{31})}{(\gamma - \beta)(\alpha - \gamma)} \quad (10)$$

$$M = \frac{C_1(0).k_{31}(k_{21} - \beta)}{(\gamma - \beta)(\beta - \alpha)} \quad (11)$$

$$N = \frac{C_1(0).k_{31}(k_{21} - \gamma)}{(\gamma - \beta)(\alpha - \gamma)} \quad (12)$$

$$L = -(M + N) \quad (13)$$

$$Q = \frac{C_1(0).k_{21}(k_{31} - \beta)}{(\gamma - \beta)(\beta - \alpha)} \quad (14)$$

$$R = \frac{C_1(0).k_{21}(k_{31} - \gamma)}{(\gamma - \beta)(\alpha - \gamma)} \quad (15)$$

$$P = -(Q + R) \quad (16)$$

where

$$C_1(0) = \frac{dose}{V_1} \quad (17)$$

Having obtained values for all the constants and exponents, equations (4), (5) and (6) can now be solved to calculate drug concentration in each of the three compartments for any value of time, t.

REFERENCES

Agoston, S., Crul, J. F., Kersten, U. W., and Scaf, A. H. J. (1977). Relationships of the serum concentration of pancuronium to its neuromuscular activity in man. *Anesthesiology*, **47**, 509.

—— Vermeer, G. A., Kersten, U. W., and Meijer, D. K. F. (1973). The fate of pancuronium bromide in man. *Acta Anaesthesiol. Scand.*, **17**, 267.

Atkins, G. L. (1969). *Multicompartment Models in Biological Systems*, p. 44. London: Methuen & Co. Ltd.

Furchgott, R. F. (1955). The pharmacology of vascular smooth muscle. *Pharmacol. Rev.*, **7**, 183.

Gibaldi, M., Levy, G., and Hayton, W. (1972). Kinetics of the elimination and neuromuscular blocking effect of d-tubocurarine in man. *Anesthesiology*, **36**, 213.

Goldfine, C. (1972). Dissociation constants of competitive antagonists at the mammalian neuromuscular junction. Thesis, London University.

Hodgman, C. D. (editor) (1957). *Handbook of Chemistry and Physics*, 39th edn, p. 295. Ohio: Chemical Rubber Publishing Co.

Holland, D. E. (1976). Aspects of the pharmacodynamics of continuous intravenous analgesia: the pharmacokinetics of fentanyl in man. B.Med.Sci. Thesis, University of Newcastle upon Tyne.

d'Hollander, A. A., Camu, F., and Sanders, M. (1978). Comparative evaluation of neuromuscular blockade after pancuronium administration in renal failure and in normal patients. *Acta Anaesthesiol. Scand.*, **22**, 21.

Hull, C. J., and McLeod, K. (1976). Pharmacokinetic analysis using an electrical analog. *Br. J. Anaesth.*, **48**, 677.

Kersten, U. W., Meijer, D. K. F., and Agoston, S. (1973). Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. *Clin. Chim. Acta*, **44**, 59.

McLeod, K., Watson, M. J., and Rawlins, M. D. (1976). Pharmacokinetics of pancuronium in patients with normal and impaired renal function. *Br. J. Anaesth.*, **48**, 341.

Miller, R. D., Stevens, W. C., and Way, W. L. (1973). The effect of renal failure and hyperkalemia on the duration of pancuronium neuromuscular blockade in man. *Anesth. Analg. (Cleve.)*, **52**, 661.

Paton, W. M. D., and Waud, D. R. (1967). The margin of safety of neuromuscular transmission. *J. Physiol. (Lond.)*, **191**, 59.

Somogyi, A. A., Shanks, C. A., and Triggs, E. J. (1976). Clinical pharmacokinetics of pancuronium bromide. *Eur. J. Clin. Pharmacol.*, **10**, 367.

Stovner, L., Theodorsen, L., and Bjelke, E. (1971). Sensitivity to gallamine and pancuronium with special reference to plasma proteins. *Br. J. Anaesth.*, **43**, 953.

Thompson, J. M. (1976). Pancuronium binding by serum proteins. *Anaesthesia*, **31**, 219.

Van Beem, H. B. H., McLeod, K., Hull, C. J., Sibbald, A., and Watson, M. J. (1977). The pharmacodynamics of pancuronium. *Br. J. Anaesth.*, **49**, 1169.

Waser, P. G. (1973). Localisation of C^{14} pancuronium by histo- and wholebody autoradiography in normal and pregnant mice. *Naunyn Schmeidebergs Arch. Pharmacol.*, **279**, 399.

Watson, M. J., and McLeod, K. (1977). A modified method for the fluorimetric determination of pancuronium bromide in plasma. *Clin. Chim. Acta*, **79**, 511.

Waud, B. E., Cheng, M. C., and Waud, D. R. (1973). Comparison of drug–receptor dissociation constants at the mammalian neuromuscular junction in the presence and absence of halothane. *J. Pharmacol. Exp. Ther.*, **187**, 40.

—— Waud, D. R. (1971). The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. *Anesthesiology*, **35**, 456.

—— —— (1972). The margin of safety of neuromuscular transmission in the muscle of the diaphragm. *Anesthesiology*, **37**, 417.

Waud, D. R. (1967). The rate of action of competitive neuromuscular blocking agents. *J. Pharmacol. Exp. Ther.*, **158**, 99.

—— (1968). Pharmacological receptors. *Pharmacol. Rev.*, **20**, 49.

—— Waud, B. E. (1975). Physiology and pharmacology of neuromuscular blocking agents; in *Muscle Relaxants* (ed. R. L. Katz), p. 1. New York: North-Holland Publishing Co.

MODELE PHARMACODYNAMIQUE POUR LE PANCURONIUM

RESUME

Il a été démontré qu'un simple modèle cinétique à deux compartiments pouvait expliquer les variations des concentrations de pancuronium dans le plasma, après administration intraveineuse. On peut néanmoins démontrer que ce modèle simple ne tient pas suffisamment compte des variations observées dans la réponse à la crispation musculaire. En ajoutant un compartiment récepteur (biophase), on peut rapprocher la réponse à la crispation et le comportement du modèle, et ses caractéristiques ressemblent à celles prévues par les études effectuées sur les animaux. On applique le modèle complet au problème de l'insuffisance rénale totale pour montrer que les malades sujets à cet état sont susceptibles de présenter une résistance marginale aux petites doses de pancuronium et d'avoir un taux normal de récupération. Des doses plus fortes sont cependant susceptibles d'entraîner un retard dans la récupération, la durée de l'effet augmentant en fonction de la dose.

EIN PHARMAKODYNAMISCHES MODELL FÜR PANCURONIUM

ZUSAMMENFASSUNG

Es wurde demonstriert, dass ein einfaches, doppelzelliges, kinetisches Modell für die Veränderungen in der Plasmakonzentration von Pancuronium nach intravenöser Verabreichung verantwortlich ist. Jedoch kann auch gezeigt werden, dass dieses einfache Modell die beobachteten Veränderungen des Muskelzuckreflexes nur ungenügend erklärt. Wenn man eine Rezeptorenzelle (Biophase) hinzufügt, kann der Muskelzuckreflex mit dem Verhalten des Modells in Einklang gebracht werden, und die Wirkungseigentümlichkeiten ähneln denen, die von Tierversuchen her zu erwarten sind. Das komplette Modell wird bei totalem Nierenversagen angewandt und zeigt, dass

man von Patienten in diesem Zustand erwarten kann, dass sie gegen kleine Dosen von Pancuronium einen begrenzten Widerstand leisten, mit normaler Wiederherstellungszeit. Jedoch ist es möglich, dass grössere Dosen die Wiederherstellung verzögern und dass die Wirkungsdauer sich je nach der Stärke der Dosis verlängert.

UN MODELO FARMACODINAMICO PARA PANCURONIO

SUMARIO

Se ha demostrado que un modelo cinético sencillo de dos compartimentos puede explicar los cambios en la concentración de pancuronio en la plasma después de su administración intravenosa. Sin embargo, puede demostrarse que este modelo sencillo no puede explicar satisfactoriamente los cambios observados en la respuesta por sacudida muscular. Mediante la añadidura de un compartimento receptor (biofásico), la respuesta por sacudida concuerda con el comportamiento del modelo y las características se asemejan a aquellas previstas por estudios con animales. El modelo completo es aplicado al problema de una falla renal total e indica que los pacientes en este estado presenten una resistencia marginal ante pequeñas dosis de pancuronio con una rapidez normal de recuperación. Sin embargo, la administración de dosis mayores posiblemente demore la recuperación y la duración de los efectos aumenta según la dosis.