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Pharmacokinetic Analysis of the Effect of Vecuronium in Surgical Patients

Pharmacokinetic and Pharmacodynamic Modeling without Plasma Concentrations

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Background: **Methods of the kinetic analysis of vecuronium based on effect only were developed but have been limited by the short time period of the studies. Using a multicompartment model and sequential dosing, the authors studied the ability of tests to determine most pharmacokinetic and pharmacodynamic parameters of vecuronium without measuring plasma concentrations.**

Methods: **The time course of neuromuscular blockade by successive bolus doses of vecuronium was recorded using electromyography. Inhibition of neuromuscular transmission by vecuronium was modeled by a biexponential decline in the concentrations in the central compartment and first-order transfer between the central and the effect compartments responsible for the inhibition of the first (T1) and fourth (T4) responses to train-of-four stimulation.**

Results: **The time course of the effect of vecuronium was described well by the model. The mean half-lives of equilibration between plasma and the effect compartments to inhibit T1 and T4 were 2.5 and 3.2 min, respectively. The mean half-lives of distribution and elimination from the central compartment were 7.7 and 78 min, respectively. From the kinetic and dynamic parameters calculated after two and three doses, the time taken to recover to 50% of the maximal block of T1 was predicted for the succeeding dose. The mean prediction errors (100 × [absolute difference between actual and predicted times]/actual) were 13.6% (range, 0–40%) and 15% (range, 0–25%) after three and four doses, respectively.**

Conclusions: **After sequential doses, measurement of the time course of the effect of vecuronium yields pharmacokinetic and pharmacodynamic parameters with clinically acceptable accuracy in individual patients. (Key words: Biophase; electromyography; neuromuscular blocker; nonlinear regression.)**

PHARMACOKINETIC studies of neuromuscular blockers and other drugs generally involve measuring the plasma concentrations of drugs. Although pharmacokinetic studies have increased our understanding of various factors that affect the response to drugs and have been useful in the rational design of drug dosage, they have been less successful for adjusting drug dosages in individual patients. Our studies have the general aim of developing methods to determine pharmacokinetic and pharmacodynamic parameters from the perspective of effect alone in individual patients for use to predict further doses. The effect of the neuromuscular blocking agents is measured easily, but there have been only four studies in which the intensity of blockade only has been used to determine clinically important pharmacokinetic and pharmacodynamic parameters of these drugs in patients.[1-4] Previous studies on the kinetics of effect of muscle relaxants have outlined many aspects of the method required to determine these parameters from the perspective of effect alone,[1-4] but the short periods (40 min) of the two previous studies of the kinetics of the effect of vecuronium make the estimates of its pharmacokinetic parameters imprecise, particularly the terminal half-life. We addressed these and other difficulties by measuring the inhibition of two neuromuscular responses and studying these effects after three or four doses of vecuronium.

Apart from the further development of methods to determine pharmacokinetic and pharmacodynamic parameters based on effect alone, our study was also designed to determine these parameters from multiple doses of vecuronium. As far as we know, there has been

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Table 1. Patient Details and Dosage of Vecuronium

Patient No.	Body Weight (kg)	Dosage (mg)	Dosage Times (min)	Total Study Time (min)
1	51.1	4, 2, 2, 2	0, 29, 84.5, 150	201
2	101	6, 2, 1, 2	0, 51, 110, 170	215
3	89.5	2, 2, 6, 2	0, 15, 50, 215	245
4	61	2, 4, 1, 2	0, 30, 130, 170	268
5	65.5	1.4, 1, 1	0, 11, 35	50
6	62	1.4, 1, 1	0, 11, 35	85
7	85.2	4, 4, 1	0, 25, 79	108
8	67.5	3, 3, 1	0, 30, 75	118
9	75.5	4, 2, 1	0, 25, 62.5	75
10	85	4, 6, 2	0, 23, 130	224
11	55	2, 2, 1	0, 23, 80	125
12	65	3, 5, 1	0, 23, 125	166
13	67	2, 4, 0.5	0, 24, 72	100
14	70	4, 4, 2	0, 30, 96	147
15	81	2, 2, 3, 1	0, 15.5, 46, 68.5	78
16	90	4, 4, 2, 2	0, 37, 90, 130	206
17	62.5	2, 4, 2, 2	0, 21, 81, 136	180
18	75.6	3, 2, 1, 1	0, 22, 54, 87	109

Anesthesia was maintained with nitrous oxide/isoflurane in patients 1–14, and patients 15–18 were maintained with nitrous oxide/propofol.

no previous study of the pharmacokinetics of the drug after multiple doses.

Methods

We obtained the records of 20 patients classified as American Society of Anesthesiologists physical status 1 and 2 (table 1) who were having elective surgery, of which 18 were used. The study was approved by the ethics committee of the Western Sydney Area Health Service. Anesthesia consisted of premedication with temazepam (20 mg) followed by induction with propofol (2–2.5 mg/kg) and fentanyl (2 μg/kg). Tracheal intubation was facilitated with topical lidocaine (140 mg) but without the use of relaxants. Maintenance consisted of nitrous oxide (70%) in oxygen with isoflurane in 14 patients (0.6% end-tidal; Capnomac, Datex Corp., Helsinki, Finland). In four patients, we used an infusion of propofol (4–8 $mg \cdot kg^{-1} \cdot h^{-1}$) instead of isoflurane. We allowed 10–15 min for the control neuromuscular response and tissue isoflurane concentration to stabilize.

Neuromuscular transmission was monitored as the integrated first and fourth electromyographic responses of the abductor digiti minimi to train-of-four stimulation of the ulnar nerve at intervals not <20 s (Monash neuromuscular block monitor; Electromed, Armadale, Australia). We analyzed data collected over at least 50 min after three or four sequential bolus doses of vecuronium (1–6 mg; table 1). We chose the initial dose to provide <90% blockade of the first response to train-of-four stimulation. Subsequent doses were administered if clinically indicated or if recovery exceeded a train-of-four ratio of 90%. We analyzed data sets if drift in the control response was <20% and if there were complete records of effect on both the first and fourth responses (T1 and T4) to train-of-four stimulation. Residual blockade was antagonized with neostigmine and atropine when surgery was complete. The final amplitude of T1 and T4 was then measured. In those cases in which drift in T1 and T4 responses occurred, compensation was made assuming a linear change during the study period,[2] consistent with our observations in patients who are not paralyzed.

Kinetic and Dynamic Modeling

The inhibition of T1 and T4 was related to the concentration of vecuronium in the effect compartment (Ce) by a form of the Hill equation in which the Ce is expressed relative to the concentration producing 50% block (EC_{50}). The form of the Hill equation was[2]:

$$f = Ce^{\gamma}/(1 + Ce^{\gamma}) \quad (1)$$

The constant, γ, is the Hill coefficient, and f is the fractional block. Thus the relation between f and Ce was assumed to be sigmoid. The time course of concen-

trations (C) in the central compartment was assumed to follow a biexponential function of time according to equation 2,

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

where α and β are rate constants, and A and B are concentration parameters calculated relative to the EC_{50} values. If the drug is transported into and out of the sites of action by first-order mechanisms and if concentrations in the effect compartment and in plasma are equal when equilibrium is established,[1-4] then the concentrations at the sites of action are described by a function containing three distinct exponential terms,[5,6]

$$Ce = k_{eo}(A(e^{-\alpha t} - e^{-k_{eo}t})/(k_{eo} - \alpha) + B(e^{-\beta t} - e^{-k_{eo}t})/(k_{eo} - \beta)) \quad (3)$$

where k_{eo} is the rate constant of loss of the drug from the effect compartment. This rate constant is also called the rate constant of equilibration between plasma and the effect compartment.[1] Thus the time course of effect of vecuronium was fitted by equation 1 in which the term Ce is given as the function of time in equation 3.

The time courses of inhibition of T1 and T4 were fitted simultaneously to equations 1 and 3. Equation 2 describes the time course of concentrations in the central compartment. It therefore follows that the inhibition of T1 and T4 must be described by the same values of α and β. From the model, the ratio A/B must be equal for inhibition of T1 and T4, but the values of A and B for T1 and T4, respectively, will not be identical. Thus

$$A_{T1}/B_{T1} = A_{T4}/B_{T4} \quad (4)$$

The kinetic parameters were determined with these constraints. The values of k_{eo} for T1 and T4 were allowed to be different.

In conventional pharmacokinetic analysis of the time course of plasma concentrations of a drug, the constants, A and B, are expressed in terms of plasma concentration, such as milligrams per liter, but, in this analysis, these constants are determined relative to the EC_{50}. Once the effect data are fitted by equations 1 and 3, the time courses of C and Ce are calculated readily (again relative to EC_{50}) from equations 2 and 3 because all the parameters in these equations have been determined. The rate of infusion required to produce 50% blockade, IR_{50}, was calculated from the quotient of the dose and the area under the time course of concentrations in the central compartment[1]:

$$IR_{50} = Dose/(A/\alpha + B/\beta) \quad (5)$$

Successive bolus doses of vecuronium were administered and it was assumed that the principle of superposition was followed. Thus the total concentrations in the effect compartment after the second dose were the sum of the concentrations from the second dose and those remaining from the first. Similarly, the concentrations from the third and fourth doses were added to the sum of the concentrations remaining from the previous doses. An assumption in the theoretical derivation of the biexponential function (equation 2) is that the constants, A and B, are directly proportional to the dose of vecuronium. Bragg *et al.*[1] and Fisher and Wright[4] used similar equations in their analyses of the time course of effect of vecuronium after single doses of the drug.

The values of T1 and T4 were acquired "off-line" for entry to the spreadsheet of MK Model (Biosoft, Cambridge, UK). A routine was incorporated into the MK Model program to perform simultaneous fitting of the theoretical equations to the inhibition of T1 and T4 after two to four doses in each patient. The parameters were determined without weighting the data points, making the method one of nonlinear ordinary least-squares regression. From each curve-fitting procedure, the MK Model program yields the coefficient of variation of each parameter, assuming that all other parameters are constant. These coefficients of variation give an indication of the uncertainty in determining the parameters. From the best-fit parameters in each of our patients, the mean ± SD was determined. Paired or unpaired *t* tests were used to determine significance.

The model parameters were tested by comparing the time course of inhibition of T1 after the third dose of vecuronium to that predicted from the analysis of effect after the first two doses of the drug in all patients. In eight patients, four doses of vecuronium were administered and the time course of effect of the fourth dose was predicted from the kinetic analysis after the three previous doses.

Analyses were performed using bi- and triexponential models. Equations 2 and 3 contain two and three distinct exponential terms, respectively. Deletion of one term in these equations (*i.e.*, setting A or B to zero) gives a biexponential function of time describing the time course of concentrations at the site of action and a monoexponential function for the plasma concentrations. The better model was determined by considering the log-likelihood and Schwarz criterion of the fit to the data.

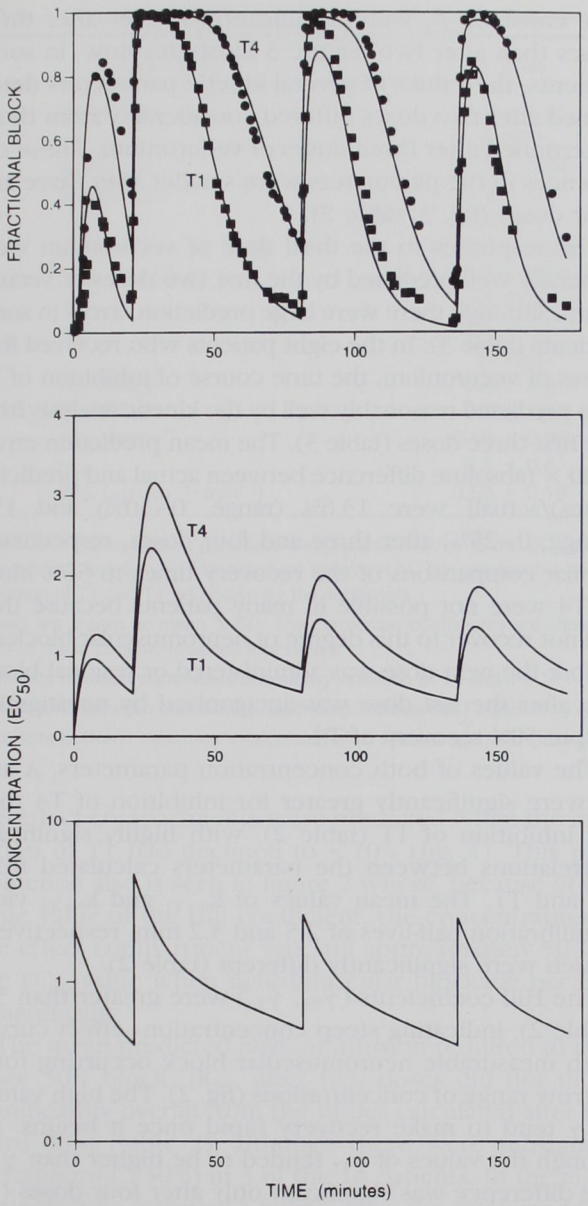

Fig. 1. (*Upper*) Time course of inhibition of T1 and T4 after stimulation of abductor digiti minimi in patient 17, who received four successive doses of vecuronium (2, 4, 2, and 2 mg). For clarity, some experimental points are not shown. The time courses of inhibition after all four doses were fitted by the theoretical equations. The equations relating inhibition (f) of T1 and T4 to the concentrations in the effect compartments (Ce) are, respectively:

$$f = Ce^{5.168}/(1 + Ce^{5.168})$$

$$f = Ce^{5.984}/(1 + Ce^{5.984})$$

The equations describing time course of Ce after the first dose are shown in the legend to the middle figure. (*Middle*) Time (t) course of the calculated concentrations of vecuronium in the effect compartments in patient 17. The concentrations are expressed relative to the EC_{50} values. From inhibition of T1 and T4, the equations for the first dose are, respectively:

$$Ce = 12.026e^{-0.164t} + 0.554e^{-0.0168t} - 12.58e^{-0.190t}$$

$$Ce = -17.067e^{-0.164t} + 0.842e^{-0.0168t} + 16.225e^{-0.144t}$$

Ce accumulates after subsequent doses as described in the text. (*Lower*) Time course of the calculated concentrations of vecuronium in the central compartment of patient 17. The concentrations (C) are expressed relative to the EC_{50} values relevant to inhibition of T1.

$$C = 1.612e^{-0.164t} + 0.505e^{-0.0168t}$$

C accumulates after the first dose as described in the text.

The value of ED_{50} for each patient was calculated from the maximum fitted response, f_m, after the first dose, D_1, of vecuronium and the Hill coefficient, γ, calculated after three doses. Rearrangement of the Hill equation yields equation 6.

$$ED_{50} = D_1[(1 - f_m)/f_m]^{1/\gamma} \quad (6)$$

Results

From the 20 patients studied, two records were unacceptable for analysis and were excluded from the results. Both exhibited excessive variation (>20%) of the control response, and one also had several prolonged periods of data loss due to noise from diathermy.

The effect of vecuronium on T1 and T4 was well

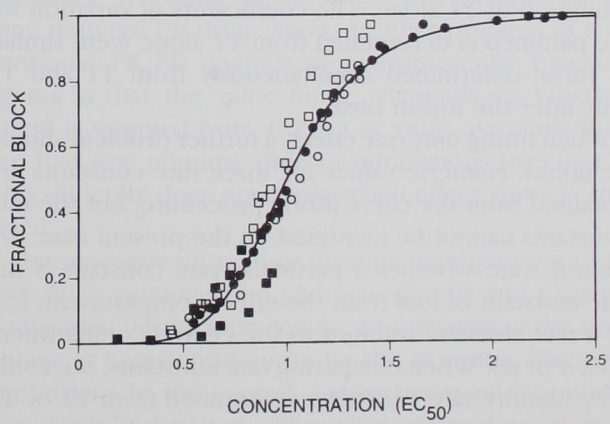

Fig. 2. Inhibition of T1 plotted against the calculated concentration of vecuronium in the effect compartment in patient 17. The concentrations in the effect compartment are expressed relative to the EC_{50} value. Data from dose 1 ■, dose 2 ●, dose 3 □, dose 4 ○. For clarity, some data are not shown. The data are from the same patient whose kinetic analysis is shown in figure 1.

described by equations 1 and 3, although small systematic deviations from the predicted time course of depression of T1 and T4 were often noted (figs. 1 and 2). There were poor fits to a simpler model in which the concentrations in the central compartment were assumed to decline monoexponentially. The log-likelihoods and Schwarz criteria were increased significantly and by considerable margins, mostly >50%, with the more complex model.

The parameters in table 2 were derived from all patients. Nine parameters were determined independently, with the remaining parameter, B_{T4}, being dependent, from equation 4, on the other three concentration parameters. For 18 patients, 162 parameter estimations were performed after each of the second and third doses, with an additional 72 estimations in the 8 patients who received a fourth dose. After two doses, 35 of the 162 parameters had coefficients of variation >25%, compared with 14 of 162 parameters after three doses. After four doses, 8 of the 72 parameters had coefficients of variation greater than 25%. Although the coefficients yield only approximate estimates of the variation of the pharmacokinetic parameters, the trend to decreased errors after three and four doses indicates greater confidence in their values. We also fitted the theoretical equations to the time course of inhibition of T1 alone and also to T4 alone (complete data are available from the authors). Although the parameters were frequently similar to those obtained simultaneously from T1 and T4, the errors in the parameters obtained from these individual indices of effect were larger, particularly for inhibition of T4 alone. The coefficients of variation for the parameters determined from T1 alone were similar to those determined simultaneously from T1 and T4 only after the fourth dose.

When fitting only one effect, a further problem should be noted. Numeric values for three rate constants are obtained from the curve-fitting procedure, but the rate constants cannot be identified. In the present case, we cannot state whether a particular rate constant is the rate constant of loss from the effect compartment, k_{eo}, or a rate constant relevant to the central compartment (*i.e.*, α or β). When comparing rate constants, we could only identify rate constants determined from T1 or T4 alone by their similarity to those from the simultaneous inhibition of T1 and T4.

In the eight patients who received four doses, the mean values of α and β were 0.090 and 0.0089 min^{-1} (table 2), corresponding to half-lives of 7.7 and 78 min, respectively. The concentration term, B, and terminal rate constant, β, were significantly smaller after three doses than after two. Figure 3 illustrates how, in some patients, the values of several kinetic parameters determined after two doses differed considerably from those determined after three doses of vecuronium. These differences in the parameters were smaller after three and four doses (fig. 3, table 2).

The responses to the third dose of vecuronium were generally well predicted by the first two doses of vecuronium, although there were large prediction errors in some patients (table 3). In the eight patients who received four doses of vecuronium, the time course of inhibition of T1 was predicted reasonably well by the kinetic analysis from the first three doses (table 3). The mean prediction errors [100 × (absolute difference between actual and predicted times)/actual] were 13.6% (range, 0–40%) and 15% (range, 0–25%) after three and four doses, respectively. Similar comparisons of the recovery times to 50% block of T4 were not possible in many patients because they did not recover to this degree of neuromuscular blockade before the next dose was administered or residual blockade after the last dose was antagonized by neostigmine before 50% recovery of T4.

The values of both concentration parameters, A and B, were significantly greater for inhibition of T4 than for inhibition of T1 (table 2), with highly significant correlations between the parameters calculated from T4 and T1. The mean values of $k_{eo\ T1}$ and $k_{eo\ T4}$ yield equilibration half-lives of 2.5 and 3.2 min, respectively, which were significantly different (table 2).

The Hill coefficients (γ_{T1}, γ_{T4}) were greater than 5.5 (table 2), indicating steep concentration–effect curves with measurable neuromuscular block occurring for a narrow range of concentrations (fig. 2). The high values of γ tend to make recovery rapid once it begins. Although the values of γ_{T1} tended to be higher than γ_{T4}, the difference was significant only after four doses (table 2). There were significant correlations between the γ values for inhibition of T1 and T4.

From equations 3 and 4, the time course of the concentrations of vecuronium at the sites responsible for inhibition of T1 and T4 (fig. 1) was determined relative to the EC_{50}. The concentrations in the central and effect compartments declined in a nearly log-linear manner after the first dose of vecuronium but demonstrated clearer biphasic behavior after the second, third, and fourth doses (fig. 1). Thus, the recovery after the first dose occurred largely during the distribution phase, but recovery shifted more to the elimination phase after multiple doses. Substantial concentrations of drug in

Table 2. Pharmacokinetic and Pharmacodynamic Parameters of Vecuronium after Two to Four Consecutive Doses

Parameter	2 Doses	3 Doses	4 Doses
A_{T1} (EC_{50})	4.6 ± 1.9*	4.6 ± 1.9*	3.9 ± 1.3*
	(0.98)‡	(0.99)‡	(0.99)‡
α (min^{-1})	0.12 ± 0.04	0.10 ± 0.04	0.09 ± 0.04
B_{T1} (EC_{50})	1.8 ± 0.7*	1.5 ± 0.8*,**	1.2 ± 0.5*
	(0.98)‡	(0.99)‡	(0.98)‡
β (min^{-1})	0.012 ± 0.006	0.009 ± 0.006**	0.009 ± 0.005
k_{eoT1} (min^{-1})	0.25 ± 0.08	0.27 ± 0.08*	0.28 ± 0.04*
	(0.93)‡	(0.91)‡	(0.81)§
γ_{T1}	6.0 ± 1.1	5.9 ± 1.2	5.5 ± 1.0†
	(0.78)‡	(0.65)¶	(0.89)¶
A_{T4} (EC_{50})	6.8 ± 2.9	6.8 ± 3.1	5.9 ± 2.1
B_{T4} (EC_{50})	2.7 ± 1.1	2.2 ± 1.2‡‡	1.8 ± 0.8
k_{eoT4} (min^{-1})	0.19 ± 0.06	0.20 ± 0.06	0.22 ± 0.05
γ_{T4}	6.1 ± 0.8	6.3 ± 1.2	6.2 ± 1.3
IR_{50} ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.53 ± 0.19	0.47 ± 0.18	0.55 ± 0.18**

A and B = concentration parameters expressed relative to the EC_{50} and normalized to a dose of 0.1 mg/kg; α, β, and k_{eo} = rate constants of the model (equations 2 and 3); γ = Hill exponent (equation 1). The values of α and β are relevant for inhibition of both T1 and T4, but A, B, k_{eo}, and γ are specific for inhibition of T1 and T4, as shown by the subscripts.

Values are shown as mean ± SD. The correlation coefficients are shown in parentheses. All 18 patients received two and three doses of vecuronium while eight of these patients received four doses.

Contrasts between parameters describing inhibition of T1 and T4: * $P < 0.001$, † $P < 0.05$.

Correlations between parameters describing inhibition of T1 and T4: ‡ $P < 0.001$, § $P < 0.05$, ¶ $P < 0.01$.

Contrasts between parameters calculated after second and third doses or between third and fourth doses: ** $P < 0.05$, ‡‡ $P < 0.01$.

the effect compartments were predicted when the inhibition of T1 had declined to <10% (fig. 1). This phenomenon also is seen in figure 2 where, because of the large value of the Hill coefficient, the concentration in the effect compartment was still approximately 50% of the EC_{50} value when neuromuscular blockade became insignificant.

The mean predicted rates of infusion required to produce 50% block, IR_{50}, after two doses did not differ significantly overall from the values calculated after the third dose (table 2), although there were substantial differences (>50%) in 3 of the 18 patients. In the eight patients who received a fourth dose, the calculated IR_{50} values changed from 0.53 ± 0.18 after three doses to 0.55 ± 0.18 $mg \cdot kg^{-1} \cdot min^{-1}$ after four doses. The difference, although very small, was significant ($P < 0.05$; table 2). The largest change was only 12% (fig. 3). The mean ED_{50} for inhibition of T1, calculated from the parameters derived after three doses, was 31 ± 7 $\mu g/kg$. There was no correlation between the IR_{50} and ED_{50} values ($r^2 < 0.1$).

Discussion

This study indicates some of the advantages and disadvantages of determining pharmacokinetic and pharmacodynamic parameters based on effect alone. Compared with studies in which both effect and plasma concentrations are measured (PK/PD studies), the greatest advantage is that the analysis of effect alone has the potential to yield predictions of further dosage in individual patients during anesthesia. Conventional PK/PD studies of muscle relaxants do not allow this because of the time required for drug assays. Another problem of conventional PK/PD analysis of neuromuscular blocking agents is that the value for k_{e0} depends on whether blood is sampled from arteries or veins, particularly in the first few minutes after an intravenous injection.[7,8] This difficulty does not apply when effect alone is analyzed.

Pharmacokinetic analysis through measurement of effect alone produces the pharmacokinetic and pharmacodynamic information required to determine the time course of concentrations at the site of action. The concentrations in the central compartment of the model can also be calculated, although these are less relevant to the activity of the drug. The major difference between this kind of analysis and pharmacokinetic studies involving plasma concentrations is that the kinetics of the effect method yields concentrations relative to the EC_{50} values rather than in units such as milligrams per

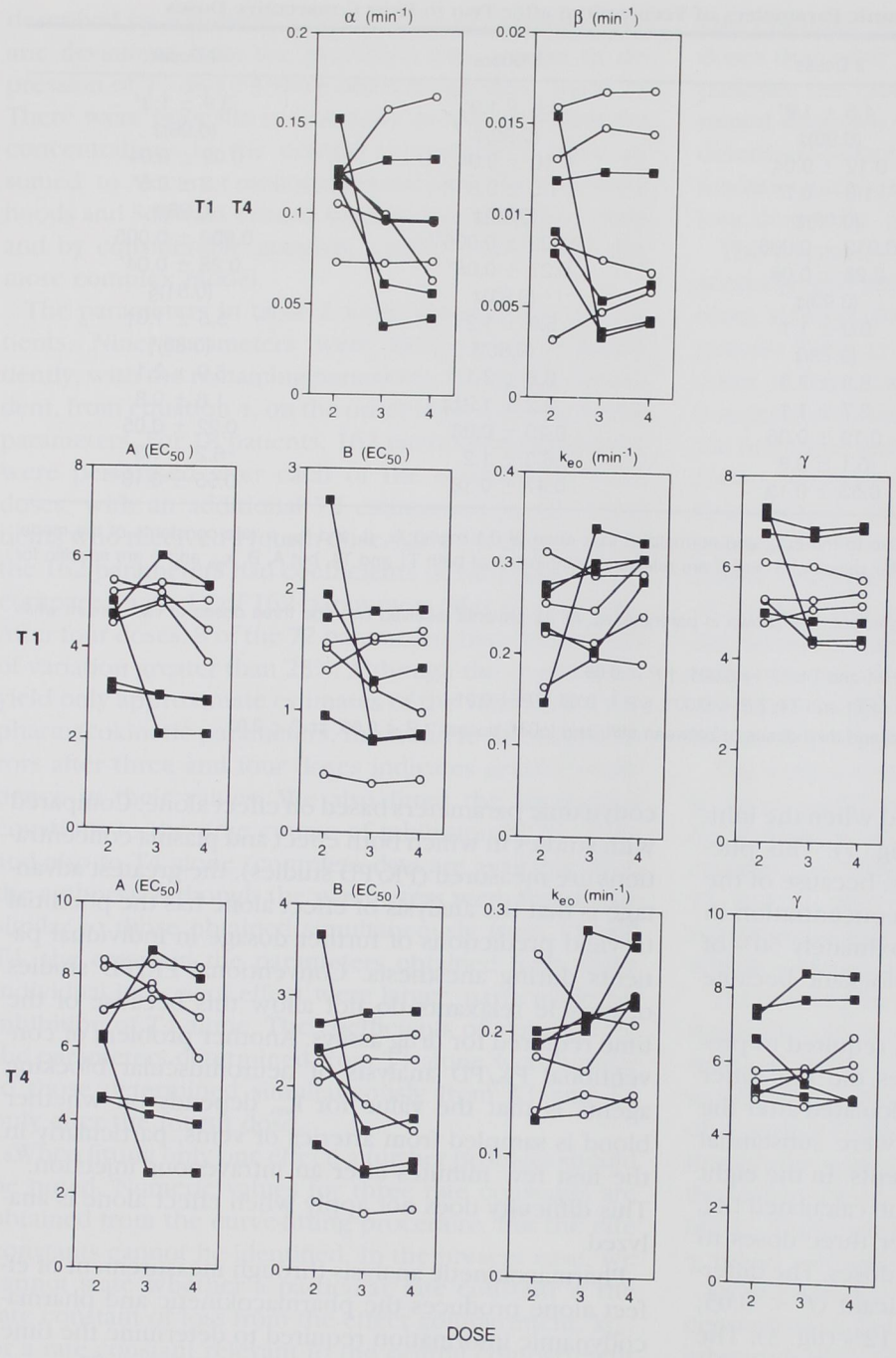

Fig. 3. Pharmacokinetic and pharmacodynamic parameters of vecuronium calculated after two, three, and four bolus doses of the drug. Data are shown only for patients who received four doses. The values of α and β are common to the time course of concentrations in the central or effect compartments responsible for inhibition of T1 and T4, but the other parameters are relevant to inhibition of T1 or T4 as shown. Anesthesia was maintained with isoflurane (*filled symbols*) or propofol (*open symbols*).

liter. The volume of distribution and clearance cannot be determined in conventional units (liters and milligrams per liter, respectively). It is, however, possible to calculate directly the IR_{50} values, or the infusion rate for any other degree of blockade, because the value of γ is also known.

The use of multiple doses greatly improves the precision of the determination of the pharmacokinetic and pharmacodynamic parameters from effect only. If effect is measured only during the elimination phase after a single dose of a drug, it is impossible to separate the Hill coefficient from the apparent rate constant of elimi-

Table 3. Tests of the Predictive Value of the Fits to the Time Course of Effect of Two and Three Doses of Vecuronium

Patient No.	Actual after 3 Doses (min)	Predicted from 2 Doses (min)	% Error	Actual after 4 Doses (min)	Predicted from 3 Doses (min)	% Error
1	23.5	21.5	8.5	25	20.9	16.4
2	23	23	0	26	30.8	18.5
3	49.6	64.2	−29.4	21.5	26.7	−24.2
4	13.5	16.7	−23.7	22.5	22.5	0
5	12.6	12	4.8			
8	15	15	0			
10	27.6	21	23.9			
11	32	28.6	10.6			
12	24	14.4	40			
13	7.2	5.2	27.8			
14	26.7	25.7	3.7			
15	19	19	0	13.5	13.1	3.0
16	20	21.9	−9.5	7.2	9	−25
17	21	19.6	6.7	17	21	−23.5
18	20	23	−15	18	19.7	−9.4

The time to 50% recovery of the maximal effect was compared with the predicted time. The percentage error is 100*(actual − predicted)/actual. Patients 6, 7, and 9 did not recovery to 50% of the peak block before the administration of neostigmine.

nation.[9] It is possible to separate pharmacokinetic and pharmacodynamic parameters of vecuronium after a single dose if the complete time course is followed,[1,4] but we have found that the precision of the estimated parameters is poor even if two responses are measured. The most efficient way to determine the pharmacokinetic and pharmacodynamic parameters of vecuronium is to measure two effects after three doses over a period of approximately 1 h.

Although determining kinetic and dynamic parameters is most convenient after multiple doses, the requirement for multiple doses might be regarded as a disadvantage of the procedure. The high value of γ and the marked distributional phase of neuromuscular blocking drugs such as vecuronium means that a window of data is obtained after each dose, and measures of effect are required over three or more doses to obtain good estimates of the parameters, particularly the terminal half-life. Further, because high doses of any muscle relaxant abolish any recordable response, little kinetic information is obtained when the effect is maximal or nearly maximal. The high value of γ also means that there is no significant effect at low concentrations (figs. 1 and 2) and, correspondingly, no kinetic information is obtained at low levels of effect that correspond to low plasma concentrations. Thus the determination of pharmacokinetic and pharmacodynamic parameters depends largely on the periods during which the effect of the muscle relaxant is 10 - 90% of the maximal. The accuracy of the determination of the parameters also depends on the precision of the drug dosage. There is considerable residual drug in the effect compartments when the second or later doses are given (figs. 1 and 2) and thus the time course of drug action depends on the magnitude of the previous doses. The high values of the Hill coefficient also mean that a small error in the doses leads to large differences in the degree of neuromuscular blockade.

The difficulty of obtaining good estimates of pharmacodynamic and pharmacokinetic parameters increases with increasing complexity of the model. In a previous study,[2] we analyzed the time course of effect of atracurium on T1 and T4 separately using methods similar to those we used in the present study. The time course of concentrations in the effect compartments were described by biexponential functions of time, and, after two doses of atracurium, the coefficients of variation of determination of the kinetic and dynamic parameters were generally $<10\%$. In contrast, we found that only by fitting simultaneously T1 and T4 data from at least three doses in this study could we achieve acceptable levels of precision in the parameters. Despite the greater precision after three doses, the prediction errors of effect after two and three doses were similar (table 3).

Apart from the lesser uncertainty in the pharmacodynamic and pharmacokinetic parameters calculated after

three and four doses, there were only small changes in the mean parameters (table 2) and the parameters in individual patients (fig. 3). The only significant changes were the smaller values of the terminal rate constant, β, and a corresponding lower concentration parameter, B, after three doses than after two doses (table 2). This contrast is consistent with a common observation in pharmacokinetic studies, namely that the terminal elimination phase becomes more apparent or is found to be slower as the study period increases. With increasing size of single doses, the recovery from vecuronium also shifts from the distribution to the elimination phase.[10] As can be seen from figure 1, this expected pattern is found with repeated doses.

Previous analyses of the kinetics of effect of vecuronium also demonstrate the difficulty of identifying an elimination phase in relatively short-term studies. In these studies, the effect of vecuronium was examined for 40 min after single doses. In one study, a monoexponential function for the central compartment was adequate to fit the data,[1] and in the other a biexponential function used in the present studies gave an improved fit in five of the six patients.[4] Longer studies involving multiple doses, the experimental design used in the present work, make the elimination phase easier to detect and to quantify. The polyexponential function that we and Fisher and Wright[4] used to describe the concentrations in the central compartment effect are simpler than those used in some conventional pharmacokinetic studies. A triexponential function was used in several studies to fit the time course of plasma concentrations,[11-15] whereas our model of the central compartment only requires a biexponential function. Consistent with our modeling, however, the time course of plasma concentrations was fitted by a biexponential function of time in several other studies.[7,16-21]

The pharmacokinetic and pharmacodynamic parameters that we found in this study are of the same order as those previously found from the measurements of plasma concentrations and effect (table 4). The determination of mean parameters from the literature is, of course, imprecise because of factors such as different conditions of anesthesia. However, except for the concentration term A, all parameters from effect alone are within the ranges found from conventional studies. The differences seen with the concentration parameters may be due, in part, to uncertainty in the EC_{50} values. A mean EC_{50} value of 130 ng/ml was used to convert the literature concentration parameters from nanograms per milliliter to units of EC_{50}, but the mean values in the literature range from 76-200 ng/ml.[4,11,12,15,16,18,21]

Table 4. Comparison of Pharmacokinetic and Pharmacodynamic Parameters of Vecuronium Determined from Effect Alone with Literature Values from Plasma Concentrations and Effect

Parameter	This Study*	Literature†
A_{T1} (EC_{50})	3.9 ± 1.3	8.8 ± 2.4[17-19,21]
α (min^{-1})	0.09 ± 0.04	0.17 ± 0.07[17-19,21]
B_{T1} (EC_{50})	1.2 ± 0.5	2.0 ± 0.9[17-19,21]
β (min^{-1})	0.009 ± 0.005	0.014 ± 0.008‡[11,12,14-21]
k_{eoT1} (min^{-1})	0.28 ± 0.04	0.17 ± 0.07[4,11,12,15,16,18,21]
γ_{T1}	5.5 ± 1.0	5.7 ± 0.8[11,12,15,16,18,21]
IR_{50} ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.55 ± 0.18	0.63 ± 0.14[4,11-15,17-21]

* Values are mean ± SD determined after four doses of vecuronium.

† Values are mean ± SE from published mean values.

‡ Recorded β or slowest rate constant of elimination.

Clearly further studies are required to compare the pharmacokinetic and pharmacodynamic parameters determined from effect only with those from studies in which plasma concentrations and effect are measured in the same patients. Little of such work has been conducted. In the only comparative study conducted to date, the mean value of $k_{eo\ T1}$ determined from effect only was 0.34 min^{-1}, but it was about 0.14 min^{-1} from effect and plasma concentrations. The discrepancy may arise from model differences particularly during the first few minutes after administration,[4,7] the limited data collected during the onset phase, or from the activity of a metabolite, 3-desacetylvecuronium, whose activity is usually not considered.[4] It may, however, be argued that the rate constants derived from drug effect may be the most appropriate to describe the kinetics of the effects of active drug at its site of action and that the pharmacokinetic and pharmacodynamic parameters estimated from effect alone are not necessarily flawed.

As has been reported with atracurium and pancuronium,[2,22,23] the k_{eo} values are smaller for T1 than for T4. However, the greater potency for the depression of T4 (figs. 1 and 3; table 2) is the major cause of the earlier loss and later recovery of this response, as was concluded in the studies of atracurium.[2,22] Although the equilibrium half-life is longer for the site of inhibition of T4, there is a correlation between the rate constants of equilibration determined from T1 and T4 (table 2), as has been observed with atracurium,[2,22] indicating some association between the sites leading to inhibition of T1 and T4. This association is sup-

ported by the correlation between the Hill exponents of the two functions (table 2).

Many volatile anesthetics potentiate the activity of the neuromuscular blockers. In this study, parameters that might indicate alterations in the sensitivity to vecuronium are A, B, IR_{50}, and ED_{50}, but we found similar values of these parameters during propofol and isoflurane supplemented anesthesia (fig. 3). The number of patients is, however, quite small. From our data, a sample size of approximately 200 patients would be needed to detect a 20% effect of isoflurane at the low concentration used (0.6% end-tidal). Thus there is a low probability of finding significant differences between the two groups in this study. The lack of any apparent effect of isoflurane is due possibly to the low concentration used during this study and is consistent with the finding that this concentration of isoflurane does not potentiate the neuromuscular blocking activity of mivacurium,[24] although a higher concentration of isoflurane (1.2%) does potentiate the activity of vecuronium.[25]

We used electromyography to measure the effect of vecuronium because of its convenience in a clinical setting. The alternative, measuring the force of contraction of the adductor pollicis, is used widely but requires arm positioning that is inconvenient and sometimes incompatible with surgical access. A major difficulty with using electromyography is interference by diathermy, as noted before. Drift in the control responses also occurs but was minimized by initial stabilization over 15 min. Further drift >20% during the study period contributed to the rejection of two data sets.

In conclusion, it is evident that there are useful aspects, as well as problems, in determining pharmacokinetic and pharmacodynamic parameters of vecuronium from effect alone. In the absence of plasma concentrations, analysis of the kinetics of effect should be valuable in the development of a new muscle relaxant, particularly if a drug assay is difficult or unavailable. The analysis of effect may also become useful to predict further doses in the clinical use of an established drug.

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