Cumulative Characteristics of Atracurium and Vecuronium

A Simultaneous Clinical and Pharmacokinetic Study

Peter M. C. Wright, M.D.,* Paul Hart, M.B.,* Marie Lau, B.S.,† Manohar L. Sharma, Ph.D.,‡
Larry Gruenke, Ph.D.,‡ Dennis M. Fisher, M.D.§

Background: Cumulative effects (increased 25–75% recovery time with increasing dose) are evident with vecuronium but not with atracurium. Pharmacokinetic simulations suggest that vecuronium's cumulation occurs as recovery shifts from distribution to elimination whereas atracurium's recovery always occurs during elimination. The purpose of this study was to examine this pharmacokinetic explanation.

Methods: We assigned 12 volunteers to receive atracurium or vecuronium on three occasions during nitrous oxide–isoflurane anesthesia. Evoked adductor pollicis twitch tension was monitored. On occasion 1, the dose expected to produce 95% block (ED$_{95}$) was estimated for each subject. On occasions 2 and 3, 1.2 or 3.0 multiples of ED$_{95}$ were given as a bolus. Plasma was sampled for 128 min to determine muscle relaxant concentrations; pharmacodynamic modeling was used to determine effect-compartment drug concentrations (Ce). For each drug, recovery time, recovery phase half-life (rate of decrease in Ce during recovery), and Ce at 25% and 75% recovery were compared between doses.

Results: Atracurium's recovery time increased 2.4 ± 2.2 min (mean ± SD) with the larger dose, less than the increase with vecuronium (8.2 ± 3.8 min). Atracurium's recovery phase half-life was 14.6 ± 1.7 and 20.1 ± 2.3 min with the small and large doses ($P < 0.05$); vecuronium's recovery phase half-life increased similarly from 13.5 ± 2.3 to 18.5 ± 5.0 min ($P < 0.05$).

At 75% recovery, vecuronium's Ce decreased from 65 ± 18 ng/ml with the small dose to 55 ± 15 ng/ml with the large dose ($P < 0.05$). Assuming that neuromuscular junction sensitivity was constant, this difference could be explained by considering neuromuscular effects of vecuronium's metabolite, 3-desacetylvecuronium.

Conclusions: Although vecuronium was cumulative (as predicted), atracurium was also slightly cumulative. Inconsistent with our hypothesis, recovery phase half-lives for both drugs increased similarly between doses; therefore, differences in cumulation were not solely explained by pharmacokinetics of the muscle relaxant. It appears that 3-desacetylvecuronium contributes to vecuronium's cumulative effect, even after usual clinical doses. (Key words: Neuromuscular relaxants: atracurium; vecuronium. Pharmacokinetics, neuromuscular relaxants: atracurium; vecuronium.)

* Visiting Assistant Professor of Anesthesia.

† Staff Research Associate.

‡ Research Biochemist.

§ Professor of Anesthesia and Pediatrics.

CUMULATIVE effect (defined either as a dose-related increase in the time for twitch tension to recover from 25% to 75% of the control value, or as a progressive increase in the duration of action of repeat doses) is considered an undesirable feature of muscle relaxants.[1] Although the initial clinical description of vecuronium reported no cumulative effects,[2] other studies suggest cumulation.[3,4] In contrast, clinical studies of atracurium suggest absent or minimal cumulation.[3,5] Subsequently, simulations from our group based on pharmacokinetic data suggested that both types of cumulative effects of both vecuronium and pancuronium did not result from dose-related changes in either pharmacokinetics or pharmacodynamics. Instead, these simulations suggested that these cumulative effects resulted from recovery being shifted from the rapid distribution phase to the less rapid elimination phase; in contrast, these same simulations suggested that atracurium entered its elimination phase early, so that recovery always occurred during elimination rather than during distribution and no cumulation would be expected.[6]

These simulations have not been verified with simultaneous pharmacokinetic–pharmacodynamic and clinical data. In the current study, we examined whether atracurium or vecuronium were cumulative (as defined by an increase in 25–75% recovery time with increasing dose). By studying each subject on repeated occasions and measuring both plasma concentrations of the muscle relaxant and effect, we were able to examine the relation between pharmacokinetics, pharmacodynamics, and the time course of two doses of the muscle relaxants. In addition, we introduce a new pharmacokinetic parameter, recovery phase half-life (the half-life for the decrease in effect-compartment concentrations [Ce] of the muscle relaxant during recovery), to evaluate whether cumulative effects can be explained by shift of recovery from the distribution to elimination phase.

Materials and Methods

After obtaining approval of the institutional review board, we studied 12 volunteers aged 19–32 yr. Potential subjects who were obese, suffering from a concurrent medical condition, or taking medication were excluded. Age, weight, height, gender, resting heart rate and arterial blood pressure of the subjects were recorded and venous blood was obtained to confirm normal hematologic and biochemical indices. The subjects were alternately allocated to receive either atracurium or vecuronium.

Experimental Conditions

Each subject was studied on three occasions at least 1 week apart. On each occasion subjects were anesthetized using propofol 2–3 mg·kg^{-1} followed by nitrous oxide 60% in oxygen with isoflurane at an end-tidal concentration of 1%; isoflurane was given for more than 45 min before administration of the muscle relaxant. An intravenous cannula was placed in a large vein in the right forearm before anesthetic induction and lactated Ringer's solution was infused. The trachea was intubated after induction of anesthesia, and the lungs were ventilated mechanically to maintain an end-tidal carbon dioxide tension of 30–35 mmHg (Datex Ultima, Helsinki, Finland). The electrocardiogram, hemoglobin oxygen saturation, and core temperature (esophageal thermistor) were continuously monitored, and leg arterial blood pressure was measured noninvasively every 3 min (Dinamap, Critikon, Tampa, FL).

The left ulnar nerve was stimulated using needle electrodes placed at the wrist. Supramaximal stimuli of 0.15 ms duration were delivered in a train-of-four at 2 Hz every 12 s. Preload was maintained at 200–300 g. The evoked twitch tension of the adductor pollicis muscle was measured with a calibrated force transducer (Myotrace, Houston, TX), amplified (DC Bridge Signal Conditioner, Gould Electronics, Valley View, OH), digitized (NB-MIO-16, National Instruments, Austin, TX) on a Macintosh IIci computer (Apple, Cupertino, CA), and displayed (LabView, National Instruments). Each train-of-four was also recorded on a strip-chart recorder (TA240, Gould Electronics). End-tidal carbon dioxide and isoflurane, heart rate, arterial blood pressure, core body temperature, and adductor pollicis twitch tension were stable for a minimum of 15 min before muscle relaxant administration.

Experimental Program

On the first occasion, vecuronium, 10 µg·kg^{-1} (n = 6), or atracurium, 75 µg·kg^{-1} (n = 6), were given. When maximal depression of the first component of the train-of-four was achieved (*i.e.*, no change in twitch tension during three consecutive trains), a second dose of the muscle relaxant was given. The size of the second dose was determined according to the peak response after the first dose, aiming to achieve 90% twitch depression after the second dose (Appendix); the size of the second dose was reported by LabView immediately after each train-of-four. This two-dose dose response technique provides accurate estimates of the potency of medium-duration muscle relaxants for which use of the traditional four- or five-dose cumulative-dose technique yields biased estimates.[7] The peak twitch response after each of the two doses was then used to estimate the dose expected to produce a 95% block in each individual (Appendix).

For each subject, on the second and third occasions, 1.2 and 3.0 multiples of that individual's estimated ED$_{95}$ were administered intravenously. Radial arterial blood was obtained to determine plasma drug concentrations before and 1, 2, 4, 8, 16, 32, 64, and 128 min after administration of the muscle relaxant and when twitch tension was approximately 25%, 50%, and 75% of the control value. Values for the first component of the train-of-four were normalized to the final value during recovery (typically 95–105% of the initial control value).

Blood samples were promptly centrifuged (and acidified in the case of atracurium) and the plasma removed

and frozen for subsequent analysis of atracurium (high-performance liquid chromatography[8]) and vecuronium and 3-desacetylvecuronium (gas chromatography with nitrogen phosphorus detection[9]). The assay for atracurium is sensitive to 10 $ng \cdot ml^{-1}$ with a coefficient of variation of 9% at 15 $ng \cdot ml^{-1}$, values for the vecuronium and 3-desacetylvecuronium assay being a sensitivity of 5 $ng \cdot ml^{-1}$ and a coefficient of variation of 15% at 10 $ng \cdot ml^{-1}$.

Data Analysis and Statistics: Occasions 2 and 3

Recovery Characteristics. Clinical duration (time from drug administration to 25% recovery), time to 75% recovery, and recovery time (time from 25% to 75% recovery) were compared between doses using a paired-sample t test. Differences between drugs were compared using an unpaired-sample t test.

Pharmacokinetic–Pharmacodynamic Modeling. For each subject, the ratio of plasma concentrations for each sampling time was calculated; mean values at each sampling interval were compared with 2.5 (the ratio of doses administered) using a one-sample t test with Bonferroni's correction for multiple comparisons. Combined pharmacokinetic–pharmacodynamic (effect-compartment[10]) models were fit to the data from each subject using an iterative nonlinear modeling program, NONMEM. Two- and three-compartment pharmacokinetic models were tested; the three-compartment pharmacokinetic model was chosen only if it was statistically justified.[11] Models were fit separately to the data from each dose to estimate the effect-compartment concentrations (Ce) at 25%, 50%, and 75% recovery ($Ce_{25\%}$, $Ce_{50\%}$, and $Ce_{75\%}$, respectively), the rate constant for equilibration between plasma concentration and Ce, and the Hill coefficient (γ), the factor that governs the sigmoidicity of the relation between Ce and effect. Values for $Ce_{25\%}$, $Ce_{50\%}$, and $Ce_{75\%}$ for the small and large doses were compared using a paired-sample t test.

To determine whether the slope of the Ce *versus* time curve was similar for the two doses (*i.e.*, whether recovery shifted from distribution to elimination as the dose increased), we calculated a recovery phase half-life, the half-life for Ce during recovery:

$$\text{recovery phase half-life} = \frac{\ln(2)\Delta t}{\ln\left(\dfrac{Ce_{25\%}}{Ce_{75\%}}\right)} \quad (1)$$

where Δt is the time from 25% to 75% recovery. If recovery shifted from distribution to elimination as the dose increased (as we hypothesized for vecuronium), we would expect recovery phase half-life to increase between doses. Values for recovery phase half-lives for the small and large doses were compared using a paired-sample t test.

When these pharmacokinetic–pharmacodynamic models suggested that vecuronium's neuromuscular junction sensitivity during recovery differed between the two doses, we tested additional models for vecuronium in which the concentrations of a metabolite, 3-desacetylvecuronium, were assumed to have neuromuscular effects. Several factors confounded these analyses. First, after the small dose of vecuronium, concentrations of 3-desacetylvecuronium were less than the limit of detection of the assay for four subjects; therefore, the plasma concentration of 3-desacetylvecuronium for the small dose for these subjects was assumed to follow the identical time course and to be proportional to that from the large dose.‖ Second, immediately after vecuronium administration, the concentration of 3-desacetylvecuronium is approximately 1% of the simultaneous vecuronium concentration, suggesting either coadministration of 3-desacetylvecuronium or immediate conversion of vecuronium to 3-desacetylvecuronium (*e.g.*, in the lung or by plasma esterases). After an initial decrease, 3-desactylvecuronium concentrations increase, then decrease, suggesting conversion from vecuronium followed by distribution or elimination. Therefore, we modeled the time course of 3-desacetylvecuronium as having two components, a value resulting from *in vivo* conversion of vecuronium to 3-desacetylvecuronium and a second value equal to 1% of the predicted simultaneous vecuronium con-

‖ After the small dose of vecuronium, concentrations of 3-desacetylvecuronium during the interval from 25% to 75% recovery were small compared with those of vecuronium. Therefore, ignoring neuromuscular effects of 3-desacetylvecuronium after the small dose minimally influenced our results and did not alter statistical significance.

Table 1. Age, Weight, and Height of the Subjects and Gender Distribution for Subjects Given Atracurium or Vecuronium

	Atracurium	Vecuronium
Age (yr)	27 ± 3	24 ± 3
Weight (kg)	77.6 ± 8.5	79.7 ± 14.1
Height (cm)	177 ± 10	178 ± 10
Gender distribution (M/F)	4/2	5/1

Values are mean ± SD. There were no differences between groups.

Table 2. Potency Estimates Determined in Occasion 1, and Doses of Atracurium or Vecuronium, Time Course of Neuromuscular Blockade during Occasions 2 and 3, and the Recovery Phase Half-life

	Atracurium	Vecuronium
ED_{95} (μg/kg)	131 ± 26	21.8 ± 7.8
Dose administered (μg/kg)		
1.2 ED_{95}	157 ± 31 (120–198)	26.2 ± 9.3 (13.2–39.6)
3.0 ED_{95}	393 ± 77 (300–495)	65.5 ± 23.3 (33.0–99.0)
Clinical duration (min)		
1.2 ED_{95}^{*}	22.7 ± 4.6	15.5 ± 3.1
3.0 ED_{95}^{*}	48.0 ± 6.0	34.3 ± 5.8
Time to 75% recovery (min)		
1.2 ED_{95}^{*}	35.4 ± 6.2	26.3 ± 6.3
3.0 ED_{95}	63.1 ± 8.6	53.2 ± 10.9
25–75% recovery time (min)		
1.2 ED_{95}	12.6 ± 1.9	10.7 ± 3.4
3.0 ED_{95}	15.1 ± 3.0†	18.9 ± 5.8†
Increase in 25–75% recovery time*	2.4 ± 2.2	8.2 ± 3.8
Recovery phase half-life (min)		
1.2 ED_{95}	14.6 ± 1.7	13.5 ± 2.3
3.0 ED_{95}	20.1 ± 2.3†	18.5 ± 5.0†
Increase in recovery phase half-life	5.5 ± 1.5	5.0 ± 4.3

Values are mean ± SD; ranges are in parentheses.

* $P < 0.05$ between drugs.

† $P < 0.05$ *versus* 1.2 ED_{95}.

centration. Third, we have no *a priori* knowledge of the quantity of 3-desacetylvecuronium administered or produced; thus, we are unable to estimate its "dose" and, therefore, its volume of distribution. In that 3-desacetylvecuronium was measured in plasma (whose volume is similar to the central compartment volume for vecuronium), we assumed that the volume of distribution of 3-desacetylvecuronium was equal to vecuronium's central compartment volume; however, additional analyses in which the distribution volume of 3-desacetylvecuronium varied from 0.2 to 5 times that of vecuronium's central compartment volume did not influence our results. A fourth consideration involved the relative potency of 3-desacetylvecuronium and its rate of equilibration with the effect compartment. Caldwell *et al.*[12] recently demonstrated that the potency of 3-desacetylvecuronium (as defined by the ratio of plasma concentrations producing 50% twitch depression) is 80% that of vecuronium and that the equilibration rate constant is similar for the two.

Therefore, we modeled 3-desacetylvecuronium as being converted from (but not to) vecuronium and being distributed to a single compartment with a volume equal to vecuronium's central compartment volume. We also assumed that equilibration of 3-desacetylvecuronium with the effect compartment occurred

at a rate identical to that of vecuronium and that the potency of 3-desacetylvecuronium was 80% that of vecuronium. Effect-compartment modeling for the small and large doses of vecuronium was then repeated to determine the "effective" Ce (Ce for vecuronium + 0.8 × Ce for 3-desacetylvecuronium) at 25%, 50%, and 75% recovery. Values for $Ce_{25\%}$, $Ce_{50\%}$, and $Ce_{75\%}$ for the small and large doses were again compared using a paired-sample *t* test.

Values are reported as mean ± SD. For all statistical tests, $P < 0.05$ was considered significant.

Results

The two groups were similar in age, weight, height and gender distribution (table 1). The ED_{50} of atracurium was 6.2 that of vecuronium (table 2). After both the small dose and large dose, all subjects developed complete neuromuscular blockade. For both doses, clinical duration was longer with atracurium than with vecuronium. Time to 75% recovery was longer with atracurium than with vecuronium after the small dose but not after the large dose. For both atracurium and vecuronium, recovery time for the large dose exceeded that of the small dose; however, the
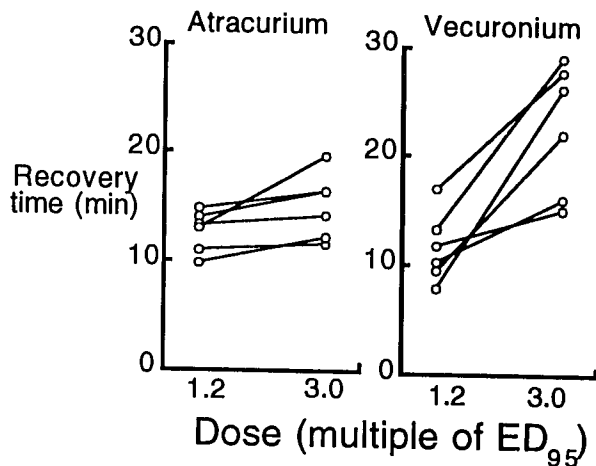
Fig. 1. Recovery times for each individual after 1.2 or 3.0 multiples of the dose of atracurium or vecuronium producing 95% block.

dose-related increase was longer for vecuronium than for atracurium (table 2 and fig. 1).

The ratio of plasma concentration after the large dose to plasma concentration after the small dose varied from 2.5 (the value expected based on the ratio of doses, assuming linear pharmacokinetics) only at 1 and 4 min after atracurium administration (fig. 2). After the small dose of vecuronium, 3-desacetylvecuronium was detected in only two of the six subjects. After the large dose of vecuronium, 3-desacetylvecuronium was detected in all subjects; Ce (3-desacetylvecuronium) was similar at 25% and 75% recovery, despite a twofold decrease in Ce(vecuronium). As a result, the ratio of 3-desacetylvecuronium to vecuronium was larger at 75% recovery than at 25% recovery.

For all subjects, two- or three-compartment pharmacokinetic models fit the vecuronium and atracurium plasma concentration data well (fig. 3); the appropriate model was selected using Akaike's information criterion.[11] Similarly, the effect-compartment model fit the neuromuscular effect data well. For both drugs, recovery phase half-life was larger with the large dose than with the small dose; the increase in recovery phase half-life was similar for the two drugs (table 2 and fig. 4). For atracurium, $Ce_{25\%}$, $Ce_{50\%}$, and $Ce_{75\%}$ were similar for the two doses (table 3).

When vecuronium's effect was modeled ignoring concentrations of its metabolite, $Ce_{25\%}$ and $Ce_{50\%}$ were similar for the two doses; however, $Ce_{75\%}$ was less after the large dose compared with the small dose (table 3). Additional models that considered conversion of ve-

curonium to 3-desacetylvecuronium fit the metabolite concentrations well (fig. 3). The sum of the potency-adjusted Ce values of vecuronium and 3-desacetylvecuronium were similar for the two doses at both 25%, 50% and 75% recovery (table 3 and fig. 5).

Discussion

We demonstrate that vecuronium is cumulative and that this can be explained only in part by a shift in recovery from the distribution phase to the elimination phase of the plasma concentration versus time curve. We also observed a dose-dependent increase in recovery time with atracurium (although smaller than that with vecuronium) and, as with vecuronium, a shift in recovery from distribution to elimination. These cumulative effects could result from one of three possible mechanisms. First, if the pharmacokinetics of the muscle relaxant varied with dose (nonlinearity, such as for theophylline or phenytoin), the shape of the plasma concentration versus time curve would vary with dose, and cumulation might be expected. Second, cumulation could have resulted from the observed shift of recovery from distribution to elimination. Third, if the sensitivity of the neuromuscular junction varied with time (nonstationarity), cumulation might also occur; an example of a nonstationary system is the occurrence of phase II block with succinylcholine. The current study permitted us to examine these three possibilities.

Linearity of the pharmacokinetics of the muscle relaxants could be determined by comparing the pharmacokinetic parameters (i.e., clearance or volume of distribution) determined from each of the doses. How-
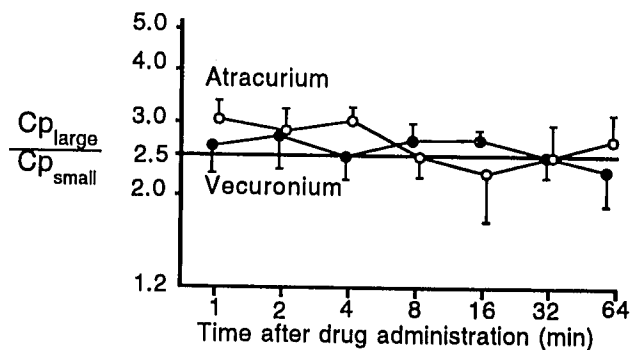

Fig. 2. The ratio of plasma concentrations at intervals after the administration of the muscle relaxant. At 1 and 4 min after atracurium this ratio differs significantly from the expected value of 2.5.
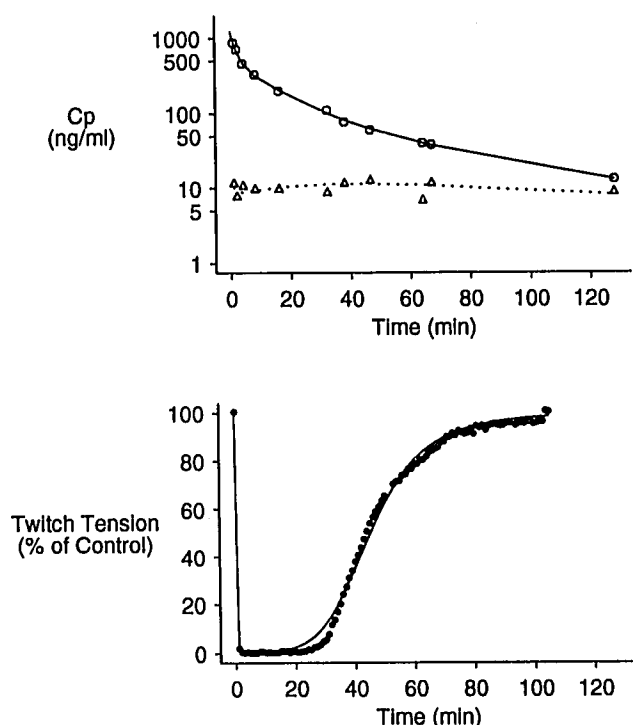
Fig. 3. Data from a representative subject is shown. (*Top*) The fit of the pharmacokinetic model to the plasma concentration data. Circles = measured plasma vecuronium concentrations; solid line = predicted concentrations; triangles = measured plasma 3-desacetylvecuronium concentrations; dashed line = the predicted concentration. (*Bottom*) The fit of the pharmacodynamic model to the effect data. Points = measured values; solid line = the predicted effect. The fitted curve was obtained from a model in which neuromuscular effects of 3-desacetylvecuronium were considered; a similar fit was obtained from a model in which 3-desacetylvecuronium was considered to have no neuromuscular effects.

amined to demonstrate if drug disposition is linear; in the presence of such linearity, plasma concentration at a given time will be proportional to dose. The ratio of atracurium's plasma concentrations after the large dose to those after the small dose exceeded the expected value of 2.5 during the initial four min after drug administration (fig. 2); this might result from various factors including saturable binding of atracurium to plasma proteins (which would become insignificant as the plasma muscle relaxant concentration fell rapidly), or a cardiovascular effect of atracurium altering its initial distribution characteristics (although no cardiovascular effects were observed in our patients). However, after the initial four min of atracurium, and throughout the entire time course for vecuronium, plasma concentrations after the large dose were, as expected, approximately 2.5 times that after the small dose, suggesting linear pharmacokinetics for both muscle relaxants. Thus, a dose-dependent change in pharmacokinetics is unlikely to explain the cumulative effects observed with either muscle relaxant.

The second explanation for cumulation was a shift of recovery from distribution to elimination. Our earlier simulations suggested differences in cumulation between muscle relaxants as a function of dose-related changes in the slope of the plasma concentration *versus* time curve during recovery. To quantify the shift of recovery from distribution to elimination, it was necessary to develop a new pharmacokinetic term, "recovery phase half-life." Although this half-life is neither a distribution half-life nor an elimination half-life, it is
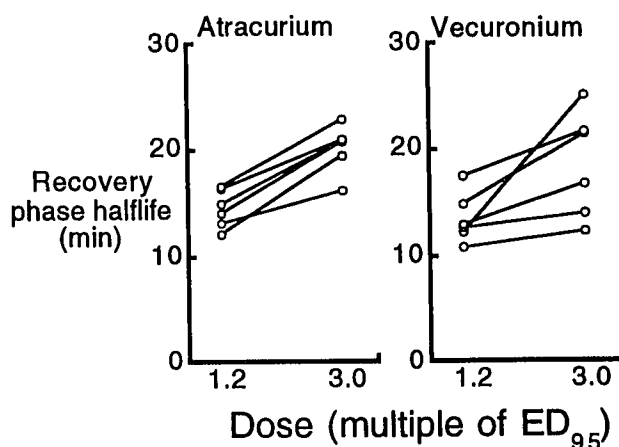
ever, we do not report these parameters because of a number of considerations. First, in some subjects the assay was not sufficiently sensitive to detect vecuronium concentrations at 128 min with the small dose; in these subjects, estimates of clearance and volume of distribution based on 64 min of plasma concentration data would differ from values obtained using 128 min of plasma concentration data from the large dose. Second, estimating the steady state distribution volume of atracurium requires knowledge of its rate of elimination from tissue (noncentral) compartments[13]; however, our pharmacodynamic modeling requires only that we can describe the plasma concentration and Ce *versus* time curves for each muscle relaxant as the sum of exponentials. In the absence of pharmacokinetic parameters, our plasma concentration *versus* time data can be ex-

Fig. 4. Recovery half-life (defined in equation 1) for each individual after 1.2 or 3.0 multiples of the dose of atracurium or vecuronium producing 95% block.

analogous to the "context-sensitive half-time" described by Hughes *et al.*[14] Whereas the context-sensitive half-time refers to the decrease in plasma concentration immediately after infusions of varying duration, the recovery phase half-life refers to the decrease in Ce at a specific epoch (recovery from 25% to 75% of control twitch tension) after bolus administration. The current study demonstrates that this shift of recovery from distribution to elimination is responsible for atracurium's cumulative effect. However, this shift is only partially responsible for the cumulative effect of vecuronium. This suggested that an additional mechanism, such as nonstationarity, must be invoked to explain vecuronium's cumulation.

To examine stationarity of effect, we compared concentrations at the neuromuscular junction (effect compartment) at the same degree of recovery after different doses. For atracurium, $Ce_{25\%}$ and $Ce_{75\%}$ were the same for the two doses (table 3), suggesting that the response to atracurium is stationary. In contrast, the $Ce_{75\%}$ with vecuronium varies with dose, suggesting that the response to vecuronium is nonstationary. This unexpected finding (coupled with the shift of recovery from distribution to elimination only partially explaining vecuronium's cumulation) can be explained by considering the neuromuscular effects of vecuronium's
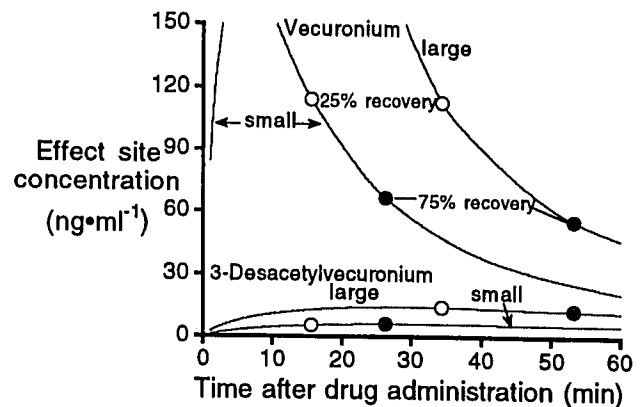

Fig. 5. Mean values for the concentration at the effect site of vecuronium and 3-desacetylvecuronium plotted against time; the time of 25% and 75% recovery is indicated. At 75% recovery, the concentration of 3-desacetylvecuronium is a greater proportion of the vecuronium concentration after the large dose compared with the small dose. For four of six subjects, plasma concentrations of 3-desacetylvecuronium after administration of a 1.2 multiple of the dose of vecuronium producing 95% block were less than the limit of detection of the assay. For these subjects, concentrations of 3-desacetylvecuronium were estimated.

metabolites: 3-desacetylvecuronium, 17-desacetylvecuronium, and 3,17-desacetylvecuronium. The neuromuscular effect of the latter two is probably unim-

Table 3. Effect Compartment Concentrations of Atracurium, Vecuronium, and 3-Desacetylvecuronium at 25%, 50%, and 75% Recovery of Twitch Tension

	Atracurium		Vecuronium	
	1.2 ED$_{95}$	3.0 ED$_{95}$	1.2 ED$_{95}$	3.0 ED$_{95}$
Parent drug (ng/ml; from model ignoring contribution of metabolite)				
25% recovery	303 ± 36	268 ± 39	112 ± 29	113 ± 31
50% recovery	237 ± 31	218 ± 35	88 ± 23	83 ± 23
75% recovery	170 ± 30	167 ± 30	65 ± 18	55 ± 15*
Potenty-adjusted sum of parent drug and active metabolites (ng/ml; from model that considers contribution of metabolite)				
25% recovery	NA	NA	119 ± 31	124 ± 33
50% recovery	NA	NA	94 ± 25	95 ± 24
75% recovery	NA	NA	72 ± 19	66 ± 17
3-Desacetylvecuronium (ng/ml; from model that considers contribution of metabolite)				
25% recovery	NA	NA	5.7 ± 2.2†	14.5 ± 3.9*
50% recovery	NA	NA	6.2 ± 2.2†	14.5 ± 3.8*
75% recovery	NA	NA	6.3 ± 2.1†	12.9 ± 3.6*

Values are mean ± SD.

NA = not applicable.

* $P < 0.05$ *versus* 1.2 ED$_{95}$.

† Four of six subjects given vecuronium had metabolite concentrations below the limit of detection of the assay; the plasma concentration of 3-desacetylvecuronium for these subjects was assumed to follow the same time course and to be proportional to that after the large dose.

portant: their potency in animals is minimal,[15,16] and plasma concentrations in humans are negligible.[17] However, 3-desacetylvecuronium is produced in measurable concentrations in humans and has neuromuscular effects. For example, Marshall *et al.*[16] suggest that the potency of 3-desacetylvecuronium in cats (as determined by bolus dose administration) is 70–80% that of vecuronium. Recent studies at our institution in which 3-desacetylvecuronium was administered to volunteers[12] suggest that its potency (as determined by modeling of the steady-state concentration producing 50% neuromuscular blockade) is 80% that of vecuronium. Thus, 3-desacetylvecuronium might contribute significantly to neuromuscular blockade. Allowing for neuromuscular effects of 3-desacetylvecuronium eliminates the need to posit changes in neuromuscular junction sensitivity; *i.e.*, relaxation is stationary with respect to the combined concentrations of vecuronium and its metabolite. Similar considerations do not apply to atracurium: its metabolites (laudanosine and acrylate) do not have neuromuscular effects.

The small, consistent, but clinically unimportant cumulative effect of atracurium confirms observations made in clinical neuromuscular studies.[3,5] The failure of our simulations to demonstrate cumulation probably resulted from the pharmacokinetic data used to generate the simulations: these data were obtained from subjects given atracurium as a 10-min infusion and from whom venous blood was sampled. These two factors lessened our ability to characterize atracurium's steep initial distribution phase (as seen in the current study) and prevented us from modeling a shift of recovery from distribution to elimination.

Our study could be criticized for the use of isoflurane anesthesia, because isoflurane alters the neuromuscular response to atracurium[18] and vecuronium[19] as well as the plasma clearance of atracurium.[20] However, anesthetic conditions were similar on all occasions so that these factors are unlikely to explain our observations. We selected isoflurane anesthesia for two reasons. First, isoflurane is widely used in clinical practice. Second, our simulations suggested that cumulative effects from bolus doses of muscle relaxants could best be demonstrated if the difference between doses was maximized. Assuming that our large dose would not exceed the usual recommended maximum bolus dose (100 $\mu g \cdot kg^{-1}$ for vecuronium, 500 $\mu g \cdot kg^{-1}$ for atracurium) and aiming for a dose ratio of 2.5:1, our small dose would not exceed 40 $\mu g \cdot kg^{-1}$ for vecuronium or 200 $\mu g \cdot kg^{-1}$ for atracurium. In the absence of an inhaled

anesthetic to potentiate the effects of the muscle relaxant,[19,21] we anticipated that these small doses would not result in complete twitch depression. We are unable to determine whether similar results would be obtained if different anesthetic conditions (*e.g.*, no potent inhaled anesthetics) were employed.

One weakness of our study is that we did not measure the concentration of 3-desacetylvecuronium in the vecuronium administered to our volunteers. This resulted from our not expecting to find a significant neuromuscular effect from this metabolite. However, knowledge of the "dose" of 3-desacetylvecuronium is not essential to our pharmacokinetic–pharmacodynamic modeling. Our approach is sufficient to describe the plasma concentration *versus* time course of this metabolite (figs. 3 and 5). Had we used a nonparametric or semiparametric approach to pharmacodynamic modeling, the concentration *versus* time relation of the metabolite (and not the "dose") would have been used to determine pharmacodynamics; similarly, the parametric approach we employ requires only that we accurately describe the plasma concentration *versus* time course for both vecuronium and 3-desacetylvecuronium.

The implications of these findings will be of limited concern during clinical anesthesia. Prolonged use of vecuronium (*e.g.*, during intensive care) occasionally does result in prolonged recovery,[22] possibly the result of cumulation of 3-desacetylvecuronium.[23] The current study suggests that 3-desacetylvecuronium may also contribute to neuromuscular effects seen with brief administration of vecuronium. Of greater importance is the implication for investigators: future studies of vecuronium's pharmacokinetics and pharmacodynamics need to consider potential neuromuscular effects of 3-desacetylvecuronium.

In summary, the pharmacokinetics of both atracurium and vecuronium are linear over the dose range tested (as evidenced by fig. 2). In addition, we have demonstrated that the cumulation of vecuronium is not explained solely by the pharmacokinetics of vecuronium alone. However, when the contribution of vecuronium's 3-desacetyl metabolite is considered, the greater increases in recovery time after vecuronium (compared with atracurium) are explained. Therefore, our results suggest that much of the increase in vecuronium's recovery time that occurs with increasing dose—even within the clinical dose range—is a result of the contribution of its metabolite, 3-desacetylvecuronium. Finally, inconsistent with the published simulations, the current analysis demonstrates that atracurium is slightly

cumulative, although not to a clinically important degree.

The authors thank Edmond I. Eger II, M.D. and James E. Caldwell M.B. for assisting with study design and interpretation of the data and Lewis Sheiner, M.D., Stuart Beal, Ph.D., and Alison Boeckman for assisting with the pharmacokinetic and pharmacodynamic modeling.

References

1. Savarese JJ, Kitz RJ: Does clinical anesthesia need new neuromuscular blocking agents? ANESTHESIOLOGY 42:236–239, 1975

2. Buzello W, Nöldge G: Repetitive administration of pancuronium and vecuronium (Org NC 45, Norcuron) in patients undergoing long lasting operations. Br J Anaesth 54:1151–1157, 1982

3. Ali HH, Savarese JJ, Basta SJ, Sunder N, Gionfriddo M: Evaluation of cumulative properties of three new non-depolarizing neuromuscular blocking drugs: BW A444U, atracurium, and vecuronium. Br J Anaesth 55:107S–111S, 1983

4. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P: Clinical pharmacology of ORG NC45 (Norcuron): A new nondepolarizing muscle relaxant. ANESTHESIOLOGY 55:6–11, 1981

5. Erkola O, Karhunen U, Sandelin HE: Spontaneous recovery of residual neuromuscular blockade after atracurium or vecuronium during isoflurane anaesthesia. Acta Anaesthesiol Scand 33:290–294, 1989

6. Fisher DM, Rosen JI: A pharmacokinetic explanation for increasing recovery time following larger or repeated doses of nondepolarizing muscle relaxants. ANESTHESIOLOGY 65:286–291, 1986

7. Meretoja OA, Wirtavuori K: Two-dose technique to create an individual dose–response curve for atracurium. ANESTHESIOLOGY 70:732–736, 1989

8. Neill EA, Jones CR: Determination of atracurium besylate in human plasma. J Chromatogr 274:409–412, 1983

9. Furuta T, Canfell PC, Castagnoli KP, Sharma ML, Miller RD: Quantitation of pancuronium, 3-desacetylpancuronium, vecuronium, 3-desacetylvecuronium, pipecuronium and 3-desacetylpipecuronium in biological fluids by capillary gas chromatography using nitrogen-sensitive detection. J Chromatogr 427:41–53, 1988

10. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin Pharmacol Ther 25:358–371, 1979

11. Yamaoka K, Nakagawa T, Uno T: Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 6:165–175, 1978

12. Caldwell JE, Szenohradszky J, Segredo V, Wright PMC, McLoughlin C, Sharma ML, Gruenke LD, Fisher DM, Miller RD: The pharmacodynamics and pharmacokinetics of the metabolite 3-desacetylvecuronium (ORG 7268) and its parent compound, vecuronium, in human volunteers. J Pharmacol Exp Ther (in press)

13. Hull CJ: A model for atracurium? (editorial). Br J Anaesth 55:95–96, 1983

14. Hughes MA, Glass PS, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. ANESTHESIOLOGY 76:334–341, 1992

15. Khuenl-Brady K, Mair P, Koller J: Antagonism of vecuronium by one of its metabolites in vitro. Eur J Pharmacol 222:153–156, 1992

16. Marshall IG, Gibb AJ, Durant NN: Neuromuscular and vagal blocking actions of pancuronium bromide, its metabolites, and ve-

curonium bromide (Org NC45) and its potential metabolites in the anaesthetized cat. Br J Anaesth 55:703–714, 1983

17. Bencini AF, Scaf AH, Sohn YJ, Meistelman C, Lienhart A, Kersten UW, Schwarz S, Agoston S: Disposition and urinary excretion of vecuronium bromide in anesthetized patients with normal renal function or renal failure. Anesth Analg 65:245–251, 1986

18. Parker CJ, Hunter JM, Snowdon SL: Effect of age, gender and anaesthetic technique on the pharmacodynamics of atracurium. Br J Anaesth 70:38–41, 1993

19. Cannon JE, Fahey MR, Castagnoli KP, Furuta T, Canfell PC, Sharma M, Miller RD: Continuous infusion of vecuronium: The effect of anesthetic agents. ANESTHESIOLOGY 67:503–506, 1987

20. Parker CJ, Hunter JM, Snowdon SL: Effect of age, sex and anaesthetic technique on the pharmacokinetics of atracurium. Br J Anaesth 69:439–443, 1992

21. Rupp SM, Fahey MR, Miller RD: Neuromuscular and cardiovascular effects of atracurium during nitrous oxide-fentanyl and nitrous oxide-isoflurane anaesthesia. Br J Anaesth 55:67S–70S, 1983

22. Vanderheyden BA, Reynolds HN, Gerold KB, Emanuele T: Prolonged paralysis after long-term vecuronium infusion. Crit Care Med 20:304–307, 1992

23. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD: Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 327:524–528, 1992

Appendix

Calculation of the Second Dose

The second dose is calculated assuming that the relation between dose and neuromuscular blockade can be expressed by the Hill equation:

$$effect = \frac{dose^\gamma}{ED_{50}^\gamma + dose^\gamma} \qquad (2)$$

where ED_{50} = the dose producing 50% block and γ = the Hill coefficient. Equation 2 can be rewritten as

$$ED_{50} = dose \times \left(\frac{1 - effect}{effect}\right)^{(1/\gamma)} \qquad (3)$$

or as

$$ED_{90} = ED_{50} \times 9^{(1/\gamma)} \qquad (4)$$

where ED_{90} = the dose producing 90% block.

To estimate a second dose likely to produce 90% block, we assume that γ equals 5, a value based on our previous studies.[6] Peak effect from the first dose is used to estimate the expected ED_{90}; a second dose equal to the difference between ED_{90} and the initial dose is then administered.

Dose–Response Calculations

Assuming that peak effect after the second dose is a result of the combined effects of the two doses (i.e., that the effect of the initial dose is minimally dissipated at the time of peak effect after the second dose), dose–response curves can be constructed for each individual. Although calculations to determine the second dose assumed that γ equals 5, this assumption is no longer necessary (although the validity of equation 2 must still be assumed). Equations 2 and 3 can be rewritten as:

$$ED_{50} = dose\ 1 \times \left(\frac{1 - effect\ 1}{effect\ 1}\right)^{(1/\gamma)} \qquad (5)$$

$$ED_{50} = (dose\ 1 + dose\ 2) \times \left(\frac{1 - effect\ 2}{effect\ 2}\right)^{(1/\gamma)} \qquad (6)$$

where effect 1 = the peak effect after the first dose (dose 1) and effect 2 = the peak effect after the second dose (dose 2). Equations 4 and 5 can be combined to determine γ:

$$\gamma = \frac{\log\left(\frac{effect\ 2/(1 - effect\ 2)}{effect\ 1/(1 - effect\ 1)}\right)}{\log\left(\frac{(dose\ 1 + dose\ 2)}{dose\ 1}\right)} \qquad (7)$$

Once γ has been determined, the dose producing 95% block (ED_{95}) can be estimated from equation 3 as

$$ED_{95} = ED_{50} \times 19^{(1/\gamma)} \qquad (8)$$