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Pharmacokinetics and Pharmacodynamics of Cisatracurium in Young and Elderly Adult Patients

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Background: **The effects of a muscle relaxant may differ in elderly compared with young adult patients for a variety of reasons. The authors compared the effects of a new muscle relaxant (cisatracurium) in young and elderly adults and used pharmacokinetic/pharmacodynamic modeling to identify factors explaining differences in time course of effect.**

Methods: **Thirty-one young (18–50 yr) and 33 elderly (>65 yr) patients anesthetized with nitrous oxide, isoflurane, and fentanyl were studied. Cisatracurium (0.1 mg/kg) was given after induction of anesthesia and later additional boluses of 0.025 mg/kg or an infusion of cisatracurium was given. Neuromuscular transmission was measured using the first twitch of the train-of-four response at the adductor pollicis after supramaximal stimulation of the ulnar nerve at 2 Hz every 15 s. Five venous blood samples were obtained for plasma drug concentration at intervals ranging from 2 to 120 min from every patient. Three additional samples were obtained from those who received an infusion. A population pharmacokinetic/pharmacodynamic model was fitted to the plasma concentration and effect data. The parameters of the model were permitted to vary with age to identify where differences existed between young and elderly adults.**

Results: **Onset of block was delayed in the elderly; values being mean 3.0 (95% confidence interval 1.75–11.4) min and 4.0 (2.4–6.5) min in the young and elderly, respectively ($P < 0.01$). Duration of action was similar in the two groups. Plasma clearance was 319 (293–345) ml/min in the study population and did not differ between young and elderly patients. Apparent volume of distribution was 13.28 (9.9–16.7) l and 9.6 (7.6–11.7) l in the elderly and young adults, respectively ($P < 0.05$). There also were differences in pharmacodynamic parameters between the young and elderly; the predominant change being a slower rate of biophase equilibration (k_{e0}) in the elderly (0.060 [0.052–0.068])/min compared with the young (0.071 [0.065–0.077]/min; $P < 0.05$).**

Conclusions: **The pharmacokinetics of cisatracurium differ only marginally between young and elderly adults. Onset is delayed in the elderly because of slower biophase equilibration. (Key words: Neuromuscular relaxants: cisatracurium. Pharmacokinetics, neuromuscular relaxants: cisatracurium.)**

CISATRACURIUM is one of the stereoisomers that make up atracurium. It appears to have similar effects as atracurium[1] and presumably has similar excretion. However, it is more potent than atracurium,[1] has a reduced tendency to release histamine,[2] and a greater autonomic:neuromuscular blocking ratio.[3] Therefore, the maximum safe dose may be greater than that of atracurium.

The clinical pharmacology of cisatracurium requires definition in those groups of patients to whom it may be administered. In this study, we observed the magnitude and time course of its neuromuscular-blocking effects in young and elderly adult patients receiving nitrous oxide, fentanyl, and isoflurane anesthesia. We also measured its concentration in plasma derived from venous blood on 5–8 occasions from each patient during a 2-h period and we used a population pharmacokinetic/pharmacodynamic model to study the observed differences between young and elderly patients.

Methods

After obtaining approval of the respective local Research Ethics Committees and informed consent of participants, we studied 64 patients of ASA physical status grades 1–3 whose ages were between 18 and 50 yr or older than 65 yr. Patients who had a history of problems during anesthesia, evidence of asthma, hepatic or renal impairment, or of recent ingestion of drugs known to effect neuromuscular transmission were excluded. Age, weight, height, gender, resting heart rate, and arterial

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blood pressure of the patients were recorded and venous blood was obtained to confirm normal hematologic and biochemical indices. Patients were premedicated with 10–30 mg temazepam by mouth according to clinical discretion.

Patients were anesthetized using 2–5 mg/kg thiopental and 1–2 μg/kg fentanyl followed by 60% nitrous oxide in oxygen with isoflurane at an end-tidal concentration of approximately 1% (this was reduced in approximately 10% of patients because of clinical necessity); isoflurane was given for >20 min before administration of the muscle relaxant. An intravenous cannula was placed in a large vein in a forearm before induction of anesthesia and crystalloid solution was infused. Electrocardiogram, oxygen saturation and finger arterial blood pressure (Finapres, Ohmeda) were continuously monitored. The ulnar nerve was stimulated using surface electrodes placed at the wrist. Supramaximal stimuli of 0.1 ms duration were delivered in a train-of-four at 2 Hz every 15 s. Preload was maintained at 180–210 g. The evoked twitch tension of the adductor pollicis muscle was measured with a calibrated force transducer, amplified, digitized, and recorded. Ulnar nerve stimulation was continued for a minimum of 15 min before muscle relaxant administration and until the value was stable. End-tidal carbon dioxide and isoflurane concentrations, heart rate, arterial blood pressure, and adductor pollicis twitch tension were stable for a minimum of 5 min before muscle relaxant administration. The amplitude of the first twitch in the train of four (T1) was taken as the control with which all subsequent responses were compared (T0).

Cisatracurium (0.1 mg/kg) was administered over 5 s into a rapidly running infusion in a large forearm vein. Additional doses of cisatracurium (0.025 mg/kg) were administered, if required, but only after at least 25% recovery of T1/T0. If more than 2 or 3 additional doses were required then cisatracurium was administered by intravenous infusion (8 patients), initially at 3 $\mu g\ kg^{-1}\ min^{-1}$, adjusted to maintain a detectable twitch response. At the end of the surgical procedure, recovery of neuromuscular block was left to the discretion of the investigator.

Venous blood was obtained to determine plasma cisatracurium concentrations according to a predetermined schedule, which varied among patients so that all possible combinations were represented. At least five samples were obtained in each patient; these being before muscle relaxant administration, at 2 or 3 min, at 6 or 8 min, at 30, 40, 50, or 60 min, and at 70, 80, 90, 100, or 120 min. Three additional samples were obtained from the eight patients who received an intravenous infusion of cisatracurium, these were at the termination of the infusion, at 25%, and at 75% recovery of neuromuscular transmission.

Blood samples were promptly iced and centrifuged. Plasma was acidified using 15 mM sulfuric acid and frozen for subsequent analysis using high-performance liquid chromatography. A Spherisorb strong cation exchange column was used and the cisatracurium was eluted with a mobile phase consisting of acetonitrile: 56 mM sodium sulfate in 0.5 mM sulfuric acid (6:4, vol/vol). Cisatracurium was detected using fluorescence detection with excitation at 202 nm and emission at 320 nm. The assay is sensitive to 10 ng/ml with a coefficient of variation of 15% at 15 ng/ml, 12.5% at 500 ng/ml, and 9% at 1500 ng/ml.

Neuromuscular transmission was monitored after administration of the muscle relaxant until complete recovery of neuromuscular function. The following variables were defined for each patient. Maximum suppression of T1 after the first dose of muscle relaxant (peak effect), time to maximum suppression of T1 after the first dose (onset), and time to 5% and time to 25% recovery of T1. In addition, the magnitude of T1 was determined at the time of each plasma concentration sample. These variables were compared between young and elderly patients using the Mann-Whitney *U* test or Fisher's exact probability test, where appropriate. They are reported as proportions or as medians with ranges.

Pharmacokinetic/Pharmacodynamic Modeling

Mixed effects pharmacokinetic/pharmacodynamic (effect compartment[4]) population models were fitted to the data from the study using an iterative nonlinear modeling program, NONMEM.[5] The mixed effects approach defines a single basic model of typical values (population means) for the pharmacokinetic and pharmacodynamic parameters. Variations in each individual from the basic model being defined by the use of a variable number of additional, user-defined, interindividual variability parameters, each defining a degree of variability in one or more of the basic parameters. For instance, clearance was modeled as:

$$\text{clearance} = Cl_{typical} \cdot \exp(\eta)$$

where clearance is the value for an individual, $Cl_{typical}$ is the typical value for the population, and η is a normally distributed random variable with mean zero. Both the basic model and the interindividual variability also

can be wholly or partially modeled as functions of physiologic covariates, the aim being to reduce the residual degree of interindividual variability. The basic parameters of the models used here were volume of the central compartment (V_1), volume of the peripheral compartment (V_2), clearance (elimination clearance equal to $V_1 \cdot k_{10}$) and distribution clearance (equal to $V_1 \cdot k_{12}$). Volume of distribution at steady state (V_{ss}) was equal to V_1 plus V_2. Models were fitted using NONMEM's first order method with which the exponential error model illustrated earlier is equivalent to a constant coefficient of variability error model.

We first tested two- and three-compartment pharmacokinetic models on plasma concentration data only; modeling was performed with and without normalization of the basic pharmacokinetic parameters for body weight. Because neither the three-compartment model nor weight normalization could be justified either visually or statistically, subsequent modeling was limited to a two-compartment model without normalization by body weight.[6] The population pharmacokinetic model was developed adding interindividual variation parameters until no further modeled variation could be justified. Next additional models were evaluated, each permitting one pharmacokinetic parameter to vary with gender. The justification for each additional effect added to the model was for it to improve the goodness of fit statistic (-2 log likelihood) by >3.8 (evaluated against the χ^2 distribution, this is equivalent to significance at the 0.05 level), and to result in a visual improvement in the goodness of fit. Using the same justification criteria, further models, each permitting one pharmacokinetic variable to vary with age (as a dichotomous variable), were tested.

After the pharmacokinetic model had been determined, we obtained Bayesian estimates of each person's pharmacokinetic parameters using NONMEM's *post hoc* step. These values were incorporated into NONMEM's input to enable the development of a population pharmacodynamic model. The model was fitted to twitch tension (T1) data corresponding with the plasma concentration data, an additional two data points during onset and the data for 5% and 25% recovery of T1. Twitch tension data after the administration of neostigmine were not included. Effect was modeled to follow a sigmoid relationship to a maximum value as muscle relaxant concentration in a hybrid effect compartment increased. The effect compartment was of minimal volume but with its own rate constant (k_{e0}). As before, interindividual variation parameters were introduced and covariation with physiologic values was modeled as justified. The process of testing for an effect of age (as a dichotomous variable) was repeated for the three pharmacodynamic parameters k_{e0}, C_{50} (the plasma concentration at steady state resulting in 50% effect), and γ (the parameter determining the sigmoidicity of the concentration/effect relationship).

For drugs eliminated from both central and peripheral compartments, volume of distribution is underestimated by a model having elimination from the central compartment only. To obtain an estimate of this underestimation we redefined our pharmacokinetic model using a naive pooled data approach, without any covariate effects, and obtained parameter estimations (the traditional model). We then introduced elimination from the peripheral compartment by permitting an elimination rate constant from the peripheral compartment set to a value obtained from *in vitro* observation of the degradation of cisatracurium in the plasma of nine healthy volunteers (0.0237/min)‖ and obtained fresh parameter estimations. This model gave identical estimates of clearance, central volume of distribution, and an identical goodness of fit statistic compared with the traditional model and also a rate constant of elimination from the central compartment that was greater than that from the peripheral compartment. We compared the volume of V_2 with that from the traditional model. This yielded a factor by which the apparent volume of distribution could, typically, be multiplied to give the 'true' estimation. This method cannot be used with mixed effects modeling because the average value that we used for the rate constant of peripheral elimination results in greater clearance by spontaneous degradation than total clearance in some persons.

Pharmacokinetic and pharmacodynamic parameters are reported as population means (typical values) with the 95% confidence interval for the estimate of the mean, where appropriate variability of a parameter within the population is indicated as a coefficient of variability.

Results

Thirty-one patients were studied in the 18–50 yr age range (young group) and 33 were studied in the >65 yr age range (elderly group). The age, weight, height, and gender distributions of the two groups are given in table 1.

‖ Schmith G: Personal communication. 1995.

Table 1. Age, Weight, Height (Mean ± SD), and Gender Distribution for Young and Elderly Patients

	Young Adult	Elderly Adult
Age (yr)	36 ± 9	74 ± 6
Weight (kg)	73 ± 16	70 ± 12
Height (cm)	168 ± 9	166 ± 10
Gender distribution (M:F)	9:22	19:14

Magnitude and Time Course of Effect

Young patients developed a marginally more intense block than the elderly patients after the first dose of muscle relaxant (peak effects of median 99% (range 96–100%) and 98% (91–100%) in young and elderly, respectively ($P < 0.05$)). Time to maximum block was more rapid in the young patients compared with the elderly patients, values being 3.0 (1.75–11.4) min and 4.0 (2.4–6.5) min ($P < 0.001$). Duration of neuromuscular block after the first dose of cisatracurium was similar in the two age ranges but with greater variability in the elderly patients. Times to 5% recovery of T1 were 39.5 (28.7–54.0) min and 39.4 (17.0–64.0) min in young and elderly (n = 31) patients respectively, corresponding times to 25% recovery of T1 were 50.0 (37.6–64.0) min and 51.4 (32.0–73.0) min.

Pharmacokinetic/Pharmacodynamic models

A two-compartment pharmacokinetic model, with interindividual variation modeled in clearance and in V_{SS}, was accepted. Of the additional parameters tested (to model an effect of either gender or age on any of the basic pharmacokinetic parameters) only one was justified. When peripheral volume of distribution was permitted to vary with age there was a statistically significant and visual improvement in the goodness of fit, and the value determined (a 37% increase in peripheral volume of distribution in the elderly compared with the young) was unequivocally different from zero. The values of the pharmacokinetic parameters thus determined using the plasma concentration data only are in table 2. The V_{SS} is typically underestimated by a factor of 1.55, this underestimation occurs entirely in the peripheral compartment which is typically underestimated by a factor of 1.94.

Based on the final pharmacokinetic model, a combined pharmacokinetic/pharmacodynamic model was developed that permitted interindividual variation in both k_{e0} and C_{50}. Examination of a plot of individual values for k_{e0} against age indicated that there was a reduction in k_{e0} with age (fig. 1). When this effect was added to the model there was a highly significant and visual improvement in the fit of the model, and the value of the difference in k_{e0} between elderly and young patients was unequivocally different from zero. Examination of a plot of individual predicted values of C_{50} against weight (fig. 2) indicated that it varied with weight. A parameter added to the model to permit C_{50} to vary with weight in a linear fashion produced a

Table 2. Pharmacokinetic and Pharmacodynamic Parameters Determined in a Population Model Fit to Plasma Concentration Data and Subsequently to Effect Data

	Coefficient of Variation* (% of typical value)	Typical Population Values	
		Young Adults	Elderly Adults
Plasma clearance (Cl, ml/min)	23	319 (293–345)	
Central volume of distribution (V_1, L)		4.76 (3.71–5.81)	
Volume at steady state (V_{SS}, L)†,‡,§	34	9.7 (7.6–11.8)	13.3 (9.9–16.7)
$T_{1/2}\alpha$ (min)		4.20	4.50
$T_{1/2}\beta$ (min)		28.4	36.3
Effect site equilibration (k_{e0}, min^{-1})†,‡	57	0.071 (0.066–0.077)	0.060 (0.052–0.068)
Potency (C_{50}, ng/ml)†,¶	89	98 (87–110)	90 (72–109)
Sigmoidicity (γ)†,‡		4.1 (3.9–4.3)	3.7 (3.4–4.1)

Values are population means with 95% confidence intervals.

* This is residual unexplained variability expressed as a percentage of the typical value; approximately 95% of the population lies between the typical value minus twice this value and the typical value plus twice this value.

† Rendered a significant improvement in the goodness of fit of the model when permitted to vary between the age groups.

‡ Values of difference in elderly and young unequivocally different from zero using 95% confidence interval.

§ Apparent volume of distribution at steady state (V_{SS}) typically underestimates "true" volume of distribution by a factor of 1.55 as a consequence of peripheral elimination of drug.

¶ The value quoted is for a 70-kg individual. C_{50} increases with body weight (10% of the value given for each 10 kg).

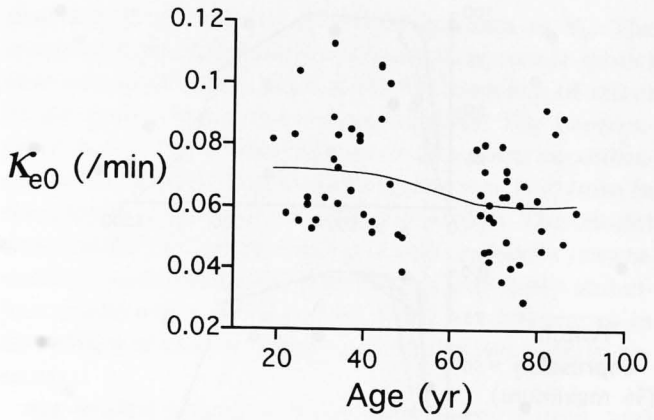

Fig. 1. A plot of individual values for the rate constant associated with the effect compartment (k_{e0}) against age from a model that did not permit k_{e0} to vary with age. The line is a "smooth" intended to assist in the interpretation of the plot. On the basis of this plot a factor was introduced to the model permitting k_{e0} to vary with age.

highly significant improvement in the goodness of fit statistic, therefore, this parameter was accepted. Parameters introduced to permit C_{50} and γ to vary with age also both produced significant improvements in the goodness of fit and were also accepted. Gender had no demonstrable effect on any of the pharmacodynamic parameters. The values of the pharmacodynamic parameters thus determined are given in table 2.

Goodness of Fit and Predictive Value of the Model

The median residual error for plasma concentration (observed value—predicted value/predicted value) was 9.1%. The time course of these residual errors had no relationship with time (fig. 3). The median residual error for prediction of twitch depression (observed value—expected value) was 2.7% of the control value, and the time course of these residual errors also is given in figure 4. Examples of the time course of predicted and observed plasma concentration, predicted and observed twitch depression, and corresponding plasma concentration/effect and effect site concentration/effect loops for three representative patients are in figure 5. In general, the model was capable of explaining well both plasma concentration and effect data for single bolus, multiple bolus, and infusion regimens. The pharmacodynamic model gave a visually satisfactory collapse of the plasma concentration/effect relationship for each person studied. Typical time course of effect predictions for young and elderly patients of average weight (70 kg) are given in table 3.

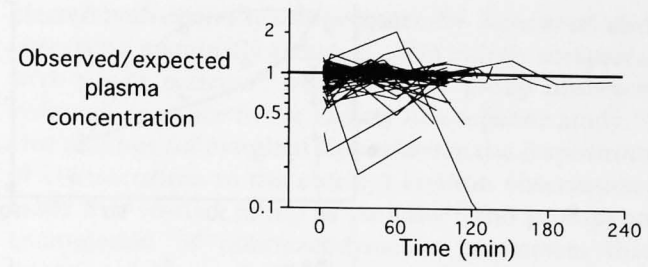

Fig. 3. The time course of residual plasma concentration values plotted as observed value/predicted value. All points are plotted and the values for an individual are joined by a line.

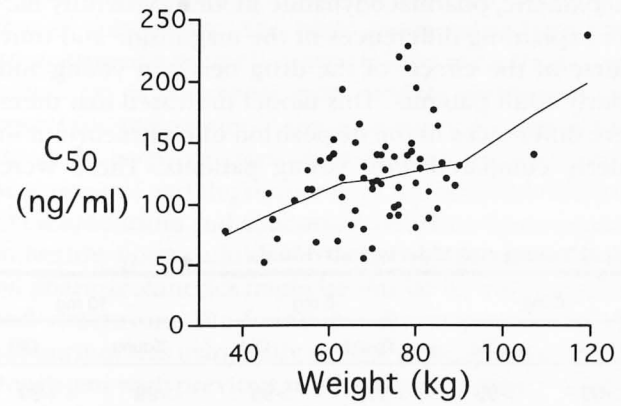

Fig. 2. A plot of individual values for the plasma concentration at steady state resulting in 50% effect (C_{50}) against weight from a model that did not permit C_{50} to vary with weight. The line is a "smooth" intended to assist in the interpretation of the plot. On the basis of this plot a factor was introduced to the model permitting C_{50} to vary with weight.

Discussion

In this study, we have observed the effect of a bolus dose of 0.1 mg/kg cisatracurium on the time course and magnitude of neuromuscular blockade at the ad-

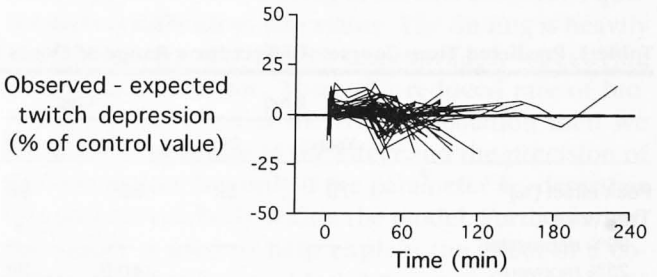

Fig. 4. The time course of residual twitch depression values plotted as observed value − predicted value. All points are plotted and the values for an individual are joined by a line.

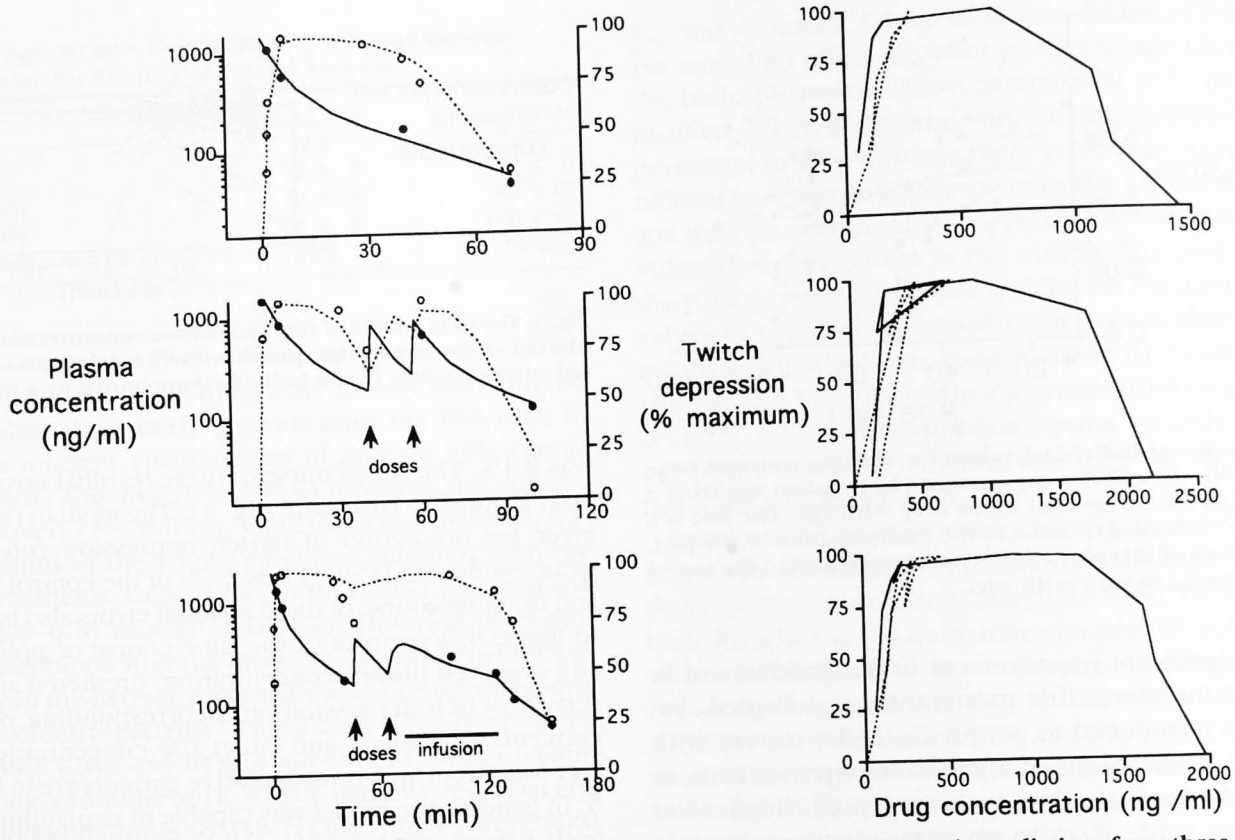

Fig. 5. Representative plots of the goodness of fit for the pharmacokinetic and pharmacodynamic predictions from three persons. (*Top*) A person who received a single bolus dose, (*middle*) a person who received multiple bolus doses, and (*bottom*) a person who received both bolus and infusion doses. (*Left*) The time course of predicted (solid lines) and observed (solid circles) plasma concentration and predicted (broken lines) and observed (open circles) twitch depression data. (*Right*) Corresponding plasma concentration/effect loops and effect site concentration/effect loops.

ductor pollicis. A bolus dose of cisatracurium caused marginally greater neuromuscular block in young compared with elderly patients and the block developed more slowly in the elderly. However the duration of neuromuscular block was similar in the young and elderly patients.

We also observed, using infrequent blood samples, the plasma concentration profile of cisatracurium after the initial bolus and a variety of different subsequent dosing regimens. We developed a population pharmacokinetic/pharmacodynamic model to identify factors explaining differences in the magnitude and time course of the effects of the drug between young and elderly adult patients. This model indicated that there were differences in the disposition of cisatracurium in elderly compared with young patients. These were

Table 3. Predicted Time Course of Effect for a Range of Doses in Typical Young and Elderly Individuals

	2 mg		4 mg		6 mg		8 mg		10 mg	
	Young	Old	Young	Old	Young	Old	Young	Old	Young	Old
Peak effect (%)	70	59	98	96	>99	>99	>99	>99	>99	>99
Time (min) to:										
99% depression	—	—	—	—	6	8.75	3.75	4.75	2.75	3.25
25% recovery			40.5	38	56	55.5	67	68.5	76	79
75% recovery	34.5	32	61	61	77	80.5	88	95	97	106
25–75% recovery time			20.5	23	21	25	21	26.5	21	27

manifest in the model as a 37% increase in V_2. The combined pharmacokinetic/pharmacodynamic model also indicated differences in the relationship of effect of the drug to its plasma concentration. The predominant factor was a reduced rate of effect site equilibration in the elderly (k_{e0} being reduced to 0.060/min in the elderly from 0.071/min in the young). This model was capable of explaining well each person's cisatracurium concentration against time relationship and effect against time relationship and also differences in the effects of the drug between young and elderly patients.

Age-related changes in the response to a drug, and the reasons behind such changes, are important in determining clinical practice. This is true for muscle relaxants. Our observation of a delay in onset (and slightly reduced effect) after a dose of muscle relaxant sufficient to ablate the twitch response has been previously documented with other relaxants, including pancuronium,[7] *d*-tubocurarine, and metocurine.[8] However, in contrast to our study these authors all reported an increased duration of action consequent from reduced clearance of the muscle relaxant. Bell *et al.* studied subparalyzing doses of atracurium, vecuronium, and pancuronium[9] and with each noted reduced effect in the elderly (although the power of their study was insufficient for firm conclusions). All these previous observations are in keeping with our findings and may be explained by the pharmacokinetic and pharmacodynamic changes with age.

Because cisatracurium is only one of several stereoisomers making up atracurium, its pharmacokinetics might be expected to be similar but not identical to that of atracurium. The basic model used here (two compartments with elimination from the central compartment) is consistent with models previously proposed for atracurium,[10] the absence of weight dependence in its parameters also has been suggested with atracurium[11] and the similarity of the pharmacokinetics of cisatracurium and atracurium has been demonstrated in healthy young adults.[12,13] Similarly, the effect of age on pharmacokinetics might be similar for cisatracurium and atracurium. We found that the disposition of cisatracurium was marginally altered with age, this is again consistent with previous studies of atracurium.[14,15] Kitts *et al.* observed a decrease in the organ-based clearance of atracurium and a slight increase in the V_{SS} in elderly patients.[15] However, the control subjects were historical and, as in this study, their model was subject to difficulties in the estimation of V_{SS} with a drug that is cleared both centrally and peripherally. Kent *et al.* also observed a marginally greater $T_{1/2}\beta$ in elderly compared with young patients[16] and the same group observed reduced clearance in the elderly in a separate study.[17] Our findings (of marginal alterations in the disposition of cisatracurium in the elderly) confirm observations made in a smaller group of patients[12] and prompt an examination of pharmacodynamic parameters that might explain the changed time course of effect.

There are three factors that can be used to explain the relationship of effect to plasma concentration with a muscle relaxant.[4] One to describe the rate of equilibration between the plasma and the neuromuscular junction (k_{e0} with a compartmental model such as we used); another to describe the potency of the drug in concentration *versus* effect terms (with our model C_{50}, being the concentration in the neuromuscular junction producing 50% twitch depression); the third (γ) describes the sigmoidicity of the concentration *versus* effect curve. For cisatracurium, the predominant finding was reduced rate of biophase equilibration in elderly patients. This was manifest as a decrease in k_{e0} by 16%. This explains the delayed onset of block in the elderly and, given that slower biophase equilibration results in a delayed and reduced peak concentration of drug at the effect site, it also explains the marginally reduced effect seen in the elderly. With reduced rate of biophase equilibration increased duration of action would be expected. However, the increased peripheral volume of distribution, which, after a single dose, would result in decreased duration of action has an opposite effect. Consequently, duration of action is similar in the two age ranges.

These pharmacodynamic changes with age are consistent with those found with other drugs (slower biophase equilibration has previously been noted for atracurium[18] and for rocuronium[19]). However, with this modeling approach the degree of confidence that can be placed in the finding of slowed biophase equilibration is difficult to determine. The finding is heavily dependent on the model appropriately specifying physiologic behavior. Thus, if a reduced rate of biophase equilibration is the true explanation then we know the magnitude of the effect and the precision of this estimation, but only if the parameter k_{e0} describes this process correctly within the model. Further, when the model is used to help explain the effect of a covariate (such as being elderly) we must first decide if a parameter modeling for the effect is justified. With NONMEM, this is determined by hypothesis testing us-

ing the −2 log likelihood statistic. Whether or not the effect selected provides the true explanation remains unknown. Hence, although our model indicated that, of the three pharmacodynamic factors, only k_{e0} varied substantially between young and elderly patients, it is possible to propose other explanations. For example, resistance to the drug (increased C_{50}) in the elderly also could explain our data (although not quite so well), and would better explain the observation of Bell *et al.* of similar times to peak effect for subparalyzing doses of atracurium, pancuronium, and vecuronium in the elderly compared with the young.[9] Alternatively, if the elderly are more sensitive to the drug a still larger reduction in their rate of biophase equilibration also could explain our findings.

There are some difficulties with modeling the pharmacokinetics of cisatracurium that complicate the interpretation of our findings. Cisatracurium (and atracurium) are drugs that are cleared not only from the compartment in which they are sampled (the plasma) but also peripherally. For these drugs, the structure of the mamillary model in which clearance takes place only from the central compartment does not reflect physiologic facts. This misspecification leads to underestimation of the volume into which the drug is truly distributed. Therefore, no inference from the value of V_{ss} we report should be made regarding what it represents in physiologic terms. Thus, our model indicated a difference in the size of V_{ss} between young and elderly patients: physiologically, this might represent true change in V_{ss} or a change in the relative magnitude of clearance by the spontaneous and metabolic routes. We found minimal differences in the disposition of cisatracurium between young and elderly patients and so these concerns are less important. The compartmental model in this setting is merely a tool describing the time course of the plasma concentration thus enabling the development of a pharmacodynamic model and for this purpose it is adequate.[10]

A second reservation involves our finding of an increase in C_{50} with weight. This is unexpected and we can suggest three possible explanations. First, and least likely, is that it represents a true finding. Second, that it is a representation in the pharmacodynamics of a subtle weight-related change in the pharmacokinetic parameters that we were unable to model. Such a reason also is unlikely because examination of a plot of residual error in plasma drug concentration (Cp) against weight would be expected to show a trend with weight, which it does not (fig. 6). Third, because pharmacokinetic parameters are not related to weight, but patients received a weight-related dose, then patients with greater weight systematically received a greater dose. The weight-related increase in C_{50} might therefore be a representation of a subtle nonlinearity of response. Modeling was carried out with and without this factor and its presence made marginal impact on the findings of increased volume of distribution and decreased rate of biophase equilibration in the elderly.

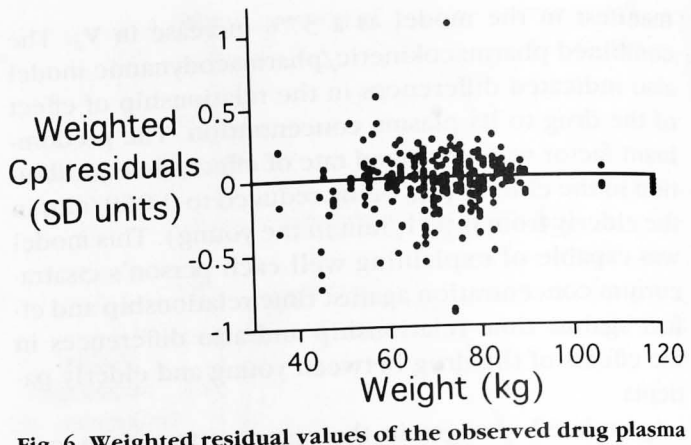

Fig. 6. Weighted residual values of the observed drug plasma concentration plotted against weight. There is no pattern; this suggests that the pharmacokinetics are truly unrelated to weight.

Some final comments that must be made about the interpretation of our findings also relate to the potency estimates. First, the study was performed using isoflurane anesthesia, which potentiates muscle relaxants and our pharmacodynamic model is therefore specific to such anesthesia. We administered isoflurane for 20 min before cisatracurium administration, which is adequate time for the potentiating effect to appear.[20] Second, we used sparse venous sampling to maximize the study sample. However, rapid early arterial sampling would have given improved confidence in the determination of muscle relaxant potency, likely giving increased estimates of C_{50} (reduced potency). Despite these reservations, our model was capable of describing well the time course and degree of effect, although our pharmacodynamic model is specific to this particular pharmacokinetic model and should not be used with pharmacokinetic models derived using different methods.

The implications of this study may be reassuring to the clinician. The predominant determinant of duration of action with a muscle relaxant is its pharmacokinetic profile. For cisatracurium, this is minimally altered in the elderly compared with the young. Because of de-

layed biophase equilibration a similar dose of cisatracurium given to a elderly person will have marginally less profound effect with marginally slowed onset compared with a young person but otherwise the effects will be indistinguishable in the elderly compared with the rest of the adult population.

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