

Concentration–Effect Relationship of Cisatracurium at Three Different Dose Levels in the Anesthetized Patient

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Background: The linearity of cisatracurium elimination and its concentration–effect relation were determined as part of a traditional rich data study with three dose levels in patients receiving balanced anesthesia.

Methods: Forty-eight adults with American Society of Anesthesiologists status I–II were randomized to receive an intravenous bolus dose of 0.075, 0.15, or 0.30 mg/kg cisatracurium. Anesthesia was induced and maintained with nitrous oxide–oxygen, propofol, and fentanyl. The mechanical response of the adductor pollicis muscle was recorded. Arterial blood samples were collected over 8 h. Cisatracurium, laudanosine, and the monoquaternary alcohol concentrations were measured by high-performance liquid chromatography. To assess the relative contribution of the input function, a parametric (assuming elimination from both the central and peripheral compartments) and a nonparametric pharmacokinetic–pharmacodynamic model were both applied to data.

Results: Dose proportionality of the body disposition of cisatracurium and its two major metabolites at doses up to 0.30 mg/kg was confirmed. With the parametric approach, the effect compartment concentration at 50% block (EC_{50}) significantly increased with the dose (136 vs. 157 vs. 209 ng/ml), whereas the effect compartment equilibration rate constant decreased (0.0675 vs. 0.0568 vs. 0.0478 min^{-1}). A similar dose-dependent effect of the pharmacokinetic–pharmacodynamic relation was observed with the nonparametric approach, but the trend was 50% less pronounced.

Conclusion: A dose-related change in pharmacokinetic–pharmacodynamic parameters was identified with both modeling approaches. A pharmacokinetic origin was ruled out, although no definite explanation of the underlying mechanism could be provided. These findings suggest that doses relevant to the anesthetic practice be used for estimation of EC_{50} .

THE pharmacokinetics of cisatracurium has been well characterized in healthy adults and different subpopulations using traditional rich data studies (> 10 blood samples drawn with gradually increasing intervals)^{1–7} and sparse sampling, population-based studies.^{8–11} The rate-limiting step in the metabolism of cisatracurium is

Hofmann elimination, an organ-independent pathway.^{5,12} Cisatracurium pharmacokinetic behavior in response to variation in dose is thus expected to be linear, as was shown for doses of 0.1 and 0.2 mg/kg in a traditional rich data study⁴ as well as in a population-based pharmacokinetic study for doses ranging from 0.1 to 0.4 mg/kg.⁹

Using a population pharmacokinetic–pharmacodynamic (PK-PD) model,¹⁰ the demographic factors affecting the concentration–effect relation of cisatracurium were characterized, and various subgroups of the population were identified. Other investigators have also reported PK-PD studies in single-dose traditional or multiple–single-dose population analysis.^{3,7,8} However, the effect of the dose on PK-PD parameters estimation (effect compartment concentration at 50% block [EC_{50}], effect compartment equilibration rate constant [k_{co}], and slope factor [γ]) has never been examined in a dose-ranging setting for cisatracurium.

The objectives of the current study were to confirm the dose proportionality of the pharmacokinetics of cisatracurium and its major metabolites after intravenous bolus doses of 0.075, 0.15, and 0.3 mg/kg (equivalent to 1.5, 3, and 6 \times ED_{95}) and to compare the PK-PD parameters at these three different dose levels.

Methods and Materials

Patients

This study protocol was approved by the Ethics Committee of the University of British Columbia (Vancouver, British Columbia, Canada). Written informed consent was obtained from each patient before entry in the study. Forty-eight adult patients with American Society of Anesthesiologists status I or II, aged 18 to 65 yr, who were scheduled for a low-risk surgical procedure participated in our study (table 1). Patients had a normal hepatic and renal function and were free of clinically significant psychiatric, neurologic, neuromuscular, or cardiovascular diseases. Female patients were nonpregnant and nonlactating as confirmed by a negative pregnancy test within 48 h before surgery and were practicing a method of contraception for at least 3 months before the study, if necessary.

Patients were randomized in a double-blind manner into three dosing groups to receive a bolus dose of cisatracurium at 0.075, 0.15, or 0.30 mg/kg. These doses approximated 1.5, 3.0, and 6.0 times the ED_{95} reported

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Table 1. Patients Demographics and Pharmacodynamic Response

	Dose (mg/kg)			P Value
	0.075	0.150	0.300	
Demographics				
Gender M/F	13/2	15/1	16/1	0.699
Age (yr)	53 ± 14	58 ± 5	53 ± 14	0.941
Weight (kg)	80 ± 15	79 ± 14	84 ± 17	0.614
ASA physical status I/II	9/6	1/15	2/15	0.0008
Pharmacodynamic parameters				
n	14	15	15	
Onset (min)	4.8 ± 2.3	2.4 ± 0.6	1.8 ± 0.5	< 0.0001
Max block (%)	99.2 ± 2.4	99.3 ± 2.6	100.0 ± 0.0	0.133
Recovery times (min)				
25% block	35.3 ± 5.8	58.9 ± 10.4	81.5 ± 15.4	< 0.0001
50% block	40.4 ± 6.3	64.9 ± 12.0	88.6 ± 17.1	< 0.0001
75% block	48.0 ± 7.0	71.5 ± 14.2	95.6 ± 16.4	< 0.0001

Data are presented as mean ± SD.

ASA = American Society of Anesthesiologists; onset = time to maximum neuromuscular block; max block = magnitude of maximum neuromuscular block.

in adults who received barbiturate, nitrous oxide–opioid anesthesia.^{13,14} Randomization was performed using sealed envelopes containing the dose attributed for each patient. Envelopes were opened, and the drug dose was drawn by an independent individual, keeping the investigators blinded.

Anesthesia

Patients were premedicated with oral diazepam (5–10 mg) 1 h before surgery. A peripheral intravenous catheter was inserted on arrival in the operating room for administration of balanced salt solution (10 ml/kg) to compensate for the fasting deficit and for subsequent intravenous anesthetic agents. Monitoring included electrocardiogram, invasive blood pressure, pulse oximetry, and end-tidal respiratory gases. While patients were breathing 100% O₂ through a mask for 5 min, anesthesia was induced with a loading dose of 1.5–2.5 mg/kg propofol and 1–2 µg/kg fentanyl. An arterial catheter with a sampling port close to the puncture site (dead space of 0.2 ml) was inserted in the same forearm as the intravenous catheter. Positive pressure ventilation was provided with 100% O₂ during calibration of the neuromuscular force transducer. Three minutes after loss of eyelash reflex, the randomized dose of 0.075, 0.15, or 0.3 mg/kg cisatracurium was blindly administered as a bolus dose given over 5 s through the intravenous line. Tracheal intubation was performed 60–120 s later. Anesthesia was maintained with continuous infusions or bolus doses of propofol (50–250 µg · kg⁻¹ · min⁻¹) and fentanyl (0.02–0.05 µg · kg⁻¹ · min⁻¹) titrated to maintain an adequate level of anesthesia while patients received mechanical ventilation of a 70:30 mixture of nitrous oxide:oxygen.

For calibration purposes, baseline measurements of twitches were recorded for 2 min after induction. If additional neuromuscular block was deemed necessary,

maintenance doses of vecuronium were administered after T₁ had recovered to at least 25% of baseline. Conversely, edrophonium or neostigmine and atropine were administered for reversal of the neuromuscular block.

Neuromuscular Monitoring

Neuromuscular monitoring was performed using a mechanomyograph (Myograph 2000, Biometer International, Odense, Denmark) or a Grass FT10 force transducer (Grass Instruments, Quincy, MA) to record the mechanomyographic isometric twitch response of the adductor pollicis, with a preload of 200–300 g, to train-of-four supramaximal stimulation of the ulnar nerve at 10-s intervals. The mechanomyographic apparatus was connected to the patient before induction of anesthesia, and the calibration sequence was completed after loss of consciousness according to criteria for Good Clinical Research Practice.¹⁵ Single stimuli at 1 Hz were administered for 3 min for stabilization before switching to train-of-four stimulation (2 Hz every 10 s) before cisatracurium administration. The arm used for neuromuscular monitoring was kept warm (peripheral skin temperature ≥ 32°C and esophageal temperature ≥ 35°C).

The first twitch (T₁) and the ratio of the fourth to the first twitch (T₄/T₁) were recorded. Onset time was defined as the time to reach maximum block. Assessments of recovery (times to T₁ 25, 75, 90, and 95% and train-of-four 0.7) were made using the final mechanomyographic baseline as a reference to calculate neuromuscular recovery.

Blood Sampling

Arterial blood samples (5 ml) were collected in chilled 7-ml heparinized vacutainer tubes before and at 1, 2, 3, 4, 6, 8, 10, 12, 15, 20, 25, 30, 45, 60, 90, 120, 180, 240, and 480 min after administration of cisatracurium. The blood was immediately transferred into chilled micro-

centrifuge tubes for a 45-s centrifugation. Within 2 min and 10 s of the sample collection, the plasma was transferred in precooled polypropylene tubes containing 25 μ l sulfuric acid 2 M for each milliliter of plasma. The plasma samples were then stored at -70°C until analysis.

High-performance Liquid Chromatography Analysis

Plasma concentrations of cisatracurium, laudanosine, and the monoquaternary alcohol metabolite were determined using high-performance liquid chromatography on a Spherisorb Strong cation exchange column (Phenomenex, Torrance, CA) coupled with a fluorescent detector set at 280 nm (excitation) and 320 nm (emission) after extraction on a phenyl solid-phase cartridge. The method published by Bryant *et al.*¹⁶ for urine samples was slightly modified and fully validated in our laboratory. The assay proved to be sensitive and linear over the range of 5–2,500 ng/ml for cisatracurium and 2–1,000 ng/ml for the metabolites. The coefficients of variation for within- and between-run precision were less than 8%. The accuracy was $99 \pm 9\%$ for cisatracurium, $101 \pm 2\%$ for laudanosine, and $100 \pm 1\%$ for the monoquaternary alcohol. The monoquaternary acid and tetrahydropapaverine metabolites did not interfere with their analysis.

Pharmacokinetic Analysis

According to the Akaike information criterion, the pharmacokinetics of a bolus dose of cisatracurium was best described by a two-compartment model.¹⁷ Each patient's plasma concentration–time profile was analyzed using two approaches: when assuming central elimination only¹⁸ and when assuming elimination from both the central (k_{10}) and peripheral (k_{20}) compartments, as previously described by Nakashima and Benet.¹⁹ A weighting function of $1/(\text{predicted } y)^2$ was applied. Point estimates and parameters were optimized for each patient using a standard minimization method (Gauss-Newton, Levenberg, and Hartley). WinNonlin 1.1 software (Scientific Consulting Inc. WinNonlin, Cary, NC) was used for pharmacokinetic analysis.

Since Hofmann elimination is the major metabolic pathway for cisatracurium,⁵ the mean *in vitro* degradation rate in human plasma published by Welch *et al.*¹² was substituted for the elimination rate constant from the peripheral compartment ($k_{20} = 0.0237 \text{ min}^{-1}$). Exit-site-independent pharmacokinetic parameters (A , α , B , β) were determined using a standard formula. The following parameters were calculated as:

$$Cl_t = V_1 \cdot (k_{10} + (k_{12} \cdot k_{20}) / (k_{20} + k_{21}));$$

$$V_{SS} = V_1 \cdot (1 + (k_{12} / (k_{20} + k_{21})))$$

and as previously described by Fisher *et al.*²⁰:

$$Cl_{org} = V_1 \cdot k_{org} = V_1 \cdot (k_{10} - k_{20}).$$

Exit-site-dependent pharmacokinetic parameters (k_{10} , k_{12} , k_{21}) were also generated.

Noncompartmental pharmacokinetic analysis was conducted for laudanosine and the monoquaternary alcohol metabolite. The area under the curve ($AUC_{0 \rightarrow \infty}$), the maximum plasma concentration (C_{max}), and the elimination rate constant (k_{el}) were calculated using standard formulae.¹⁸

Pharmacokinetic-Pharmacodynamic Analysis

Parametric Approach. Using the pharmacokinetic parameters previously derived for cisatracurium, a simultaneous PK-PD link model²¹ with a sigmoid E_{max} model was used to derive the k_{co} , EC_{50} , and γ . The time to peak concentration in the effect compartment (t_{ECmax}) was derived. A weighting function of 1 was applied. WinNonlin software was used for all PK-PD analyses. Goodness of fit was assessed by the Akaike information criterion.

Nonparametric Approach. A second analysis was performed to verify if a bias was introduced by the input function of the parametric pharmacokinetic model (monotonic decay in the first minute). With this approach, time zero concentration was fixed to zero, and no interpolation of plasma concentrations was made between 0 and 1 min. For the first minute and thereafter, pharmacokinetic parameters derived with the two-compartment model were used to simulate the plasma concentrations at times corresponding to pharmacodynamic measurements. PK-PD parameters were then derived according to the method of Unadkat *et al.*²² with the input of time, its corresponding plasma concentration, and percentage of neuromuscular block. The t_{ECmax} was compiled and goodness of fit assessed by the Akaike information criterion.

Statistical Analysis

Data are presented as mean \pm SD. Between-group comparisons of demographic parameters were made us-

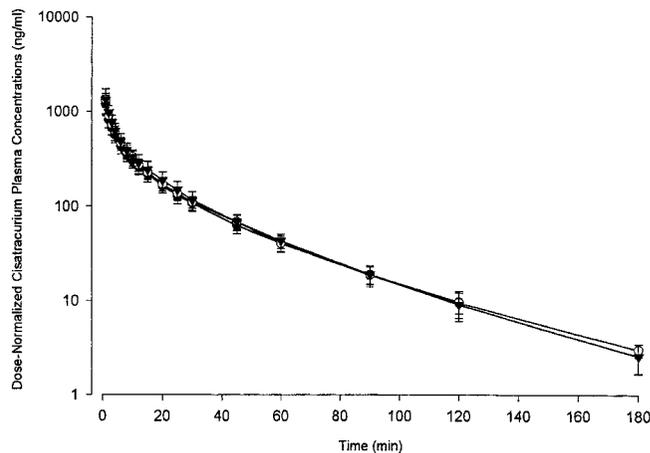


Fig. 1. Mean dose-normalized cisatracurium plasma concentration-versus-time curves for healthy adults after a single intravenous dose of 0.075 mg/kg ($n = 15$; black circles), 0.150 mg/kg ($n = 16$; white circles), and 0.300 mg/kg ($n = 17$; triangles).

Table 2. Two-compartment Model with Elimination from Both Central and Peripheral Compartments: Exit-site-independent Parameters of Cisatracurium

	0.075 mg/kg (n = 15)	0.150 mg/kg (n = 16)	0.300 mg/kg (n = 17)	P Value
A (ng/ml)	1,004 ± 281	2,171 ± 381	4,504 ± 1,806	
B (ng/ml)	251 ± 40	509 ± 74	969 ± 179	
α (min ⁻¹)	0.234 ± 0.0060	0.222 ± 0.040	0.208 ± 0.071	0.468
β (min ⁻¹)	0.0282 ± 0.0023	0.0281 ± 0.0032	0.0267 ± 0.0032	0.254
V ₁	63.2 ± 17.0	54.8 ± 11.5	60.3 ± 11.1	0.212
AUC/D (min · kg · ml ⁻¹)	0.1326 ± 0.0209	0.1409 ± 0.0179	0.1453 ± 0.0269	0.284
Cl _T (ml · min ⁻¹ · kg ⁻¹)	5.77 ± 0.96 (4.61–7.84)	5.24 ± 1.05 (2.45–7.15)	5.27 ± 1.08 (3.96–8.28)	0.281

Data are presented as mean ± SD (range).

A = plasma concentration at t₀ corresponding to the extrapolation from the distribution curve; B = plasma concentration at t₀ corresponding to the extrapolation from the elimination curve; α = initial distribution rate constant; β = terminal elimination rate constant; V₁ = volume of distribution in the central compartment; AUC/D = dose-normalized area under the curve; Cl_T = total clearance.

ing the chi-square analysis and Kruskal-Wallis one-way analysis of variance on ranks, when appropriate. Between-group comparisons of pharmacokinetic and pharmacodynamic parameters were made with one-way analysis of variance or Kruskal-Wallis when normality or homoscedasticity tests failed. The Student-Newman-Keuls test (parametric) or the Dunn test (nonparametric) was used for multiple comparisons between groups. The paired *t* test was used to compare, for each patient, the pharmacokinetic parameters obtained with both models. The threshold for statistical significance (α) was set to 0.05.

Results

Forty-eight patients aged between 19 and 65 yr were enrolled in the study protocol between March 1995 and May 1996. Demographic data for the three groups are presented in table 1. Groups were similar for gender, age, and weight. Male patients undergoing radical prostatectomy were in a large majority (9:8:10). In 32 of 35 patients who required rescue doses of a neuromuscular

blocker, vecuronium was administered after 90% recovery was achieved. Vecuronium was given after 75 and 40% recovery in two and one patients, respectively. Among the 13 patients who received only cisatracurium, seven had their block reversed at 70–160 min (*i.e.*, after > 95% recovery) with either neostigmine or edrophonium; five of these patients were in the 0.300-mg/kg dose group.

Pharmacodynamics

Pharmacodynamic data are presented in table 1. The average maximum neuromuscular block was 99 or 100% percent in each group. There was a twofold decrease in the onset time between the 0.075- and 0.150-mg/kg dose ($P < 0.05$), but the difference was not significantly different between the 0.150- and 0.300-mg/kg dose ($P > 0.05$). Times to recovery to 25, 50, and 75% block increased by approximately 24 min when the dose was doubled. Problems with neuromuscular monitoring occurred in four patients (one in groups I and II and two in group III). These patients were therefore excluded from the pharmacodynamic and PK-PD analysis.

Table 3. Comparison of Exit-site-dependent Pharmacokinetic Parameters when Assuming or Not Peripheral Elimination for Cisatracurium

	Pharmacokinetics Parameters					
	n	V _{ss} * (ml/kg)	k ₁₀ * (min ⁻¹)	k ₁₂ * (min ⁻¹)	k ₂₁ * (min ⁻¹)	Cl _{org} * (ml · min ⁻¹ · kg ⁻¹)
Central elimination only						
0.075 mg/kg	15	83 ± 15	0.0945 ± 0.0190	0.0977 ± 0.0349	0.0695 ± 0.0101	2.40 ± 0.41 (1.85–3.06)
0.150 mg/kg	16	75 ± 11	0.0953 ± 0.0125	0.0891 ± 0.0234	0.0655 ± 0.0114	2.27 ± 0.35 (1.79–3.08)
0.300 mg/kg	17	76 ± 16	0.0923 ± 0.0269	0.0790 ± 0.0419	0.0575 ± 0.0154	2.17 ± 0.50 (1.48–3.46)
Central and peripheral elimination						
0.075 mg/kg	15	108 ± 19	0.0448 ± 0.0114	0.1478 ± 0.0436	0.0458 ± 0.0101	0.69 ± 0.33 (0.23–1.32)
0.150 mg/kg	15	98 ± 17	0.0436 ± 0.0142	0.1411 ± 0.0265	0.0417 ± 0.0113	0.63 ± 0.44 (0.00–1.40)
0.300 mg/kg	14	107 ± 22	0.0368 ± 0.0159	0.1387 ± 0.0591	0.0357 ± 0.0132	0.49 ± 0.38 (0.00–1.37)

Data are presented mean ± SD (range).

* $P < 0.0001$ (pooled data) between the two models (paired *t* test).

V_{ss} = volume of distribution at steady state; k₁₀ = elimination rate constant for the first compartment; k₁₂ = transfer rate constant from the first to the second compartment; k₂₁ = transfer rate constant from the second to the first compartment; Cl_{org} = organ clearance.

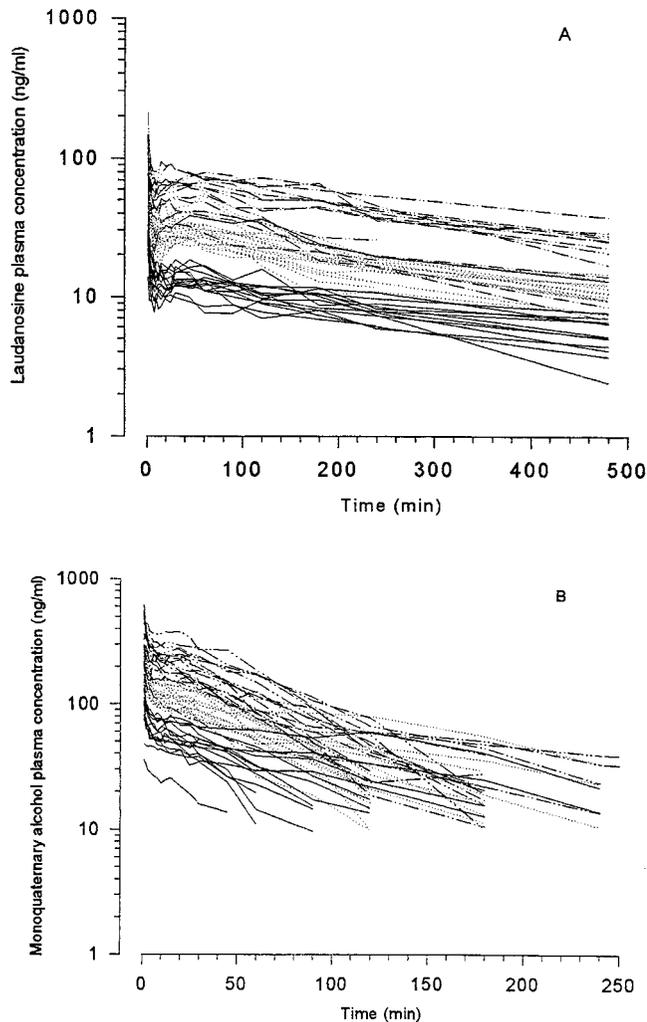


Fig. 2. Individual laudanosine (A) and monoquaternary alcohol (B) plasma concentration-versus-time curves for 48 healthy patients who received cisatracurium at 0.075 mg/kg (solid lines), 0.150 mg/kg (dotted lines), and 0.300 mg/kg (broken lines).

Pharmacokinetics of Cisatracurium

Cisatracurium plasma concentrations were quantifiable up to 180 min in 21 patients and 120 min in 26 patients. In one patient who received the lowest dose, cisatracurium could only be detected up to 90 min. For the three dose groups, the mean dose-normalized plasma concentration-time curves were superimposed (fig. 1). Exit-site-independent parameters are presented in table 2.

Cisatracurium pharmacokinetics proved to be linear because no significant differences were observed between the Cl_T for each dose level. Similarly, in absence of any significant dose effect, exit-site-dependent parameters derived from the traditional ($k_{20} = 0$) and the nontraditional ($k_{20} = 0.0237$) models were compared using pooled data from the three dose levels (table 3). The apparent volume of distribution at steady state was underestimated by an average of 25% when central elimination only was assumed. In four patients (one in the

0.15-mg/kg group and three in the 0.3-mg/kg group), the value derived for k_{10} using the nontraditional model was smaller than k_{20} . K_{org} was therefore given a value of 0 for the calculation of Cl_{org} . The contribution of organ clearance ($100 \times Cl_{org}/Cl_{tot}$), accounted for $21.1 \pm 8.4\%$ (0.075 mg/kg), $21.7 \pm 15.6\%$ (0.15 mg/kg), and $15.6 \pm 11.3\%$ (0.3 mg/kg) of the total body clearance when assuming elimination from both the central and peripheral compartments.

Metabolites

Figures 2A and B present the individual concentration-versus-time curves for laudanosine and the monoquaternary alcohol at each dose level. Laudanosine could be detected in plasma samples up to 480 min after the administration of cisatracurium in 38 patients and up to 240 min in 9 patients. In one patient receiving the lowest dose, laudanosine could be detected up to 180 min only. Pharmacokinetic parameters for the metabolites are presented in table 4. Laudanosine plasma concentrations plateaued in three patients who received the 0.3-mg/kg dose; these patients were therefore excluded from the pharmacokinetic analysis. For both laudanosine and the monoquaternary alcohol, the k_{eo} did not change with dose, and the mean overall half-life was 312 ± 109 min and 46.2 ± 16.4 min, respectively. C_{max} and AUC increased proportionally with the dose for both metabolites.

Pharmacokinetic-Pharmacodynamic Modeling

Results of the analysis at each dose level are presented in table 5. Because of insufficient twitch measurements, four patients were excluded from the PK-PD analysis.

Using the parametric approach, the mean plasma effect compartment equilibration half-lives ($T_{1/2keo}$) for the three ascending doses were 10.3, 12.2, and 14.5 min, respectively. When pairwise comparisons were made for k_{eo} values, only the difference between the two higher doses was not statistically significant. The mean dose-normalized cisatracurium effect compartment concentrations are represented in figure 3, and the mean values of t_{ECmax} derived at each dose level in are shown in table 5. There was a dose-dependent increase in the EC_{50} value. The hysteresis curves obtained when the effect is plotted against the plasma concentration of cisatracurium in a representative patient of each dose group is represented graphically in figure 4A. The dose-dependent shift to the right of the sigmoid E_{max} curves derived with the parametric PK-PD analysis is illustrated in figure 4B.

Using the nonparametric approach, $T_{1/2keo}$ values for the three ascending doses were 8.0, 8.5, and 9.9 min, respectively. Therefore, no statistically significant dose-dependent effect was observed for k_{eo} values with the nonparametric analysis, but the power of the test was 0.655. In contrast, the EC_{50} and t_{ECmax} values for the

Table 4. Noncompartmental Pharmacokinetic Parameters for Laudanosine and the Monoquaternary Alcohol Metabolite

	Dose (mg/kg)			P Value
	0.075	0.150	0.300	
Laudanosine	n = 15	n = 16	n = 14	
AUC _{0→t_{end}} /D (min · kg · ml ⁻¹)	0.0448 ± 0.0215	0.0452 ± 0.0133	0.0480 ± 0.0212	0.367
Kel (min ⁻¹)	0.0029 ± 0.0021	0.0024 ± 0.0007	0.0026 ± 0.0010	0.742
C _{max} (ng/ml)	29 ± 8	30 ± 8	30 ± 10	0.936
Monoquaternary alcohol	n = 15	n = 16	n = 17	
AUC _{0→∞} /D (min · kg · ml ⁻¹)	0.0475 ± 0.0162	0.0527 ± 0.0125	0.0473 ± 0.0155	0.495
Kel (min ⁻¹)	0.0170 ± 0.0035	0.0156 ± 0.0040	0.0159 ± 0.0036	0.561
C _{max} (ng/ml)	98 ± 30	202 ± 42	386 ± 125	< 0.0001

Data are presented as mean ± SD.

AUC_{0→t_{end}}/D = dose-normalized area under the curve to the last quantifiable point; AUC_{0→∞}/D = dose-normalized area under the curve to the infinite; Kel = elimination rate constant; C_{max} = maximum plasma concentration.

highest dose were significantly higher than their corresponding value at the two lower doses.

Comparison of PK-PD parameter estimates obtained with the parametric and nonparametric approaches indicate that significantly faster k_{eo} were observed at each dose level with the parametric approach. For the two higher doses, the EC₅₀ values and t_{ECmax} derived with the nonparametric analysis were significantly lower than those obtained with the parametric analysis. However, goodness of fit (as measured by the Akaike information criterion value) of the predicted effect was significantly better with the parametric approach.

Discussion

To our knowledge, this is the first time PK-PD modeling of cisatracurium has been conducted systematically

in a traditional rich data study using three dose levels. This study confirms the linearity of the pharmacokinetics of cisatracurium and of its principal metabolites, laudanosine and the monoquaternary alcohol, when cisatracurium is administered at doses ranging from 0.075 to 0.300 mg/kg. However, our analyses reveal dose-related changes in cisatracurium PK-PD parameters that vary in intensity with the modeling approach.

The linearity of cisatracurium pharmacokinetics has been previously established by Lien *et al.*⁴ after bolus doses of 0.1 and 0.2 mg/kg using a traditional rich data and by Schmith *et al.*⁹ for doses varying from 0.1 to 0.4 mg/kg using a population approach. The overall total body clearance reported herein is in agreement with that obtained by most other groups.^{4,6,7,9,10} Because Hofmann elimination is thought to be the major metabolic pathway for cisatracurium,¹² such a consistent pattern is

Table 5. Pharmacokinetic–pharmacodynamic Analysis when Assuming Central and Peripheral Elimination for Cisatracurium

	Dose (mg/kg)			P Value
	0.075 (n = 14)	0.150 (n = 15)	0.300 (n = 15)	
Parametric approach				
k_{eo} (min ⁻¹)	0.0675 ± 0.0160	0.0568 ± 0.0142	0.0478 ± 0.0090	< 0.001*
t_{ECmax} (min)	10.9 ± 1.3	11.8 ± 1.7	14.6 ± 1.8	< 0.001†
EC _{max} (ng/ml)	272 ± 33	260 ± 44	232 ± 42	0.034‡
EC ₅₀ (ng/ml)	136 ± 17	157 ± 35	209 ± 27	< 0.001†
γ	7.66 ± 1.51	6.70 ± 1.12	7.26 ± 1.3	0.189
AIC	208 ± 34	162 ± 35	138 ± 24	< 0.001*
Nonparametric approach				
k_{eo} (min ⁻¹)	0.0872 ± 0.0244	0.0812 ± 0.0241	0.0702 ± 0.0161	0.211
t_{ECmax} (min)	10.5 ± 1.4	10.4 ± 1.6	12.0 ± 1.7	0.014†
EC _{max} (ng/ml)	292 ± 39	302 ± 36	281 ± 59	0.486
EC ₅₀ (ng/ml)	126 ± 21	131 ± 30	158 ± 27	< 0.004†
γ	5.10 ± 1.30	4.98 ± 1.24	5.39 ± 0.94	0.342
AIC	274 ± 41	228 ± 43	208 ± 49	< 0.001*

Data are presented as mean ± SD.

* $P < 0.05$ between 0.075 and 0.300 and between 0.075 and 0.150 mg/kg. † $P < 0.05$ between 0.075 and 0.300 and between 0.150 and 0.300 mg/kg. ‡ $P < 0.05$ between 0.075 and 0.300 mg/kg after multiple pairwise comparisons.

k_{eo} = effect compartment equilibration rate constant; t_{ECmax} = time required to reach EC_{max}; EC_{max} = dose-normalized maximum concentration in effect compartment; EC₅₀ = effect compartment concentration at 50% block; γ = slope factor; AIC = Akaike information criterion.

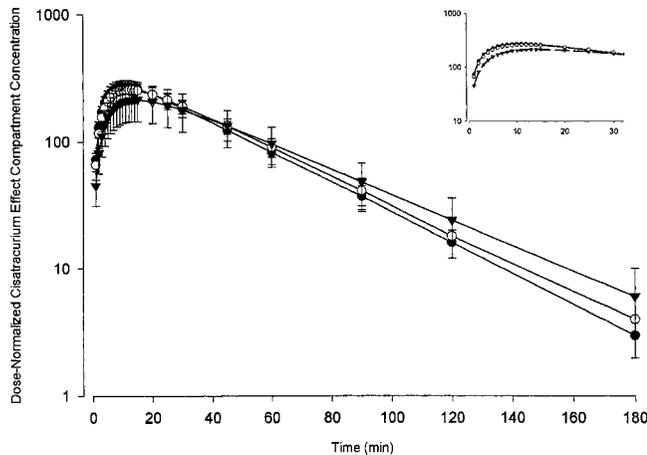


Fig. 3. Mean dose-normalized cisatracurium effect compartment concentration-versus-time curves for healthy adults after a single intravenous dose of 0.075 mg/kg ($n = 14$; black circles), 0.150 mg/kg ($n = 15$; white circles), and 0.300 mg/kg ($n = 15$; triangles).

compatible with the pH and temperature-dependent characteristics of this route.

As mentioned previously, cisatracurium *in vitro* rate of degradation was substituted for k_{20} in the model, assuming both central and peripheral elimination, and gave an overall contribution of organ clearance of 23%. Kisor *et al.*,⁵ in a retrospective analysis of three pharmacokinetic studies on cisatracurium, found similar values, of which 16% could be accounted for by renal clearance. This small contribution may explain why the disposition of cisatracurium is not altered in patients with liver³ or renal¹ diseases.

Assuming both central and peripheral elimination for cisatracurium pharmacokinetic modeling is now widely accepted.^{4,5,7-11} Ideally, $k_{in\ vitro}$ values should be determined for each patient instead of using a predetermined value. As this was not planned in our study design, we used the $k_{in\ vitro}$ values published by Welch *et al.*¹² for cisatracurium in the plasma of nine subjects (mean, 0.0237; range, 0.0209–0.0284 min^{-1}). In our study, an estimate of organ clearance could not be calculated in four patients; in two, k_{10} was much slower (0.0130 and 0.0002 min^{-1}) than these reported rates. These obvious limitations when using a predetermined $k_{in\ vitro}$ value have been reviewed in detail elsewhere.²³ However, we believe that accounting for peripheral elimination is appropriate for cisatracurium because its elimination relies mostly on Hofmann elimination. Therefore, the rate of elimination of cisatracurium from the central or peripheral compartment is probably very similar. When peripheral elimination is ignored, the apparent steady state volume of distribution, an exit-site-dependent parameter, is underestimated.^{4,7} It follows that organ clearance determined with the central elimination model would be clearly overestimated.

In our study, there was a dose proportional increase in $\text{AUC}_{0-\infty}$ and C_{max} for laudanosine and the alcohol metabolite over the dose range studied. Although laudanosine mean elimination half-life was similar for the three dose studied, a large interpatient variability was observed and was attributed to the fact that the sampling time did not cover more than two half-lives. These findings are in agreement with those published by Lien *et al.*⁴

In agreement with previous pharmacodynamic studies,^{13,14,24} the duration of the effect was proportional to the dose for cisatracurium after administration of single bolus doses. Recovery times increased by 23–24 min each time the dose was doubled, which is consistent with the estimates of the elimination half-life made in previous pharmacodynamic studies.^{13,14,22} In our study, the clinical duration (time to 25% twitch recovery) at the 0.15-mg/kg dose (59 min) is comparable to the 55 min reported by Bluestein *et al.*²⁴ at the same dose and under similar anesthetic conditions. Although a twofold decrease in onset time was observed between the two lower doses, the decrease in onset time was consider-

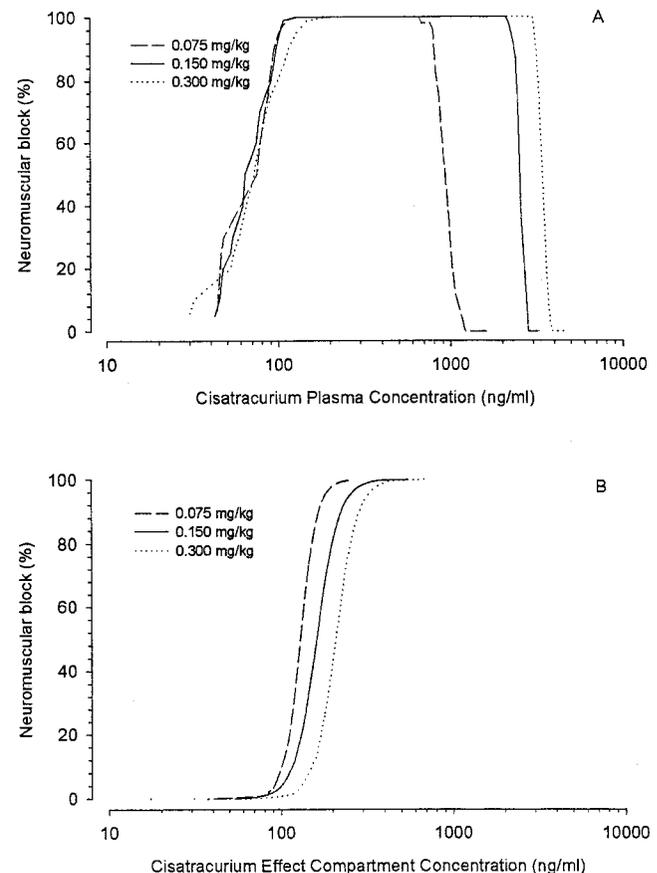


Fig. 4. Individual hysteresis curves for three patients from the three different dosing groups. Plasma concentrations were simulated for each neuromuscular block measure (A). The resulting individual sigmoid E_{max} curves using the derived effect compartment concentrations after the parametric link with the pharmacodynamic model for the same three patients are shown (B).

ably less between the two higher doses, suggesting the establishment of a plateau. This could be explained either by the saturation of the muscle end-plate receptors or by reduced diffusion to the synaptic cleft caused by steric hindrance (buffering hypothesis), as demonstrated by other groups for several myorelaxants.²⁵⁻²⁷

In most PK-PD studies for cisatracurium, isoflurane was used as the anesthetic agent.^{3,8} During these conditions, administration of a 0.1-mg/kg bolus dose of cisatracurium ($2 \times \text{ED}_{95}$) resulted in mean EC_{50} values of 98 ng/ml using a traditional rich data³ or population approach.⁸ This lower EC_{50} value is in agreement with the known potentiating effect of isoflurane. When propofol was used as the anesthetic agent,⁷ the mean EC_{50} and k_{eo} values derived after a 5-min infusion of a 0.1-mg/kg dose of cisatracurium in 15 patients were 153 ng/ml and 0.054 min^{-1} , respectively. The latter values are comparable to those reported herein.

Using a population approach and a parametric PK-PD model, Schmith *et al.*¹⁰ obtained mean k_{eo} and EC_{50} values of 0.0575 min^{-1} and 141 ng/ml, respectively, after doses of cisatracurium varying from 0.015 to 0.8 mg/kg. These findings are in full agreement with the overall mean obtained after pooling data from our three dose groups for k_{eo} (0.0574 min^{-1}) and EC_{50} (167 ng/ml) using the parametric PK-PD model. However, when each dose group is dealt with separately, a dose-related change in cisatracurium EC_{50} and k_{eo} values becomes obvious. As the dose was not considered as a covariant in the population study by Schmith *et al.*,¹⁰ the possibility of a dose-related change in the PK-PD parameters cannot be excluded.

Explanations for the dose dependency of the EC_{50} derived with the parametric approach were therefore sought. It was first verified that experimental error was not responsible for the increase in EC_{50} . Because the intraindividual variability in the estimation of the EC_{50} was always less than 5%, the dose-dependent effect could not be attributed to a systematic bias. In a sequential PK-PD analysis, pharmacokinetic parameters (α , β , k_{21} , V_1) derived in the first step are held constant when deriving the effect compartment concentration-time profile. As cisatracurium pharmacokinetics proved to be linear, the dose-related changes observed in the pharmacodynamic parameters cannot be of pharmacokinetic origin.

To further elucidate the nature of the dose dependency, the kinetics of cisatracurium concentrations in the effect compartment were simulated. A 15% decrease in the dose-normalized EC_{max} and a 30% increase in $t_{\text{EC}_{\text{max}}}$ were observed at the highest dose. Our modeling approach was questioned because, in a full parametric model, the link (k_{eo}) and pharmacodynamic (EC_{50} and γ) parameters are optimized simultaneously. Preliminary analyses were previously conducted for the first eight patients in the 0.3-mg/kg dose group using a semipara-

metric PK-PD model. With this approach, the compartmental pharmacokinetic model and nonparametric link model²² are run sequentially and their estimates fixed when optimizing the pharmacodynamic parameters. For these patients, the PK-PD parameters were identical to those obtained herein with the full parametric analysis. Therefore, the simultaneous estimation of k_{eo} and EC_{50} is probably not responsible for the increase in EC_{50} .

Another possible explanation for the dose-related effect in EC_{50} was an artefact of the input function. A bolus input was used in our compartmental analysis. This implies that plasma concentrations before the first sampling time are back-extrapolated, yielding a maximum concentration at time zero (instantaneous input). In doing so, the intravascular mixing phase is not adequately described. In our experience, peak arterial concentrations of muscle relaxants are generally obtained within 35-45 s and reach values several-fold higher than those observed 1 min after injection.²⁸⁻³⁰ Our experimental design did not include extensive sampling during the intravascular mixing phase (i.e., samples drawn at 10-s intervals for the first 2 min) but limited sampling (i.e., 1 and 2 min after injection). This decision was based on results obtained in a previous study²⁸ in which the influence of blood sampling schedule on PK-PD parameter estimation was evaluated after the administration of a 0.1-mg/kg intravenous bolus dose of vecuronium in anesthetized patients. Indeed, the EC_{50} values derived with the parametric analysis (with limited sampling) were not different from those obtained with the nonparametric analysis (with extensive sampling). However, the EC_{50} values derived with the parametric approach were 14% higher than those derived with the nonparametric analysis when only limited data sets were available (as herein).

To assess the influence of the input function, a nonparametric analysis was performed on the three dose groups. This type of analysis requires that effect and concentration data be provided at each time point. The first detectable block was observed at approximately 0.43 min when the highest dose of cisatracurium was given, but there was no blood sample drawn at that time. Moreover, the degree of block was significant in some patients when the first sample was drawn 1 min after the bolus dose. To evaluate the potential bias introduced by the lack of samples during that critical period and to test the hypothesis that the effect would be more pronounced as the dose increased, an additional nonparametric analysis was conducted. For all patients showing more than 20% block at 1 min, plasma concentrations were simulated for the first minute at times corresponding to effect data using the function interpolate of the Sigma plot v.5 software (Jandel Scientific, San Rafael, CA). Inclusion of these interpolated concentration in the PK-PD analysis proved to have no significant effect on

cisatracurium EC_{50} or k_{eo} values. Therefore, only the results obtained with the raw data are reported herein.

One might argue that such comparisons between the two noncompartmental approaches are not fair because cisatracurium concentrations were not actually measured during the intravascular mixing phase. In the vecuronium study,²⁸ the EC_{50} values derived when the intravascular mixing phase was properly characterized proved to be 18% higher than those obtained with limited sampling data sets. If a similar trend was observed herein for cisatracurium, the net result would be an increase in the EC_{50} . This would, in turn, reduce the gap between the EC_{50} values obtained with the parametric and nonparametric analyses. However, this may not hold at the highest dose where significant effect is observed during the first minute.

The results obtained with the nonparametric analysis are not easy to interpret. The dose-dependent trend is completely abolished for EC_{max} but not for EC_{50} and t_{ECmax} . According to our results, the input function would explain only 50% of the dose-dependent changes observed with the parametric model. However, the bias introduced by the input function increased as the dose increased. At the lowest dose, EC_{50} and t_{ECmax} values derived with the nonparametric analysis were not different from those obtained with the parametric analysis. However, a difference of 30% ($P < 0.001$) and 22% ($P < 0.001$), respectively, was observed at the highest dose.

Dose dependency of EC_{50} is thus confirmed for both modeling approaches, but the trend is not as pronounced with the nonparametric analysis. Whether the effect has a mathematical or pharmacologic origin is uncertain. If one compares the hysteresis curves obtained for a representative patient at each dose level (fig. 4A), a large span of plasma concentrations are observed for a given degree of block during onset of action (ascending limb), while the concentrations associated to a given effect do not vary greatly during recovery (descending limb). We believe that any mathematical approach that derives effect compartment concentrations by minimizing the differences in plasma concentrations associated to a given effect during onset and recovery is prone to yield higher values of EC_{50} at very high doses. However, one cannot exclude a pharmacodynamic contribution. Indeed, dose nonlinearity in the PK-PD relation of muscle relaxants has been reported by other investigators. Using a pharmacodynamic model, Bragg *et al.*³¹ observed that the steady state infusion rate associated with a 50% neuromuscular block varied with different bolus doses of vecuronium. In a later PK-PD study in volunteers, Fisher *et al.*³² reported a 28% increase in the EC_{50} of vecuronium when the dose was doubled from 0.5 and $1 \times ED_{90}$, but without any significant changes in k_{eo} . Although many hypotheses were proposed to explain such dose-related differences, no definite explanation was provided. A pharmacologic interpretation of

the shift to the right of the concentration-effect relation would be a competitive auto-inhibition at very high doses, which is compatible with either a saturation of the receptors or steric hindrance, as discussed previously.

In the current study, a dose-related change in the PK-PD parameters of cisatracurium was detected at doses varying from a commonly used ($1.5 \times ED_{95}$) to a high pharmacologic dose ($6 \times ED_{95}$). As PK-PD population analyses conducted during drug development often include data obtained from a wide array of doses, further studies are needed to determine if dose should or not be included as a covariate. In the meanwhile, it would be advisable that doses relevant to the anesthetic practice be used for the estimation of EC_{50} values.

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