Pharmacokinetics and Pharmacodynamics of Cisatracurium After a Short Infusion in Patients Under Propofol Anesthesia

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Fourteen patients, ASA physical status I or II, were recruited to assess the pharmacokinetic-pharmacodynamic relationship of cisatracurium under nitrous oxide/sufentanil/propofol anesthesia. The electromyographic response of the abductor digiti minimi muscle was recorded on train-of-four stimulation of the ulnar nerve. A 0.1-mg/kg dose of cisatracurium was given as an infusion over 5 min. Arterial plasma concentrations of cisatracurium and its major metabolites were measured by using high-performance liquid chromatography. A nontraditional two-compartment pharmacokinetic model with elimination from central and peripheral compartments was used. The elimination rate constant from the peripheral compartment was fixed to the *in vitro* rate of degradation of cisatracurium in human plasma (0.0237 min^{-1}). The mean terminal half-life of cisatracurium was 23.9 ± 3.3 min, and its total clearance averaged 3.7 ± 0.8 mL · $min^{-1} \cdot kg^{-1}$. Using this model, the volume of distribution at steady state was significantly increased compared with that obtained when central elimination only was assumed (0.118 ± 0.027 vs 0.089 ± 0.017 L/kg). The effect-plasma equilibration rate constant was 0.054 ± 0.013 min^{-1}. The 50% effective concentration (153 ± 33 ng/mL) was 56% higher than that reported in patients anesthetized with volatile anesthetics, which suggests that, compared with inhaled anesthetics, a cisatracurium neuromuscular block is less enhanced by propofol. **Implications:** The drug concentration-effect relationship of the muscle relaxant cisatracurium has been characterized under balanced and isoflurane anesthesia. Because propofol is now widely used as an IV anesthetic, it is important to characterize the biological fate and the concentration-effect relationship of cisatracurium under propofol anesthesia as well.

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Several studies have been conducted to evaluate the pharmacokinetics of cisatracurium in healthy anesthetized patients under balanced or isoflurane anesthesia (1–7), in which cisatracurium was given either as a bolus (1,4,5,7) or a bolus followed by a bolus or as an infusion (2,3,6). In most of these studies (1–3,6), peripheral elimination was accounted for in the pharmacokinetic analysis of cisatracurium and the corresponding rate constant given the *in vitro* degradation rate in human plasma previously determined by Welch et al. (8). The pharmacokinetic/pharmacodynamic (PK/PD) relationship of cisatracurium has already been characterized in patients using a population approach (3,6) or a traditional design, which allowed for the administration of an intubating dose of succinylcholine before cisatracurium (5). In view of the widespread use of propofol as an IV anesthetic, it is important to characterize the biological fate and the concentration-effect relationship of cisatracurium under propofol anesthesia as well. Therefore, we designed this study to determine the pharmacokinetic and PK/PD profile of cisatracurium after a 5-min infusion of cisatracurium in patients undergoing elective surgery under propofol anesthesia.

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Methods

The study protocol was approved by the Royal Victoria Hospital Ethics Committee, and all participating patients gave written, informed consent. Patients aged 18–65 yr, ASA physical status I or II, scheduled for elective surgery of >1 h were recruited. Patients were excluded if they showed any evidence of clinically significant pulmonary, psychiatric, neurologic, neuromuscular, or cardiovascular disease, as well as significant renal or liver impairment. A history of malignant hyperthermia, unusual sensitivity to neuromuscular blocking drugs, or intake of medications known or suspected to affect neuromuscular function constituted other exclusion criteria.

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Usual monitors were used. Of 14 patients, 7 were premedicated with IV midazolam (1–2 mg). An arterial line and an indwelling catheter were placed in the radial artery and a peripheral vein of the forearm, respectively. Surface electrodes for electromyographic (EMG) recording were placed in the contralateral arm. General anesthesia was induced with a bolus of sufentanil 0.2–0.3 μg/kg and propofol 1–2 mg/kg. Immediately after induction, the EMG response of the abductor digiti minimi muscle to the train-of-four stimulation of the ulnar nerve (2 Hz for 2 s) was measured every 10 s. Once calibration of the T1 response (first twitch of the train-of-four) was obtained, cisatracurium 0.1 mg/kg was administered IV over 5 min. The trachea was then intubated. Anesthesia was maintained with propofol 75–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$, sufentanil 0.2–0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and N_2O/O_2 (70%/30%). If a patient required maintenance of neuromuscular block, the protocol allowed for the administration of vecuronium after 75% T1 recovery from the initial dose of cisatracurium. Muscle relaxation was measured until complete spontaneous recovery or full reversal with neostigmine/glycopyrrolate (if incomplete recovery by the end of the surgery).

Because of a drift of the EMG response, the T1 response after complete recovery often did not return to the initial level. When this happened, we applied a correction factor, $F = T1_{start}/T1_{end}$, to obtain $T1_{corrected}$ where $T1_{start}$ is the T1 value at calibration and $T1_{end}$ is the T1 value at complete recovery. $T1_{corrected}$ was obtained only for the data measured during the recovery phase and was used for PK/PD modeling. Because the infusion of cisatracurium was started immediately after the calibration, we assumed that the drift was negligible during the installation of the neuromuscular block.

Arterial blood samples (5 mL) were drawn before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20, 25, 30, 45, 60, 90, 120, 180, and 240 min after the start of the infusion, and a venous sample was taken at 480 min. Additional samples were taken at approximately 25%, 50%, and 75% neuromuscular block. Blood samples were collected in precooled tubes containing heparin and were immediately centrifuged in Eppendorf tubes (45 s at 10,000 rpm). After centrifugation, the plasma was acidified to pH 3–4 with sulfuric acid 2 M (30 μL/mL plasma) and frozen on dry ice. The samples were stored at −70°C until analyzed.

Cisatracurium, laudanosine, and monoquaternary alcohol plasma concentrations were determined by using high-performance liquid chromatography coupled with fluorescence detection. This method is similar to that for cisatracurium and its metabolites in human urine (9). Bond Elut® phenyl solid-phase extraction cartridges (Varian, Harbor City, CA) were used for the extraction of cisatracurium and its metabolites. *N*-methyl laudanosine (500 ng/mL plasma) was used as an internal standard. After several purification steps, the eluent was reduced in volume, and an aliquot was injected directly into the high-performance liquid chromatography system by using an autosampler (Shimadzu, Kyoto, Japan). Cisatracurium and its metabolites were separated by using a Phenomenex Spherisorb® strong cation exchanger column (150 × 4.6 mm, inner diameter 5 μm; Phenomenex, Torrance, CA) using a stepwise gradient (Thermo Separation Products, Riviera Beach, FL). The mobile phase changed from a first phase (14 mM Na_2SO_4 in 0.5 mM H_2SO_4:ACN [40:60]) during 5 min to a second phase (70 mM Na_2SO_4 in 0.5 mM H_2SO_4:ACN [40:60]) during 6 min. The column was maintained at 50°C. The fluorescence detector (Hewlett Packard, Waldbronn, Germany) excitation and emission wavelengths were set at 280 and 320 nm, respectively. The coefficients of variation for cisatracurium and the metabolites for between-run precision were <8% at concentrations of 4.88–2500 ng/mL for cisatracurium and 1.95–1000 ng/mL for the metabolites. The percentage of accuracy of the assay was 99% ± 9% for cisatracurium, 101% ± 2% for laudanosine, and 100% ± 1% for monoquaternary alcohol.

The pharmacokinetics of cisatracurium was evaluated by using a nontraditional two-compartment model with a zero-order input rate and elimination from both central and peripheral compartments. In preliminary analysis, a three-compartment model was not justified according to Akaike's criterion. The following exit-site dependent variables were derived: volume of distribution at steady state (Vdss), first-order rate constant associated with the elimination of drug from compartment 1 (K_{10}), first-order rate constant associated with the movement of drug from compartment 1 to compartment 2 (K_{12}), and first-order rate constant associated with the movement of drug from compartment 2 to compartment 1 (K_{21}). The elimination rate constant from the peripheral compartment (K_{20}) was fixed at a value of 0.0237 min^{-1}, which corresponds to the *in vitro* rate of degradation of cisatracurium in human plasma (pH 7.4 and 37°C) as reported by Welch et al. (8). In that model, K_{20} is assumed to be equivalent to the Hofmann elimination rate constant because Hofmann degradation is thought to be the only elimination pathway from the peripheral compartment. The organ clearance (Cl_{org}) was calculated using the following equation: $Cl_{org} = V_1(K_{10} - K_{20})$, as previously described by Fisher et al. (10). The relative contribution of organ clearance ($\%Cl_{org}$) was obtained as follows: $\%Cl_{org} = Cl_{org}/Cl_{tot} \times 100$ where Cl_{tot} is the total clearance. Traditional pharmacokinetic analysis considering central elimination only was performed to characterize the magnitude of the underestimation of the Vdss by this model.

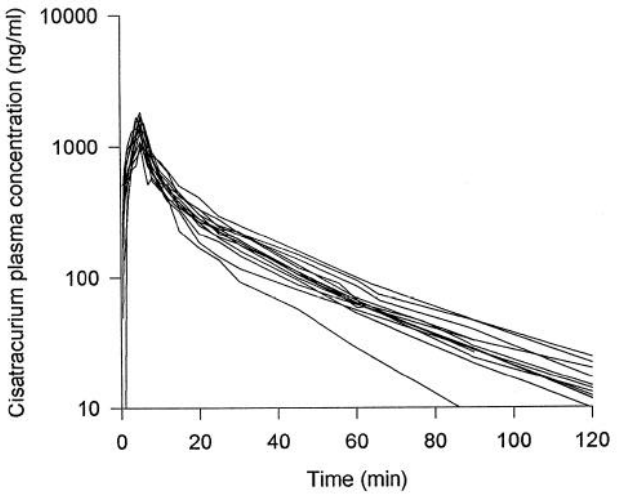

Figure 1. Individual cisatracurium plasma concentration-time curves in patients who received a 5-min infusion of 0.1 mg/kg cisatracurium.

The PK/PD analysis was performed in a sequential manner using the variables derived from the nontraditional two-compartment pharmacokinetic analysis, a parametric link (Keo) and the sigmoid maximal effect (E_{max}) model (50% effective concentration [EC_{50}]). A weighting function of 1/(predicted Y)^2 and 1 was applied for pharmacokinetic and PK/PD data, respectively.

The pharmacokinetic variables (elimination half-life [$t_{1/2}$], maximal concentration [C_{max}], area under the curve [$AUC_{0\rightarrow\infty}$]) of the two major metabolites of cisatracurium—laudanosine and monoquaternary alcohol—were obtained using a noncompartmental approach with standard equation formulas (11).

Results obtained for both models were compared using paired *t*-tests (K_{10} and K_{12}) or Wilcoxon signed rank tests (V_{Dss} and K_{21}) when the normality test failed. The threshold for statistical significance was set at $P < 0.05$.

Results

The study group consisted of five men and nine women aged 25–65 yr (mean 46 ± 12 yr). Ten ASA physical status I and four ASA physical status II patients underwent general and gynecological surgical procedures. The mean height of the patients was 168 ± 10 cm, and their average weight was 72 ± 15 kg. Of the 14 patients, 12 were within 30% of their ideal body weight.

Figure 1 shows the individual cisatracurium plasma concentration-time curves observed in 14 healthy patients after a 5-min infusion of 0.1 mg/kg. The average C_{max} was 1429 ± 283 ng/mL.

When both central and peripheral elimination were assumed, the micro rate constants K_{10} and K_{21} were decreased by 53% ($P < 0.0001$) and 34% ($P = 0.0001$), respectively, whereas K_{12} was increased by 52% ($P < 0.0001$) compared with the values obtained when assuming central elimination only (Table 1). This resulted in a 31% significant increase ($P = 0.0001$) of the V_{Dss}, an exit-site–dependent variable. The organ clearance of cisatracurium accounted for 25% ± 13% (range 0%–48%) of Cl_{tot}. In one case, a negative value was observed, probably as a result of a model misspecification, and Cl_{org} was given a zero value.

Table 1. Analysis of Cisatracurium After a Five-Minute Infusion of 0.1 mg/kg Cisatracurium Besylate

	Exit site		
PK variables			
Exit-site–independent			
A (ng/mL)		1908 ± 645	
B (ng/mL)		402 ± 92	
$t_{1/2\alpha}$ (min)		2.8 ± 1.0	
$t_{1/2\beta}$ (min)		23.9 ± 3.3	
V_1 (L/kg)		0.035 ± 0.011	
Cl_{tot} (mL · min^{-1} · kg^{-1})		3.7 ± 0.8	
Exit-site–dependent	Central		Central and peripheral
V_{Dss} (L/kg)	0.089 ± 0.017		0.118 ± 0.027*
K_{10} (min^{-1})	0.112 ± 0.027		0.053 ± 0.020*
K_{12} (min^{-1})	0.126 ± 0.058		0.185 ± 0.074*
K_{21} (min^{-1})	0.073 ± 0.015		0.049 ± 0.015*
PK/PD variables			
Keo (min^{-1})		0.054 ± 0.013	
$t_{1/2}$Keo (min)		13.6 ± 3.2	
EC_{50} (ng/mL)		153 ± 33	
γ		6.9 ± 1.3	

Values are expressed as mean ± SD.
n = 14 for PK; n = 12 for PK/PD.
A, B = coefficients, $t_{1/2\alpha}$ = distribution half-life, $t_{1/2\beta}$ = elimination half-life, V_1 = volume of central compartment, Cl_{tot} = total clearance, V_{Dss} = volume of distribution at steady state, K_{10} = first-order rate constant associated with the elimination of drug from compartment 1, K_{12} = first-order rate constant associated with the movement of drug from compartment 1 to compartment 2, K_{21} = first-order rate constant associated with the movement of drug from compartment 2 to compartment 1, Keo and $t_{1/2}$Keo = equilibration rate constant and half-life between central and effect compartments, respectively, EC_{50} = effect compartment concentration corresponding to 50% neuromuscular block, γ = slope factor, PK = pharmacokinetic, PD = pharmacodynamic.
* $P < 0.05$.

The individual neuromuscular block-time curves are shown in Figure 2A. After a 5-min infusion, onset times to 90% and maximal T1 suppression (99% ± 2%) were achieved in 5.4 ± 1.2 and 6.7 ± 2.2 min, respectively. The time to 25%, 50%, and 75% T1 recovery averaged 53 ± 9, 59 ± 10 and 65 ± 11 min, respectively, and the recovery index (time from 25% to 75% T1 recovery) was 13 ± 3 min.

Two patients were excluded from the PK/PD analysis because of technical problems during neuromuscular monitoring (Table 1). Using the variables derived with the sigmoid E_{max} model, predicted blocks in function of time were obtained for each patient using a rearrangement of the equation. In Figure 2B,

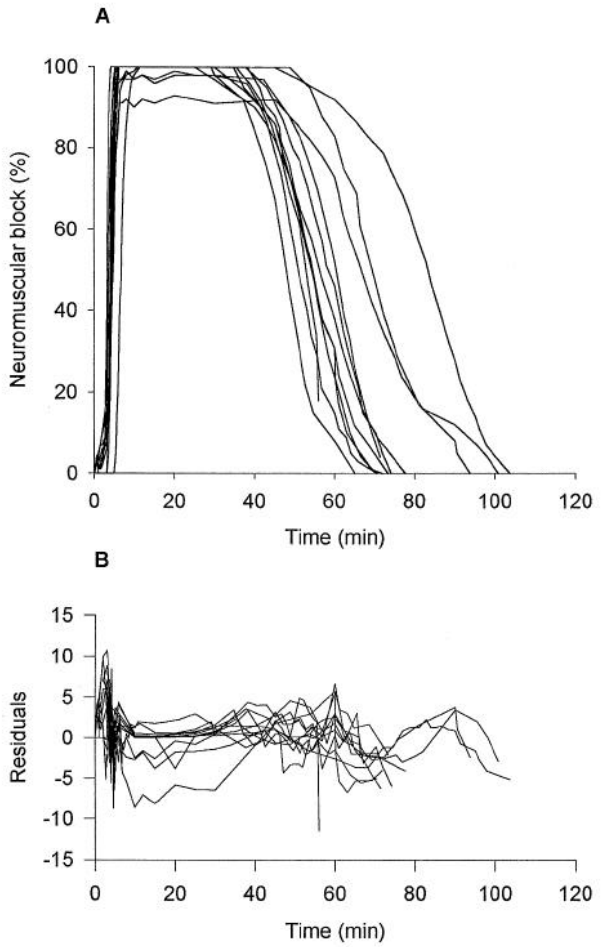

Figure 2. Individual neuromuscular block-time curves (A) and residuals of neuromuscular block (B) after a 5-min infusion of 0.1 mg/kg cisatracurium.

the residuals (i.e., the difference between the predicted and observed values of neuromuscular block for each individual) are plotted in function of time. These residuals were evenly distributed. The predicted blocks were comprised ±10% of the observed value, except for two measurements. Figure 3 illustrates the individual sigmoid E_{max} curves (neuromuscular block versus predicted effect compartment concentration of cisatracurium) in these patients.

The laudanosine and monoquaternary alcohol plasma concentration-time curves are shown in Figure 4. For laudanosine, one patient was excluded from the pharmacokinetic analysis because plasma concentrations plateaued and the terminal half-life could not be estimated. The average (range) C_{max} values of laudanosine and monoquaternary alcohol were 58 ± 31 ng/mL (32–146 ng/mL) and 163 ± 41 ng/mL (95–243 ng/mL), respectively. The C_{max} occurred at 5.2 ± 0.7 min for laudanosine and at 5.2 ± 0.6 min for monoquaternary alcohol. In most cases, monoquaternary alcohol plasma levels were below the assay sensitivity after 120 min, whereas laudanosine levels were

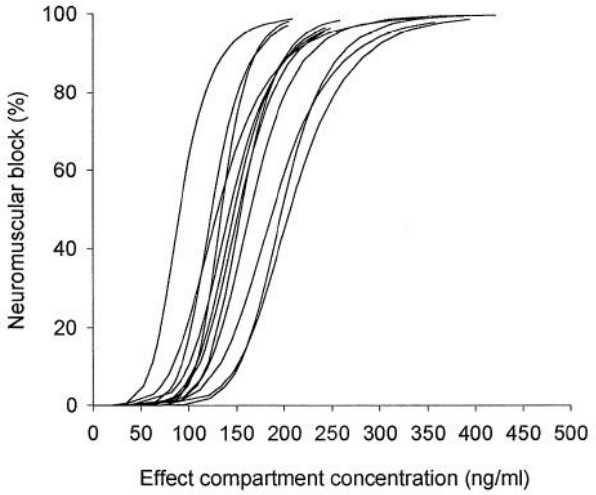

Figure 3. Individual neuromuscular block versus predicted effect-compartment concentration after a 5-min infusion of 0.1 mg/kg cisatracurium.

detectable throughout the sampling period. Table 2 shows the data obtained from the noncompartmental pharmacokinetic analysis of laudanosine and monoquaternary alcohol.

Discussion

Although cisatracurium pharmacokinetics has been well characterized in healthy patients under balanced (1,4) or isoflurane anesthesia (2,3,5–7), this study is the first to evaluate the pharmacokinetics of cisatracurium in patients under propofol anesthesia. The mean V_{Dss} reported herein for cisatracurium is slightly smaller than previously reported mean values (0.139–0.175 L/kg) (1–3,6). This effect is observed regardless of whether peripheral elimination is assumed and is mostly the result from differences in sampling site and schedule. In our study, arterial samples were drawn with the first sample taken 30 s after cisatracurium administration. In other studies, either venous (1,6) or both venous and arterial samples (2,3) were drawn 2 or 3 min after cisatracurium administration. The central volume of distribution reported herein is approximately twofold lower than that reported in the retrospective analysis of three pharmacokinetic studies on cisatracurium (1,5,7) published by Kisor et al. (12) and is mostly responsible for the smaller V_{Dss} value observed in our study. This observation is consistent with a fast arterial sampling schedule. However, differences in anesthetic procedures cannot be excluded.

In our study, the mean Cl_{tot} (3.7 mL · min^{-1} · kg^{-1}) for cisatracurium is slightly lower than that reported elsewhere (4.2–5.7 mL · min^{-1} · kg^{-1}) (1–7), which is most probably the result of our smaller V_{Dss} values. Indeed, because of the organ-independent nature of

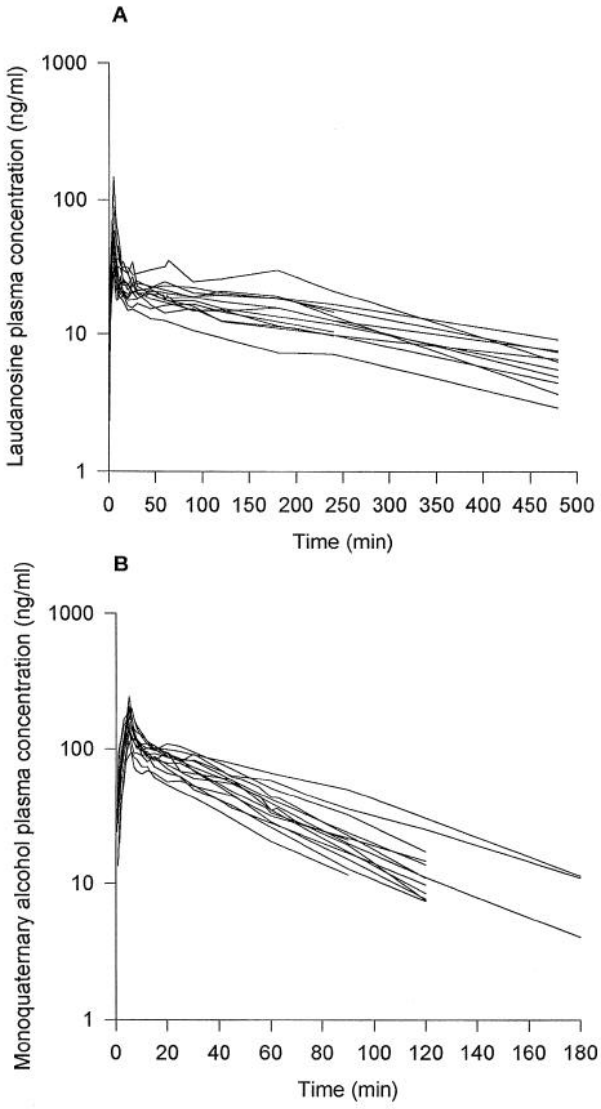

Figure 4. Individual plasma concentration-time curves for laudanosine (A) and monoquaternary alcohol (B) after a 5-min infusion of 0.1 mg/kg cisatracurium.

cisatracurium elimination, there is a positive correlation between Vdss and Cl_{tot}. This effect has been documented for the two benzylisoquinolinium compounds, cisatracurium (12) and atracurium (13). Because the relative decrease in Cl_{tot} is proportional to that in Vdss, our cisatracurium $t_{1/2\beta b}$ value (23.9 min) is within the range of previously published mean values (21.5–30.0 min) (1,4–7).

Neglecting the potential contribution of peripheral elimination in the two-compartment pharmacokinetic model led to an overall underestimation of 25% for Vdss, compared with the Vdss derived when assuming both central and peripheral elimination. A similar trend was also observed in Kisor et al.'s retrospective analysis (12).

The relative contribution of organ clearance to the overall cisatracurium elimination is almost identical to that reported by Kisor et al. (12) and shows a large

Table 2. Analysis of Laudanosine and Monoquaternary Alcohol (MQA) After a Five-Minute Infusion of 0.1 mg/kg Cisatracurium Besylate

PK variables	
Laudanosine	
$t_{1/2}$ (min)	249 ± 81 (127–399)
C_{max} (ng/mL)	58 ± 31 (32–146)
$AUC_{0\to\infty}$ (ng · mL^{-1} · min^{-1})	8866 ± 2352 (4,639–12,263)
$AUC_{laudanosine}/AUC_{cisatracurium}$ (ng · mL^{-1} · min^{-1})	0.43 ± 0.10 (0.34–0.69)
MQA	
$t_{1/2}$ (min)	36 ± 8 (27–52)
C_{max} (ng/mL)	163 ± 41 (95–243)
$AUC_{0\to\infty}$ (ng · mL^{-1} · min^{-1})	6458 ± 1690 (3,709–10,404)
$AUC_{MQA}/AUC_{cisatracurium}$ (ng · mL^{-1} · min^{-1})	0.31 ± 0.05 (0.24–0.41)

Values are mean ± SD (range).
n = 13 for laudanosine; n = 14 for monoquaternary alcohol.
$t_{1/2}$ = elimination half-life, C_{max} = maximal concentration, $AUC_{0\to\infty}$ = area under the curve from time 0 to infinity, PK = pharmacokinetic.

intersubject variability (25% ± 13% vs 23% ± 12%). A negative value for Cl_{org} was observed in one of our patients and was given a zero value. This model misspecification happens when the value assigned to K_{20} is larger than the K_{10} rate constant estimated for a particular patient. Kisor et al. (12) also reported that fixing K_{20} to previously determined mean *in vitro* Hofmann elimination rate constant (8) led to an inaccurate estimation of Cl_{org} in 3 of 31 patients.

Ideally, $K_{in\ vitro}$ should be estimated for each patient; however, this was not done in our study for two reasons. First, the amount of blood taken for the study was at the limit of what is ethically acceptable. Second, although assuming peripheral elimination (K_{20}) in the pharmacokinetic analysis of neuromuscular blocking drugs is not a new concept, its systematic application is quite recent. Because K_{20} cannot be determined independently, the accepted model (10) assumes that K_{20} is equal to $K_{in\ vitro}$. This may explain why the $K_{in\ vitro}$ value determined by Welch's group (8) for cisatracurium was systematically used in pharmacokinetic studies when the $K_{in\ vitro}$ value for each patient was not determined *a priori* (1–3,6,12).

In our study, the $t_{1/2}$ of laudanosine is approximately 4 h. Therefore, during the 8-h collection period, only two half-lives could be covered. This half-life is in the same order as the value obtained by Lien et al. (1) (4.2 ± 1.4 vs 3.6 ± 2.6 h) after a 0.1-mg/kg dose of cisatracurium. The variability in the estimation of $t_{1/2}$ is probably due to the insufficient sampling duration. For the same dose, the monoquaternary alcohol $t_{1/2}$ is compatible with the values reported by Lien et al. (36 ± 8 vs 34 ± 6 min) (1). The values of the $AUC_{metabolite}/AUC_{cisatracurium}$ ratio are also similar to those previously published for laudanosine (0.43 ± 0.10 vs 0.47 ± 0.28) and for monoquaternary alcohol (0.31 ± 0.05 vs 0.31 ± 0.08) after a 0.1-mg/kg dose of cisatracurium (1).

Differences in methodology are often responsible for the large variability of PK/PD variables obtained by different investigators. Arterial versus venous blood sampling can influence the Keo value and the EC_{50} of neuromuscular blocking drugs (14). Arterial sampling tends to decrease the Keo value of cisatracurium and to increase its EC_{50} value. This may explain the faster Keo (0.071 min^{-1}) and smaller EC_{50} (98 ng/mL) values reported in Sorooshian et al.'s study (6), in which venous samples were drawn.

The anesthetic procedure may also influence the estimation of PK/PD variables for neuromuscular blocking drugs. In particular, inhaled drugs (15) or a succinylcholine intubating dose (16) has been shown to decrease the EC_{50} value. Previously reported EC_{50} values (5,6) may be smaller than the values we determined because isoflurane was used as the anesthetic drug in the previous studies. This finding suggests that, in contrast to isoflurane, propofol may not enhance the effect of cisatracurium. However, a contribution of the neuromuscular monitoring technique (EMG versus twitch tension) cannot be excluded.

Despite obvious differences in methodology, the Keo and EC_{50} values reported herein are almost identical to those obtained in a population study in which 241 patients received various regimens (bolus or infusion) of cisatracurium under different types of anesthetic procedures (inhaled or opioid) (3).

In conclusion, this is the first report to document the pharmacokinetics and PK/PD of cisatracurium and its metabolites under propofol anesthesia. We compared our results with those obtained in previous studies, in which different anesthetic or methodological approaches were used, with all the limitations associated with historical comparisons. Although our results are in general agreement with those previously reported, they suggest that, compared with inhaled anesthetics, a cisatracurium neuromuscular block is less enhanced by propofol.

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References

1. Lien CA, Schmith VD, Belmont MR, et al. Pharmacokinetics of cisatracurium in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1996;84:300–8.
2. Schmith VD, Fiedler-Kelly J, Phillips L, Grasela TH Jr. Dose proportionality of cisatracurium. J Clin Pharmacol 1997;37:625–9.
3. Schmith VD, Fiedler-Kelly J, Phillips L, Grasela TH Jr. Prospective use of population pharmacokinetics/pharmacodynamics in the development of cisatracurium. Pharm Res 1997;14:91–7.
4. Eastwood NB, Boyd AH, Parker CJR, Hunter JM. Pharmacokinetics of 1R-*cis* 1′R-*cis* atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. Br J Anaesth 1995;75:431–5.
5. De Wolf AM, Freeman JA, Scott VL, et al. Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation. Br J Anaesth 1996;76:624–8.
6. Sorooshian SS, Stafford MA, Eastwood NB, et al. Pharmacokinetics and pharmacodynamics of cisatracurium in young and elderly adult patients. Anesthesiology 1996;84:1083–91.
7. Ornstein E, Lien CA, Matteo RS, et al. Pharmacodynamics and pharmacokinetics of cisatracurium in geriatric surgical patients. Anesthesiology 1996;84:520–5.
8. Welch RM, Brown A, Ravitch J, Dahl R. The *in vitro* degradation of cisatracurium, the R, *cis*-R′-isomer of atracurium, in human and rat plasma. Clin Pharmacol Ther 1995;58:132–42.
9. Bryant BJ, James CD Jr, Cook DR, Harrelson JC. High performance liquid chromatographic assay for cisatracurium and its metabolites in human urine. J Liquid Chromatogr Relat Technol 1997;20:2041–51.
10. Fisher DM, Canfell PC, Fahey MR, et al. Elimination of atracurium in humans: contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. Anesthesiology 1986;65:6–12.
11. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, 1982.
12. Kisor DF, Schmith VD, Wargin WA, et al. Importance of the organ-independent elimination of cisatracurium. Anesth Analg 1996;83:1065–71.
13. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 1989;62:177–83.
14. Donati F, Varin F, Ducharme J, et al. Pharmacokinetics and pharmacodynamics of atracurium obtained with arterial and venous samples. Clin Pharmacol Ther 1991;49:515–22.
15. Stanski DR, Ham J, Miller RD, et al. Pharmacokinetics and pharmacodynamics of *d*-tubocurarine during nitrous oxide-narcotic and halothane anesthesia in man. Anesthesiology 1979;51:235–41.
16. Donati F, Gill SS, Bevan DR, et al. Pharmacokinetics and pharmacodynamics of atracurium with and without previous suxamethonium administration. Br J Anaesth 1991;66:557–61.