Pharmacokinetics of Cisatracurium in Patients Receiving Nitrous Oxide/Opioid/Barbiturate Anesthesia

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Background: Cisatracurium, one of the ten isomers in atracurium, is a nondepolarizing muscle relaxant with an intermediate duration of action. It is more potent and less likely to release histamine than atracurium. As one of the isomers composing atracurium, it presumably undergoes Hofmann elimination. This study was conducted to describe the pharmacokinetics of cisatracurium and its metabolites and to determine the dose proportionality of cisatracurium after administration of 2 or 4 times the ED95.

Methods: Twenty ASA physical status 1 or 2 patients undergoing elective surgery under nitrous oxide/opioid/barbiturate anesthesia were studied. Patients received a single rapid intravenous bolus dose of 0.1 or 0.2 mg·kg⁻¹ (2 or 4 times the ED95, respectively) cisatracurium. All patients were allowed to recover spontaneously to a train of four ratio ≥0.70 after cisatracurium-induced neuromuscular block. Plasma was extracted, acidified, and stored frozen before analysis for cisatracurium, laudanosine, the monooxynuqetary alcohol, and the monooxynuqetary alcohol metabolite.

Results: The clearances (5.28 ± 1.23 vs. 6.68 ± 0.67 ml·min⁻¹·kg⁻¹) and terminal elimination half-lives (22.4 ± 2.7 vs. 25.5 ± 4.1 min) were not statistically different between patients receiving 0.1 mg·kg⁻¹ and 0.2 mg·kg⁻¹, respectively. Maximum concentration values for laudanosine averaged 58 ± 21 and 103 ± 34 ng·ml⁻¹ for patients receiving the 0.1 and 0.2 mg·kg⁻¹ doses, respectively. Maximum concentration values for monooxynuqetary alcohol averaged 101 ± 27 and 253 ± 51 ng·ml⁻¹, respectively. Monooxynuqetary acid was not quantified in any plasma sample.

Conclusions: Cisatracurium undergoes Hofmann elimination to form laudanosine. The pharmacokinetics of cisatracurium are independent of dose after single intravenous doses of 0.1 and 0.2 mg·kg⁻¹. (Key words: Neuromuscular relaxants; cisatracurium. Pharmacokinetics: cisatracurium.)

Atracurium consists of ten stereoisomers. Cisatracurium (S1W89), which has the 1 R-cis, 1 R-cis configuration (fig. 1), is a nondepolarizing neuromuscular blocking agent. With an ED50 of 0.05 mg·kg⁻¹ in healthy patients receiving nitrous oxide/opioid/barbiturate anesthesia, it is on a molar basis, approximately 3.5 times more potent than atracurium. The clinical duration of action after a dose 2 times the ED50 of cisatracurium is 45 min, and it appears to be non-cumulative in that its recovery indexes remain constant regardless of the total dose given.

Because cisatracurium is one of the isomers of atracurium, it was expected to undergo spontaneous base catalyzed and temperature-dependent Hofmann elimination to form laudanosine as well as ester hydrolysis to monooxynuqetary alcohol and monooxynuqetary acid. In vitro studies of metabolism, however, suggest that Hofmann elimination, and not ester hydrolysis, is responsible for the breakdown of cisatracurium. The purposes of the present study were to determine the pharmacokinetics of cisatracurium and its metabolites in healthy surgical patients receiving nitrous oxide/opioid/barbiturate anesthesia and to determine the dose proportionality of cisatracurium after administration of doses of 2 and 4 mg·kg⁻¹, respectively.

Methods

Patient Selection

After obtaining approval from the New York Hospital-Cornell Medical Center Institutional Review Board, 20 patients, aged 16 to 65 yr, consented to participate. Patients were ASA physical status 1 or 2, scheduled to undergo elective surgery under general anesthesia. Patients with morbid obesity, chronic respiratory disease, or chronic renal disease were excluded from the study. None had a history of neoplastic disease, previous exposure to anticholinergic agents or muscle relaxants, or positive test for pregnancy. No patient had a history of atopy, asthma, or chronic obstructive pulmonary disease. No patient was at risk of having anaphylactic reactions to the study drugs.

On entering the recovery room, patients were assigned to receive cisatracurium (0.1 mg·kg⁻¹) and sufentanil (10 μg·kg⁻¹). These doses were repeated every 2 h until patients attained a normal level of consciousness (scores of 7 to 8 on a 10-point scale) and were able to follow commands. All patients were then extubated and transferred to the Anesthesiology Unit. After receiving a bolus injection of 2 mg·kg⁻¹ of cisatracurium, patients were scheduled to undergo a second series of injections. After the third injection of cisatracurium, patients were transferred to the surgical suite, where they were intubated and ventilated with nitrous oxide (50%), oxygen (40%), and sevoflurane (5%).

Anesthesia Management

General anesthesia was provided with fentanyl (20–85 μg·kg⁻¹·h⁻¹), sufentanil (2–10 μg·kg⁻¹·h⁻¹), and isoflurane (0.5–1.5 MAC).

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Fig. 1. Chemical formula of cisatracurium.

tion of doses of 2 and 4 times its ED₉₅ (0.1 and 0.2 mg·kg⁻¹, respectively).

Methods

Patient Selection

After obtaining approval from The New York Hospital—Cornell Medical Center Committee on Human Rights in Research, 20 patients, ranging in age from 23 to 65 yr, consented to participate in the study. All patients were ASA physical status 1 or 2 and were scheduled to undergo elective minor surgical procedures under general anesthesia. Patients were free of neuromuscular, hepatic, renal, pulmonary, or cardiovascular disease. None had a history of unusual susceptibility to neuromuscular blocking agents or of malignant hyperthermia. No patient had received antibiotics, with the exception of penicillin, cephalosporins, or tetracyclines, within the 48 h before enrollment in the study. None had received anticonvulsants, antidepressants, or antihistamines during the week before enrollment in the study. Female patients of childbearing potential were not pregnant as documented by a negative urine pregnancy test the morning of surgery, were using an approved method of birth control, or were scheduled to undergo a hysterectomy.

On consenting to participate in the study, ten patients were assigned to receive 2 times the ED₉₅ of cisatracurium (0.1 mg·kg⁻¹) and ten patients were assigned to receive 4 times the ED₉₅ of cisatracurium (0.2 mg·kg⁻¹).

Anesthetic Management and Patient Monitoring

General anesthesia was induced with intravenous midazolam (20–85 µg·kg⁻¹), fentanyl (5–7 µg·kg⁻¹), and thiopental (2–10 mg·kg⁻¹). The patients’ tracheae were intubated before the administration of cisatracurium and anesthesia was maintained with oxygen (30%), nitrous oxide (70%) and additional doses of intravenous fentanyl, midazolam, and thiopental as required to maintain an adequate depth of anesthesia. Mechanical ventilation was adjusted to maintain normocapnea.

Esophageal temperature was maintained between 35.1°C and 36.4°C with warmed intravenous fluids, blankets, and gas humidifiers. After induction of anesthesia, a second large-bore (16-G) intravenous catheter was inserted for venous blood sampling in the arm not containing the initial intravenous catheter.

Muscle Relaxant Administration

After a 3-min period of stabilization of the twitch response to neuromuscular stimulation, patients received either 2 (n = 10) or 4 (n = 10) times the ED₉₅ of cisatracurium (0.1 or 0.2 mg·kg⁻¹, respectively) into the tubing of a rapidly flowing intravenous infusion. Once neuromuscular function had recovered to a train-of-four ratio of ≥0.70, further neuromuscular block was provided, if required, with intermittent bolus doses of vecuronium (1–4 mg).

Determination of Plasma Concentrations of Cisatracurium and Its Metabolites

Five-milliliter venous blood samples were collected before and at 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 45, 60, 90, 120, 240, and 480 min after the administration of cisatracurium. Each sample was immediately transferred to a chilled 5-ml vacutainer tube (Becton Dickinson, Franklin Lakes, NJ) containing ethylenediaminetetraacetic acid and centrifuged. Within 3 min of the beginning of sample collection, 1 ml of plasma was decanted, mixed thoroughly with 4 ml of 15% sulfuric acid and placed on ice. The samples were stored frozen and later analyzed with a high-performance liquid chromatographic method with fluorescence detection for cisatracurium, laudanosine, and the monoquaternary alcohol metabolite. The lower limit of quantitation was 10 ng·ml⁻¹ for each analyte. The coefficients of variation for cisatracurium were less than 14% at concentrations between 10 and 2000 ng·ml⁻¹ for each analyte. The presence of the monoquaternary acid metabolite was assessed qualitatively by examination of chromatograms.

Pharmacokinetic Analysis

Noncompartmental. Noncompartmental analysis was performed using Microsoft Excel 4.0 (Redmond, WA). Cisatracurium plasma concentration versus time data were analyzed by log-linear regression for esti-
mation of the terminal slope (β). The area under the plasma cisatracurium concentration-time curve from time 0 until the last measured concentration was calculated using the linear trapezoidal rule. The terminal slope was used to extrapolate the area under the plasma cisatracurium concentration versus time curve from the last measured time point to infinity. The total area under the cisatracurium concentration-time curve (AUC_{con-\infty}) was calculated as the sum of the area under the curve from time 0 to the last measured concentration plus the area under the curve extrapolated to time infinity. Cisatracurium clearance was calculated using the equation Cl = Dose/AUC_{con-\infty}, where Dose is the intravenous bolus dose of cisatracurium. The steady-state volume of distribution (Vss) was calculated as Vss = Cl ∙ AUC_{0-\infty}/AUC_{con-\infty}, where AUC_{0-\infty} is the area under the first moment curve from time 0 to time infinity (AUC_{0-\infty} = AUC_{0-\infty} + Cp/β^2 + t ∙ Cp/β) and Cp is the last measured concentration and t is the time of the last measured concentration. The terminal elimination phase half-life of cisatracurium was calculated as the ln(2) divided by the terminal slope (β).

Compartmental. A nontraditional two-compartment model (i.e., with elimination from both the central compartment and the peripheral compartment) was fitted to the plasma cisatracurium concentration-time data from individual patients using NONLIN. The rate constant (k_{in}) describing elimination from the peripheral compartment could not be estimated independently and was, therefore, fixed to 0.0237 min^{-1}; the average rate constant describing the in vitro degradation of cisatracurium in plasma from nine healthy volunteers. The NONLIN user-defined subroutine was written with k_{20} fixed at 0.0237 min^{-1}) to generate estimates of Vc and the micro rate constants k_{in}, k_{12}, and k_{21}. The Cl and Vss were then calculated using the following two equations:

\[ Cl = Vc ∙ [k_{in} + (k_{20} ∙ k_{12} / (k_{20} + k_{21}))], \]  

\[ Vss = Vc ∙ [1 + k_{12} / (k_{21} + k_{20})]. \]

Metabolite Pharmacokinetics. The pharmacokinetics of laudanosine and the monooquaternary alcohol metabolite were evaluated using noncompartmental methods. The maximum concentration (C_{max}) and the time of occurrence of C_{max} (T_{max}) were determined by direct inspection of the plasma concentration-time data for each of the metabolites. The elimination half-life, AUC_{0-\infty}, and the ratio of the AUC_{0-\infty} for each metabolite to AUC_{0-\infty} for cisatracurium were calculated.

Statistical Analysis

Demographic data (age, weight, height, and gender composition), end-tidal carbon dioxide concentration, and temperature data were compared between the two study groups with Student's t test, Fisher's exact test, or Wilcoxon's rank sum test as appropriate. P ≤ 0.05 was considered to be statistically significant.

Frequency distribution plots and box plots of data were examined to assess the distribution of pharmacokinetic parameter value estimates. Log (ln) transformations were performed on data where appropriate. Values of parameters suspected as being outliers were tested using the Dixon test. Those found to be outliers were omitted from data analysis. Student's t test for unpaired data with unequal variance was performed using Minitab (Minitab Inc., State College, PA) to examine differences in pharmacokinetic values between the dose groups receiving 2 times the ED_{95} and 4 times the ED_{95}.

Results

Demographics

As shown in table 1, the study groups were similar in terms of age and weight. The patients receiving 4 times the ED_{95} of cisatracurium tended to be taller than those receiving 2 times the ED_{95} of relaxant. All patients studied were within 30% of their ideal body weight. All of the patients receiving 4 times the ED_{95} of cisatracurium were men, whereas 40% of the patients receiving the smaller dose of drug were women. This difference in gender composition of the two study groups was not statistically significant (table 1). The end-tidal carbon dioxide concentration for patients receiving either 2 or 4 times the ED_{95} of cisatracurium was not significantly different (31.6 ± 0.9 and 30.2 ±

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics</th>
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<tbody>
<tr>
<td>2× ED_{95}</td>
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<tr>
<td>(0.1 mg·kg^{-1})</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>% IBW</td>
</tr>
<tr>
<td>Gender (M/F)</td>
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</tbody>
</table>

Values are mean ± SD.

IBW = ideal body weight.

* P < 0.05.
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Fig. 2. Individual patient plasma concentration versus time-course data for cisatracurium after single intravenous doses of 0.1 mg · kg⁻¹ (---) and 0.2 mg · kg⁻¹ (-----). Data are mean ± SD; n = 10 in each group. The Cₘₐₓ for cisatracurium were 1,400 ± 663 and 3,519 ± 929 ng · ml⁻¹ for the 2× and 4× ED₉₅ groups, respectively.

1.9 mmHg, respectively). Similarly, patient temperature was the same in the two study groups (35.5 ± 0.3 vs. 35.7 ± 0.7°C, in the 2 and 4 times the ED₉₅ groups, respectively).

Cisatracurium

The cisatracurium plasma concentration versus time data are presented in figure 2. The dose-normalized mean concentration versus time data are presented in figure 3. The plasma concentrations of cisatracurium declined in a biexponential fashion. The highest observed cisatracurium concentration occurred at 2 min after dosing for each of the patients (the earliest sampling point). Dose-normalized cisatracurium concentration-time curves were similar, although dose-normalized concentrations were slightly higher in patients receiving the 0.2 mg · kg⁻¹ dose (mean ± SD dose-normalized Cₘₐₓ: 1,400 ± 663 and 1,760 ± 465 ng · ml⁻¹ for the 0.1 and 0.2 mg · kg⁻¹ dose groups, respectively). This difference did not reach statistical significance (P = 0.18).

The pharmacokinetic parameter values (determined using compartmental and noncompartmental methods) for cisatracurium are presented in table 2. Whether
Table 2. Pharmacokinetics of Cisatracurium

<table>
<thead>
<tr>
<th>Noncompartmental (elimination from central compartment only)</th>
<th>Compartmental (elimination from both compartments)</th>
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<tr>
<td>2× ED₉₅ (0.1 mg·kg⁻¹)</td>
<td>4× ED₉₅ (0.2 mg·kg⁻¹)</td>
</tr>
<tr>
<td>Clearance (ml·min⁻¹·kg⁻¹)</td>
<td>5.28 ± 1.23</td>
</tr>
<tr>
<td>tₑ₀/₂ (min)</td>
<td>22.4 ± 2.7</td>
</tr>
<tr>
<td>Vₙ (ml·kg⁻¹)</td>
<td>144 ± 34</td>
</tr>
</tbody>
</table>

Vₙ = volume of distribution at steady state; tₑ₀/₂ = elimination half-life. Values are mean ± SD.
* Vₙ determined using noncompartmental methods is underestimated.

determined using compartmental or noncompartmental methods, there were no significant differences between the dose groups in CI, Vₙ, and elimination half-life. The power to detect a 20% difference in CI was 0.96. For all other pharmacokinetic parameters, the power ranged from 0.85 to 1.00. The Vₙ (calculated using noncompartmental methods) was underestimated by 17.2 ± 11.9% and 20.2 ± 14.4% in the 2 and 4 times the ED₉₅, groups, respectively. The mean ± SD AUC₀→∞ values (calculated using noncompartmental methods) were 21.07 ± 4.05 and 46.81 ± 6.66 min·µg⁻¹·ml⁻¹, for the groups receiving 2 and 4 times the ED₉₅ of cisatracurium, respectively. The ratio of this value for the two groups, therefore, was 2.25. Comparison of the dose-normalized AUC₀→∞ between patient groups did not reach statistical significance (P = 0.17).

Metabolites
The laudanosine plasma concentration-time data are shown in figure 4. The calculated pharmacokinetic variables for laudanosine are presented in table 3. The Cₘ₉₅ of laudanosine ranged from 13 to 86 ng·ml⁻¹ in the 2 times the ED₉₅ group and from 66 to 174 ng·ml⁻¹ in the 4 times the ED₉₅ group. The Tₘ₉₅ ranged from 2 to 90 min and from 2 to 60 min after the administration of 2 or 4 times the ED₉₅ of cisatracurium, respectively.

The monoquaternary alcohol plasma concentration-time profile is shown in figure 5. The pharmacokinetics of the monoquaternary alcohol are summarized in table 4. The Cₘ₉₅ for the monoquaternary alcohol metabolite was 101 ± 27 ng·ml⁻¹ and 253 ± 51 ng·ml⁻¹ after administration of the 2 and 4 times the ED₉₅ doses, respectively. The Tₘ₉₅ occurred from 2 to 25 min after a dose 2 times the ED₉₅ and from 2 to 15 min after a dose 4 times the ED₉₅.

Discussion
The pharmacokinetics of cisatracurium are independent of dose after doses of 0.1 and 0.2 mg·kg⁻¹ (2 and 4 times the ED₉₅, respectively). The plasma concentration-time data for patients receiving 0.1 or 0.2 mg·kg⁻¹ cisatracurium are shown in figure 5. The laudanosine plasma concentration-time data for patients receiving 2 and 4 times the ED₉₅ of cisatracurium are shown in figure 4. The elimination half-life of laudanosine appears to be longer than the elimination half-life of cisatracurium in humans (53 min). Therefore, the elimination appears to be delayed.
Table 3. Pharmacokinetics of Laudanosine

<table>
<thead>
<tr>
<th></th>
<th>2× ED₉₅ (0.1 mg · kg⁻¹)</th>
<th>4× ED₉₅ (0.2 mg · kg⁻¹)</th>
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<tbody>
<tr>
<td>AUC₀⁻∞ * (min · µg · ml⁻¹)</td>
<td>10.15 ± 6.73</td>
<td>25.04 ± 5.84†</td>
</tr>
<tr>
<td>Cmax (ng · ml⁻¹)</td>
<td>38 ± 21</td>
<td>103 ± 34†</td>
</tr>
<tr>
<td>t₁/₂β (h)</td>
<td>3.6 ± 2.6</td>
<td>4.3 ± 1.6</td>
</tr>
<tr>
<td>β⁺ (L · hr⁻¹)</td>
<td>0.271 ± 0.157</td>
<td>0.176 ± 0.063</td>
</tr>
<tr>
<td>AUC₀⁻∞/AUC₀⁻∞</td>
<td>0.47 ± 0.28</td>
<td>0.54 ± 0.36</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

AUC₀⁻∞ * = area under the curve from time₀⁻∞; Cmax = maximum concentration; t₁/₂β = terminal half-life; β⁺ = elimination rate constant.

* Data from one patient were determined to be outliers using Dixon's criteria and were excluded from summary statistics.

† P < 0.05.

Table 4. Pharmacokinetics for the Monoquaternary Alcohol

<table>
<thead>
<tr>
<th></th>
<th>2× ED₉₅ (0.1 mg · kg⁻¹)</th>
<th>4× ED₉₅ (0.2 mg · kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀⁻∞ * (min · µg · ml⁻¹)</td>
<td>6.39 ± 1.31</td>
<td>15.85 ± 4.38†</td>
</tr>
<tr>
<td>Cmax (mg · ml⁻¹)</td>
<td>101 ± 27</td>
<td>253 ± 51†</td>
</tr>
<tr>
<td>t₁/₂β* (min)</td>
<td>34.4 ± 5.9</td>
<td>41.4 ± 12.9</td>
</tr>
<tr>
<td>β⁺ (L · min⁻¹)</td>
<td>0.0195 ± 0.0049</td>
<td>0.185 ± 0.0064</td>
</tr>
<tr>
<td>AUC₀⁻∞/AUC₀⁻∞</td>
<td>0.31 ± 0.08</td>
<td>0.34 ± 0.08</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

AUC₀⁻∞ * = area under the curve from time₀⁻∞; Cmax = maximum concentration; t₁/₂β = terminal half-life; β⁺ = elimination rate constant.

* Data from one patient were determined to be outliers using Dixon's criteria and were excluded from summary statistics.

† P < 0.05.

The pharmacokinetic analyses of cisatracurium are complicated by the finding that cisatracurium undergoes Hofmann elimination, which can occur in the plasma and the tissues. One must assume that elimination occurs only from the central compartment to use noncompartmental pharmacokinetic methods. Violation of this assumption does not affect the estimation of CI, but results in an underestimation of Vₐ. For the nontraditional two-compartment model (with elimination from both compartments), one must assume that: (1) the rate constant describing elimination from the peripheral compartment is the same as the average rate constant describing the in vitro degradation of cisatracurium in plasma from nine healthy volunteers, and (2) Hofmann elimination occurs at the same rate.
in the central and peripheral compartments. These are considered reasonable because (1) Hofmann elimination is pH- and temperature-dependent and the physiologic ranges of pH and temperature are small, (2) the coefficient of variation of the in vitro rate constant in plasma from nine healthy volunteers was small (1%), and (3) the in vitro rate constant does not change substantially when cisatracurium is incubated in buffer or plasma. Violation of the assumptions may have impact on the estimation of $V_e$. Analysis of the data using both methods (noncompartmental and compartmental) have provided insight into the pharmacokinetic characteristics of cisatracurium.

Clearance values were similar when calculated using noncompartmental methods or a nontraditional two-compartment model (with elimination from central and peripheral compartments). This finding is expected because CI is an exit-site-independent parameter (i.e., independent of whether elimination is occurring from only the central or from both the central and peripheral compartments). The $V_e$ values were 17–20% lower when calculated using noncompartmental methods than when calculated using the nontraditional two-compartment model (with elimination from the central and peripheral compartments); this finding is not surprising because $V_e$ is underestimated when ignoring elimination from the peripheral compartment.

This study demonstrates that the pharmacokinetics of cisatracurium are proportional to dose. This finding is not unexpected because cisatracurium, one of the isomers comprising atracurium, undergoes degradation by Hofmann elimination. Because Hofmann elimination is a nonenzymatic chemical process, one would not anticipate nonlinear metabolism (i.e., a dose-dependent clearance). One would also not anticipate saturable tissue binding because of the limited distribution of cisatracurium in tissues. Small differences (11–12%) in $V_e$ and CI were observed between patient groups, although these differences were not statistically significant. The 11% smaller $V_e$ in patients receiving the higher dose can be explained only by saturable tissue binding, a highly unlikely event considering the limited distribution of cisatracurium (i.e., $V_e$ is not greater than extracellular fluid volume). These small differences more likely represent interpatient variability. The 11% smaller $V_e$ could account for the 12% lower CI, a relationship that has been reported for atracurium. Most importantly, even with adequate power, no statistically significant differences between groups were detected in any pharmacokinetic parameters. Thus, as with atracurium, the pharmacokinetics of cisatracurium are proportional to dose.

The clearance of 2 and 4 times the ED$_{95}$ of cisatracurium (5.28 and 4.66 ml·kg$^{-1}$·min$^{-1}$, respectively) is consistent with values reported previously for atracurium (5.5$^{11}$ and 6.1$^{12}$ ml·kg$^{-1}$·min$^{-1}$) and for the intermediate-duration steroidal relaxants vecuronium (ranging from 5.5 to 7.6 ml·kg$^{-1}$·min$^{-1}$)$^{15,16}$ and rocuronium (ranging from 2.9 to 5.0 ml·kg$^{-1}$·min$^{-1}$)$^{15,16}$ in young adults free of hepatic or renal disease receiving 2 times the ED$_{95}$ of either relaxant.

Hofmann elimination is a spontaneous temperature- and concentration-dependent decomposition of the parent compound resulting in the formation of laudanosine. Previous studies have demonstrated that as a result of in vitro decreases of temperature of 14°C, from 37°C to 23°C, the in vitro plasma half-life of atracurium increases from 18 to 49 min. Hypothermic patients undergoing cardiopulmonary bypass have a lower atracurium dose requirement presumably because of an altered response of muscles or because of the relaxant's lower clearance and prolonged elimination half-life. Patients in both study groups were the same temperature, eliminating this as a factor affecting the clearance of cisatracurium.

Hofmann elimination is also a base catalyzed process. In cats, average increases of pH of 0.32–0.40, with either hyperventilation or infusion of sodium bicarbonate (Na$_2$CO$_3$), decreased the depth of atracurium-induced neuromuscular block by approximately two-fold. Although pH was not specifically measured in the patients in this study, none had evidence of pulmonary disease and mean end-tidal carbon dioxide concentrations in all the patients in each group were indistinguishable. Furthermore, no patient had evidence of end-organ disease that could have affected acid-base status, such as renal disease.

In compliance with the standards of the Committee on Human Rights in Research at The New York Hospital-Cornell Medical Center, the study was undertaken using venous, rather than arterial, blood. Donati et al.$^{20}$ reported on pharmacokinetics and pharmacodynamics of atracurium determined with arterial and venous blood. While they found that relaxant concentrations were greater than 50% greater in the arterial than in the venous blood for the first 3 min after administration of atracurium, the concentration of atracurium in venous samples was approximately 90% of that measured in arterial samples by 20 min. In contrast, the CI of atracurium in patients in this study was only 6% higher than that reported by others in whom venous blood was sampled. Most importantly, venous blood sampling was performed in the current study in both patient groups.

Although we were able to confirm that alcohol as a metabolite of propofol does not appear to undergo Hofmann elimination in contrast to the elimination of atracurium, which occurs by cleavage of ester hydrolysis and Hofmann elimination, it is unclear whether the unusual organ-dependent elimination of atracurium undergoes Hofmann elimination, a monoquaternary amine with the acrylne carbonyl moiety most likely undergoes Hofmann elimination. The lack of ester hydrolysis and Hofmann elimination may explain our inability to detect any metabolites that undergo Hofmann elimination in any plasma sample.

Although the elimination half-life reported in this study, 3.3 days, was similar to previous values calculated previously and the administration of atracurium was not associated with the ED$_{95}$ dose of cisatracurium that is expected for an effective anesthetic level (1.5 times the ED$_{95}$ of atracurium), direct comparisons are not possible because the patients were in different states of anesthesia. In part, by relative potent effect of atracurium and are administered with a loading dose of 0.5 mg. For this reason, we speculate that the effect of atracurium, by infusing a maximum plasma concentrations of cisatracurium, is unlikely to be lower than the ED$_{95}$ dose of atracurium.
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Ataracurium in patients in whom arterial blood was collected was only 4% higher than the CI in patients from other studies in whom venous blood was collected. Most importantly, venous blood was collected in all patients in the current study and therefore is consistent between patient groups.

Although we were able to detect the monoquaternary alcohol as a metabolite of cisatracurium, cisatracurium does not appear to undergo ester hydrolysis. This is in contrast to the elimination of atracurium from the plasma, which occurs by a number of mechanisms including ester hydrolysis as well as Hofmann elimination and organ-dependent elimination. Cisatracurium undergoes Hofmann elimination to form laudanosine and a monoquaternary acrylate. The monoquaternary acrylate most likely undergoes hydrolysis by non-specific plasma esterases to form a monoquaternary alcohol. The lack of ester hydrolysis of cisatracurium may explain our inability to detect monoquaternary acid in any plasma sample.

Although the elimination half-life of laudanosine reported in this study, 3.6 h, is not very different from values calculated previously for laudanosine after the administration of atracurium, 3.3 h, the maximum concentration of laudanosine measured after 2 times the ED_{50} dose of cisatracurium, 38 ng·mL^{-1}, is far less than that reported after administration of approximately 1.5 times the ED_{50} of atracurium, 190 ng·mL^{-1}. While direct comparisons are not possible because these values were obtained in different studies, a lower maximum plasma concentration of laudanosine after administration of cisatracurium can be explained, at least in part, by relative potencies. Cisatracurium is 3.5 times more potent than atracurium and thus, fewer molecules are administered with an initial bolus dose. As a result of this, we speculate that, on long-term administration of cisatracurium, by infusion or repeat bolus doses, the maximum plasma concentrations of laudanosine should likely be lower than those observed after administration of atracurium.

The C_{max} for laudanosine ranged from 13 to 86 ng·mL^{-1} and from 66 to 174 ng·mL^{-1} in healthy adult patients receiving 0.1 and 0.2 mg·kg^{-1} cisatracurium, respectively. These concentrations are approximately 30-fold and >100-fold lower than the plasma laudanosine concentrations associated with cerebral excitatory effects in rabbits or dogs, respectively. In addition, no clinical evidence of cerebral irritation or excitation attributable to cisatracurium has been reported in surgical or in intensive care patients.

In summary, the pharmacokinetics of cisatracurium are independent of dose after doses of 0.1 and 0.2 mg·kg^{-1} (2 and 4 times the ED_{50}, respectively) of cisatracurium. This finding was expected due to its degradation by Hofmann elimination. The pharmacodynamic results are consistent with the dose-proportional pharmacokinetic results from this study. Increasing the dose has a predictable effect on the duration of block. The rate of spontaneous recovery is independent of dose up to doses of 8× ED_{50} and duration of infusion.

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References


Mechanical Strength Activity in Human Intercostal Muscles

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Background: Prior human studies have demonstrated that mechanical activity in intercostal muscle is increased during mechanical ventilation (MV) compared to quiet breathing (QB). The purpose of this study was to determine if the mechanical significance of external intercostal muscle during halothane anesthesia and to inspiratory rib cage muscle activity during halothane anesthesia was modified by the administration of an MV device.

Methods: Six subjects (3 male and 3 female) were studied in a randomized, double-blind, placebo-controlled, randomized, placebo-controlled, crossover design. 

The study was approved by the Institutional Review Board, and informed consent was obtained from all patients. The study was conducted with the knowledge and approval of the institutional review board.

Results: The mechanical activity of intercostal muscle increased significantly during MV compared to quiet breathing. The mechanical activity was not significantly different between the two anesthetic regimens, and no significant effects were detected on the mechanical activity of intercostal muscle during MV.

Conclusion: The mechanical activity of intercostal muscle during MV increased significantly compared to quiet breathing. The mechanical activity was not significantly different between the two anesthetic regimens, and no significant effects were detected on the mechanical activity of intercostal muscle during MV.

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