Pharmacodynamics and Pharmacokinetics of Cisatracurium in Geriatric Surgical Patients

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Background: Cisatracurium, one of ten stereoisomers that comprise atracurium, is more potent than atracurium and has less propensity to release histamine. This study compares the pharmacokinetics and pharmacodynamics of cisatracurium in elderly and young patients.

Methods: Twelve elderly (aged 65–82 yr) and 12 younger patients (aged 30–49 yr) were anesthetized with nitrous oxide, fentanyl, and isoflurane (0.7%, end-tidal). The mechanomyographic response to train-of-four stimulation was assessed every 15 s after the administration of cisatracurium (0.1 mg/kg). Arterial samples were obtained over 6 h. Plasma cisatracurium concentration versus time data were fit to compartmental models. Pharmacokinetic parameters were determined assuming that elimination occurred from the central compartment only. This provides accurate clearance and half-life estimates but underestimates \( V_e \) (reported herein as \( V_{\text{m}} \)). The pharmacodynamic response was described by the neuromuscular blocking profile.

Results: Onset to 90% paralysis (mean ± SD) was delayed in the elderly (3.4 ± 1.0 vs. 2.5 ± 0.6 min). Recovery profiles were the same for both groups. Elimination half-life was minimally prolonged in the elderly (25.5 ± 3.7 vs. 21.5 ± 2.4 min). The \( V_{\text{m}} \) was larger in the elderly (126 ± 16 vs. 108 ± 13 ml/kg), although the clearances were the same for the two groups (5.0 ± 0.9 vs. 4.6 ± 0.8 ml·kg\(^{-1}\)·min\(^{-1}\)).

Conclusions: There are minor differences in the pharmacokinetics of cisatracurium between elderly and young patients. These differences are not associated with changes in recovery profile after a single bolus dose, although the mean time to onset was approximately 1 min longer in elderly patients. (Key words: Cisatracurium. Elderly. Neuromuscular relaxants. Pharmacodynamics. Pharmacokinetics.)

CISATRACURIUM (NIMBEX), an investigational muscle relaxant, is one of ten stereoisomers that comprise atracurium. The clinical pharmacology of cisatracurium has been studied in adult patients by Belmont et al.¹ and Lien et al.² Cisatracurium was found to be approximately three times more potent than atracurium and was devoid of cardiovascular side effects in doses of up to 8 times the ED\(_{50}\). The duration of cisatracurium-induced neuromuscular blockade was similar to atracurium.

The elimination of atracurium is primarily dependent on spontaneous degradation by Hofmann elimination and hydrolysis by plasma esterases.³ These pathways are not likely to be markedly affected by advancing age. However, some studies reported larger volumes of distribution and longer elimination half-lives in elderly patients than in younger patients.⁴⁻⁶

Hofmann elimination may have a greater role in the elimination of cisatracurium than in the elimination of atracurium.⁷ Thus, it is likely that the clearance of cisatracurium would not be altered by advancing age. The purpose of the current study was to delineate any differences in the pharmacokinetics and pharmacodynamics of cisatracurium in elderly patients compared to younger control patients.
PHARMACOLOGY OF CISATRACURIUM IN THE ELDERLY

Methods and Materials

This study was approved by the Institutional Review Board of the Columbia University College of Physicians and Surgeons. Written informed consent was obtained from 12 elderly (aged 65–82 yr) and 12 younger (aged 30–49 yr) adult patients scheduled for elective neurosurgical procedures. All patients were ASA physical status 1 or 2. Patients with significant renal, hepatic, metabolic, or neuromuscular disorders or whose body weights exceeded 150% of ideal body weight were excluded, as were those receiving anticonvulsants or other medications known to affect the response to neuromuscular blockers.

At the discretion of the anesthesiologist, patients were premedicated with 5–15 mg oral diazepam and/or 0.2 mg intramuscular glycopyrrolate approximately 90 min before arrival to the operating room. During placement of intravenous and intraarterial catheters, 0.01–0.04 µg/kg midazolam was administered intravenously. Anesthesia was induced with thiopental up to 10 mg/kg and fentanyl in 50–100 µg increments as needed to treat increases in heart rate and blood pressure. Maintenance anesthesia consisted of 0.7% isoflurane, end-tidal in nitrous oxide/oxygen (70/30), and additional fentanyl, as necessary.

Neuromuscular transmission was assessed in response to supramaximal train-of-four stimulation (0.2 ms at 2 Hz for 2 s) from a Grass S-88 stimulator and stimulus isolation unit to the ulnar nerve at the wrist repeated every 15 s. Evoked adductor pollicis twitch tension was measured with a Grass FT-10 force-displacement transducer. Baseline twitch response was obtained over 3 min, commencing at least 15 min after initiation of isoflurane. Cisatracurium (0.1 mg/kg, 2 x the ED95 reported for adults during balanced anesthesia) was administered intravenously over 5–10 s. Calculations of the degree of neuromuscular block were based on comparison of the first component of the train-of-four (T1) to baseline. For recovery data, comparisons were made to the final baseline, which averaged 99.5 ± 14.2% of the initial baseline. Variables used to define the pharmacodynamic response included the times to onset of 90% and maximum blockade, the maximum intensity of muscle paralysis, and the times of return of twitch response to 5%, 25%, 75%, and 95% of baseline twitch. The 25–75% recovery index was calculated. The time at which the ratio of the fourth to first twitch of the train-of-four equaled or exceeded 70% was noted. The percent twitch suppression relative to baseline was also measured at the time of each blood sample.

Five-milliliter arterial blood samples were obtained in chilled tripotassium EDTA vacutainer tubes 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 and placed in chilled microcentrifuge tubes. Each sample was immediately centrifuged for 5 s. Exactly 1 ml of the separated plasma was added to 4 ml of 15 mm H2SO4 and mixed thoroughly. All processed samples were placed in ice within 2 min, 10 s of collection and frozen within 30 min of collection to prevent degradation. Plasma concentration of cisatracurium and laudanosine were determined using a validated high performance liquid chromatographic method with fluorescence detection. The assay was sensitive to 10 ng/ml with an accuracy of 9% and precision of 13% between the ranges of 10–2,000 ng/ml for cisatracurium and 10–1,000 ng/ml for laudanosine.

In patients requiring bladder catheterization, urine was collected for up to 10 h into 0.5 m sodium citrate buffer at pH 3.0. These samples were used to estimate the amounts of unchanged cisatracurium and its metabolites excreted by the kidney.

Bi- and triexponential functions were fit to the plasma cisatracurium concentration versus time data by generalized least-squares regression, with the inverse square of the predicted concentration used as the iterative weighting function. Boxenbaum’s method was used to determine whether a two- or three-compartment model provided a more appropriate fit to the data. Pharmacokinetic parameters, including plasma clearance, half-life of elimination, initial volume of distribution, and steady-state volume of distribution were calculated using standard equations for bolus intravenous injection with elimination solely from the central compartment.

Data are expressed as mean values ± SD. Comparison between groups were made with two-tailed Student’s t-test. The threshold for statistical significance was set at P ≤ 0.05.

Results

Demographic, pharmacokinetic, and pharmacodynamic data appear in table 1. Because of the short du-
Table 1. Summary of Demographic, Pharmacokinetic, and Pharmacodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Elderly</th>
<th>Young</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>72 ± 5</td>
<td>42 ± 5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.9 ± 10.8</td>
<td>77.6 ± 16.2</td>
<td>NS</td>
</tr>
<tr>
<td>Onset (min)</td>
<td>3.4 ± 1.0</td>
<td>2.5 ± 0.6</td>
<td>0.015</td>
</tr>
<tr>
<td>T_max (min)</td>
<td>5.2 ± 1.3</td>
<td>4.2 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Max (%)</td>
<td>99.0 ± 1.8</td>
<td>99.5 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>T5 (min)</td>
<td>44.8 ± 11.5</td>
<td>44.8 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>T25 (min)</td>
<td>61.1 ± 13.8</td>
<td>55.6 ± 9.2</td>
<td>NS</td>
</tr>
<tr>
<td>T75 (min)</td>
<td>78.2 ± 16.8</td>
<td>71.1 ± 11.0</td>
<td>NS</td>
</tr>
<tr>
<td>T95 (min)</td>
<td>88.6 ± 10.2</td>
<td>83.7 ± 12.1</td>
<td>NS</td>
</tr>
<tr>
<td>TT4o</td>
<td>81.6 ± 12.7</td>
<td>82.5 ± 10.3</td>
<td>NS</td>
</tr>
<tr>
<td>RI (min)</td>
<td>19.0 ± 4.5</td>
<td>16.1 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Clp (ml·kg⁻¹·min⁻¹)</td>
<td>5.0 ± 0.9</td>
<td>4.6 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Vl (ml/kg)</td>
<td>57.8 ± 16.3</td>
<td>57.2 ± 15.2</td>
<td>NS</td>
</tr>
<tr>
<td>Vss (ml/kg)</td>
<td>126 ± 16</td>
<td>108 ± 13</td>
<td>0.008</td>
</tr>
<tr>
<td>Tss (min)</td>
<td>25.5 ± 3.7</td>
<td>21.5 ± 2.4</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Data are mean ± SD. For demographic data, n = 12 for both groups. For time of onset to 90% block (Onset), time to maximum block (T_max), magnitude of maximum block (Max), and recovery times to 5% and 25% of baseline (T5 and T25), n = 11 for both groups. For recovery to 75% of baseline (T75) and recovery index (RI), n = 10 in both groups. For 95% recovery (T95) and 70% tramod-four ratio (TT4o), n = 9 in the elderly and n = 10 in the control group.

For the pharmacokinetic variables, plasma clearance (Clp), elimination half-life (T1/2β), initial (Vl), and steady-state (Vss) volumes of distribution, n = 12 in the elderly and n = 11 in the control group.

NS = not significant.

* This term underestimated the actual Vss.

One elderly patient was chronically receiving diltiazem. Because calcium channel blockers may potentiate the effect of neuromuscular blockers, this patient was eliminated from the pharmacodynamic analysis. Recovery to 25% of baseline was delayed in this patient (71 min) with an increased recovery index (26 min).

Onset of paralysis to 90% twitch depression was delayed by approximately 1 min in the elderly group. Maximum twitch depression equaled or exceeded 95% in all patients. No significant differences were noted in spontaneous recovery profile between the two groups (fig. 1).

Cisatracurium could be detected in plasma up to 120 min in 18 patients (10 elderly and 8 young), and in the remaining 6 patients (2 elderly and 4 young), up to 90 min. Pharmacokinetic data was described by a biexponential function. The plasma concentration versus time curves for the two groups (fig 2) are almost superimposable. There was a 4-min prolongation (19%) in the elimination half-life in the elderly compared to the control group. There was a 17% increase in the volume of distribution in elderly patients; there

ration of the surgical procedure, two elderly patients received neostigmine for antagonism of residual neuromuscular blockade before the attainment of 90% recovery. Of note, spontaneous recovery was moderately prolonged in these two elderly patients requiring neostigmine (T25 of 81 and 87 min).

On examination of the pharmacokinetic data, Clp (9.9 ml·kg⁻¹·min⁻¹) and Vss (257 ml/kg) from one of the younger control patients were determined to be outliers based on Dixon's criterion, or t-ratio test, comparing the distance of one end observation from its nearest neighbor with the range of all observations.11,12 This patient was eliminated from summary statistics. Retrospective analysis suggests that this patient may have received a dose of cisatracurium that was lower than that required by the study protocol inasmuch as plasma cisatracurium concentrations for this patient ranged between 40% and 55% of the average for the young patients. Recovery to 25% of baseline was accelerated (33 min), with a recovery index (17 min) and elimination half-life (24.8 min) that was consistent with the other patients.

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Fig. 1. Times from injection of 0.1 mg/kg cisatracurium to recovery of 5%, 25%, 75%, and 95% of baseline twitch (n = 11 in each group). Data are mean with error bars denoting standard deviation.
was no difference in plasma clearance between elderly and younger patients.

Urine was collected from only two elderly and four young patients and hence was not subjected to statistical analysis. Renal excretion of unchanged cisatracurium accounted for 9–15% of the injected dose in the elderly patients and 11–24% of the dose in the young patients.

The maximum plasma concentrations of laudanosine, a product of Hofmann elimination, were 22 ± 5 ng/ml in elderly patients and 20 ± 5 ng/ml in the younger patients (NS). In most patients, laudanosine concentrations were quantifiable until up to 4 h (one predicted elimination half-life for laudanosine following atracurium administration). The half-life of laudanosine could only be determined in six elderly patients and three younger patients and ranged from 4.4 to 10.9 h.

Discussion

The onset of neuromuscular block after a 2× ED₉₅ dose of cisatracurium is approximately 1 min longer in the elderly, possibly related to a slower circulation time. Slight prolongation of onset time for atracurium in elderly patients has been reported by other investigators. The recovery profile is similar for both groups and prolonged by approximately one-third compared to previously reported data in patients not exposed to volatile anesthetics.

A larger distribution volume in the elderly contributed to a small increase in elimination half-life. The similar total clearances observed are consistent with the minor role played by renal elimination. Recent simulations suggest that organ-dependent elimination of cisatracurium is much less significant than previously reported for atracurium. The age-related differences in distribution volume and half-life reported here lie within those reported for atracurium by Kitts et al. and Kent et al. It is of interest that the distribution volume for cisatracurium in the elderly was greater than in the young despite the decrease in extracellular fluid space associated with the aging process. Similar findings by Kitts et al. for atracurium were attributed to a potential decrease in plasma binding.

The two-compartment model used in this study assumed elimination from only the central compartment. As described by Fisher et al., a more accurate model would also account for elimination from the peripheral compartment. Unfortunately, the inability to obtain an in vivo estimate for Hofmann elimination precluded
the use of a model that included elimination from the peripheral compartment. Of note, Hull has suggested that inasmuch as plasma concentration is the only basis for the model, the single output model used in this study, despite conceptual limitations, is equally valid as a model with an additional output from the peripheral compartment.\textsuperscript{18} Other limitations of the more complex model include the assumption that the rate constants for non-organ elimination are the same in the two compartments and are equal to that observed in vitro.\textsuperscript{15} The choice of model does not affect the calculations of $C_{\text{eq}}$ and $V_{\text{t}}$, because these parameters are exit-site independent parameters. $V_{\text{ss}}$, however, is underestimated if elimination from the peripheral (tissue) compartment is ignored.\textsuperscript{19}

Because the pharmacokinetic profile for cisatracurium is minimally affected by the aging process, there appears to be no difference between age groups in plasma laudanosine concentration. Laudanosine has been found to produce cerebral excitation or seizures when administered intravenously alone at high concentrations in some animal species.\textsuperscript{20,21} The relationship between plasma laudanosine concentrations and adverse experiences in humans is unknown. Peak plasma laudanosine concentration of between 0.29 and 8.65 $\mu$g/ml during atracurium administration have been reported in patients in intensive care units.\textsuperscript{22-28} No clinical evidence of cerebral irritation or excitation attributable to atracurium was reported in these cases.

In this study, the $C_{\text{max}}$ for laudanosine ranged from 15 to 29 ng/ml and from 13 to 30 ng/ml in elderly patients and younger control patients, respectively. These concentrations are >100-fold lower than those associated with cerebral excitatory effects in rabbits\textsuperscript{20} or dogs.\textsuperscript{21} In addition, no cerebral irritation or excitation attributable to cisatracurium has been reported in the current study or in studies in ICU patients.\textsuperscript{29}

It is noteworthy that the small pharmacokinetic changes reported are almost imperceptible on examination of the plasma concentration versus time curve and that the recovery profiles are similar for the two groups. Because isoflurane dose was not adjusted for age, some of this small difference may be attributed to the slightly (\approx 10\%) higher MAC exposure in the elderly.\textsuperscript{20}

In summary, the minor differences in the pharmacokinetics of cisatracurium in elderly patients were not associated with significant differences in the recovery profile after a single bolus dose of cisatracurium. The time to onset is approximately one-minute longer in elderly patients than in young patients.

References

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