Pharmacokinetics and Pharmacodynamics of a 0.1 mg/kg Dose of Cisatracurium Besylate in Children During N_2O/O_2/Propofol Anesthesia

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We studied the pharmacokinetics and pharmacodynamics of cisatracurium in 9 children (mean weight, 17.1 kg) aged 1–6 yr (mean, 3.75 yr) during propofol-nitrous oxide anesthesia. Neuromuscular monitoring was performed. Venous samples were taken before injection of a 0.1 mg/kg dose of cisatracurium and then at 2, 5, 10, 30, 60, 90, and 120 min. Cisatracurium plasma concentrations were determined by high performance liquid chromatography. Onset time was 2.5 ± 0.8 min, recovery to 25% of baseline twitch height was 37.6 ± 10.2 min, and the 25%–75% recovery index was 10.9 ± 3.7 min. Distribution and elimination half-lives were 3.5 ± 0.9 min and 22.9 ± 4.5 min, respectively. Steady-state volume of distribution (0.207 ± 0.031 L/kg) and total body clearance (6.8 ± 0.7 mL/min/kg) were significantly larger than those published for adults. Pharmacodynamic results were comparable to those obtained in pediatric studies during halothane or opioid anesthesia with the exception of a longer recovery to 25% baseline. Although the plasma-effect compartment equilibration rate constant was twofold faster (0.115 ± 0.025 min^{-1}) than that published for cisatracurium in adults, the effect compartment concentration corresponding to 50% block was similar (129 ± 27 ng/mL).

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All medications to be used for children should be evaluated in children. The lack of available data on many routinely used drugs has led to children being described as "therapeutic orphans." Dosages and administration regimens have frequently been extrapolated from adult data because of a complete absence of clinical trials in the pediatric population during drug development (1,2). The effects of drugs are age-dependent because of the ensuing changes in body composition and metabolic capacity. It is thus essential that new medications should be evaluated in different age ranges.

Previous pediatric studies have examined cisatracurium pharmacology during nitrous oxide (N_2O)-narcotic anesthesia (3–5) and during halothane anesthesia (3,5–7) but not during propofol anesthesia. de Ruiter and Crawford (4) performed a dose-response study of cisatracurium in children aged 3 to 10 yr using N_2O-narcotic anesthesia to determine effective dose and infusion requirements. They found an ED_{50} 25% larger than that reported by Meretoja et al. (3), although similar to values in adults undergoing a N_2O-narcotic technique (8). It is unclear whether this difference is merely the result of methodological factors.

The pharmacokinetic-pharmacodynamic (PK/PD) relationship of cisatracurium has been well characterized in adults, including 2 studies in which a $2 \times ED_{95}$ dose was given during propofol anesthesia (9,10). However, there have been no PK or PK/PD studies conducted for cisatracurium in children. The objective of the present study was therefore to characterize the concentration-effect relation of cisatracurium in children during N_2O/O_2/propofol anesthesia.

We used a dose of 0.1 mg/kg because it is the $2 \times ED_{95}$ dose reported in adult dose-response studies during balanced anesthesia (8,11). Moreover, because de Ruiter and Crawford (4) described a $2 \times ED_{95}$ of

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0.094 mg/kg and because no enhancement is expected with propofol (12), we hypothesized that the $2 \times ED_{95}$ dose should be the same for children compared to adults in the absence of potent inhaled anesthetics.

Methods

Nine children undergoing dental surgery and classified as ASA physical status I–II were included in the study. Children were aged from 1- to 6-yr-old with a body weight within 10% of normal. Patients with clinical evidence of neurologic, neuromuscular, or cardiovascular disease as well as significant renal or liver impairment were excluded. Also excluded were patients with history of major thermal injury or exposure to antibiotics (other than penicillins or cephalosporins), lidocaine, or trimetaphan within 48 h before anesthesia. If needed, patients were premedicated with midazolam orally.

The protocol was approved by the Montreal Children's Hospital Ethics Committee and the Quebec Health Minister. Written informed consent was given by the parents. On entering the operating room, each patient received N_2O/O_2 by mask while an IV cannula was inserted. General anesthesia was induced with a bolus dose of fentanyl (1–2 $\mu g/kg$) and propofol (2–4 mg/kg) and maintained with propofol (150 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and N_2O/O_2 (70:30). Once anesthesia was judged to be sufficient, neuromuscular monitoring was instituted and an IV cannula was inserted for blood sampling in the arm opposite to that used for medication injection. Arterial sampling would not have been clinically appropriate in these healthy children for dental surgery. As in all pediatric cases, patients were anesthetized in a warm OR and covered with warm coverings. Central (nasopharyngeal or rectal) temperatures were monitored. Fluid intake was recorded and continuous hemodynamic and respiratory monitoring (arterial blood pressure, heart rate, O_2 saturation, end-tidal CO_2, and peak inspiratory pressure) were performed throughout the study.

After a baseline sample was taken, a $2 \times ED_{95}$ (0.1 mg/kg) IV bolus of cisatracurium besylate (Nimbex®) was administered over 5 s. If a patient needed supplemental doses of neuromuscular blocking drugs, vecuronium or rocuronium was administered and the neuromuscular monitoring component of the study was then discontinued. Endotracheal intubation was performed once T_1 was <5% of baseline and completed 2-3 min after the administration of the cisatracurium bolus. When necessary, at the end of the surgery and when at least 75% of twitch recovery was reached, neostigmine 0.05 mg/kg was given with atropine 0.02 mg/kg to antagonize the neuromuscular blockade.

A Grass FT03 force displacement transducer was used to measure the electromechanical response of the adductor pollicis muscle to the train-of-four (TOF) stimulation (0.2 ms duration and 2 Hz frequency) of the ulnar nerve every 12 s. The forearm was immobilized and the transducer applied to the thumb while stimulating surface electrodes were applied over the ulnar nerve. A baseline value was established after a stabilization period of 5–10 min without the application of tetanic stimulation. After administration of cisatracurium in the opposite arm, muscle relaxation was continuously monitored until full recovery or until injection of another neuromuscular blocking drug occurred. Pharmacodynamic data were derived from the first response (T1) to the TOF stimuli.

Three-milliliter blood samples were drawn from the dedicated IV cannula and placed into chilled vacutainer tubes containing EDTA for the baseline sample and heparin for all others. Eight venous samples were drawn for each patient: at baseline (blank) and at 2, 5, 10, 30, 60, 90, and 120 min after cisatracurium administration. The blood was immediately transferred into chilled microcentrifuge tubes for a 45-s centrifugation at 14,000 rpm. Within 2 min of the sample collection, the plasma was transferred in precooled polypropylene tubes containing 25 μL sulfuric acid (2 M) for each milliliter of plasma. The samples were frozen in dry ice, and the plasma samples were then stored at −70°C until analysis. If necessary, blood sampling was continued in the recovery room.

Cisatracurium plasma concentrations were determined by using high performance liquid chromatography. The method published by Bryant et al. (13) for urine samples was slightly modified and fully validated in our laboratory. Bond-Elut® phenyl solid-phase extraction cartridges (Varian, Harbor City, CA) were used for extraction of cisatracurium. N-methyl laudanosine (500 ng/mL plasma) was used as the internal standard. After several purification steps, the eluent was half evaporated using a Speed-Vac concentrator (Model SC210A; Savant Instruments, Farmingdale, NY). An aliquot was injected directly into the high performance liquid chromatography system by using an autosampler SIL-9A (Shimadzu, Kyoto, Japan). The separation of cisatracurium from its metabolites was made by using a Spherisorb® SCX 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 solvent flow rate was 2.0 mL/min and the column maintained at 50°C. The excitation and emission wavelengths of the fluorescence detector (Hewlett-Packard, Waldbronn, Germany) were set at 280 and 320 nm, respectively. The assay proved to be sensitive and linear over the range of 5 to 2500 $ng \cdot mL^{-1}$ for cisatracurium, and 2 to 1000 $ng \cdot mL^{-1}$

for the metabolites. The coefficients of variation for within and between run precision were <8%. The accuracy was 99% ± 9% for cisatracurium.

According to the Akaike's information criterion (test for goodness of fit) (14) and visual inspection, the PK of a bolus dose of cisatracurium were best described by a two-compartment model (15). Each patient's plasma concentration-time profile was analyzed assuming elimination from both the central (k_{10}) and peripheral (k_{20}) compartments as previously described by Nakashima and Benet (16). Because Hofmann elimination is the major metabolic pathway for cisatracurium (2), the mean *in vitro* degradation rate in human plasma published by Welch et al. (17) was substituted for the elimination rate constant from the peripheral compartment (k_{20} = 0.0237 min^{-1}). A weighting function 1/(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 PK analysis. Exit-site independent PK parameters (A, α, B, β) were determined using standard formula. Calculations were as follows: total body clearance (Cl_{tot}) = *Dose/AUC* and volume of distribution at steady-state (V_{ss}) = $V_1 \cdot (1 + (k_{12}/(k_{20} + k_{21})))$. Exit-site dependent PK parameters (k_{10}, k_{12}, k_{21}) were also generated.

Using the PK parameters previously derived for each patient, a simultaneous PK-PDlink model with a sigmoid E_{max} model was used to derive individual values for the effect compartment equilibration rate constant (k_{eo}), the effect compartment concentration at 50% block (EC_{50}), and the slope factor (γ). WinNonlin software was used. Goodness of fit was assessed by the Akaike information criterion (AIC) and visual inspection. Data are presented using descriptive statistics (as mean values ± SD).

Results

Nine ASA I patients between 1 and 6 yr of age were enrolled in the study protocol in 1998 and 1999. Demographic data for the patients are presented in Table 1. Patients were similar for gender, age, and weight. The overall mean infusion rate of propofol was 195 ± 38.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Central temperatures remained normal. The maintenance fluid was Ringer's lactate solution at 40 mL + 2 mL $\cdot kg^{-1} \cdot h^{-1}$ for patients weighing 10–20 kg (n = 7) and 60 mL + 1 mL $\cdot kg^{-1} \cdot h^{-1}$ for patients weighing more than 20 kg (n = 2). The hemodynamic effects of cisatracurium were negligible.

The cisatracurium plasma concentrations over time for each of the nine patients are represented in Figure 1A and the effect (percentage of neuromuscular block) over time is shown in Figure 1B. Neuromuscular responses are presented in Table 2. One patient was given rocuronium as clinically indicated when TOF was 75%. During the recovery period, the reference for

Table 1. Demographic Data

Patient	Age	Gender	Weight (kg)	Height (cm)
1	3.8	F	14.2	97
2	3.5	M	15.4	102
3	4.8	M	20.4	109
4	3.5	M	18.2	111
5	1.3	M	12.0	79
6	4.0	F	18.9	102
7	6.5	M	25.0	121
8	2.5	M	14.2	97
9	4.0	M	15.2	93
Mean	3.8	2/9 (F/M)	17.1	101
SD	1.4		4.0	12

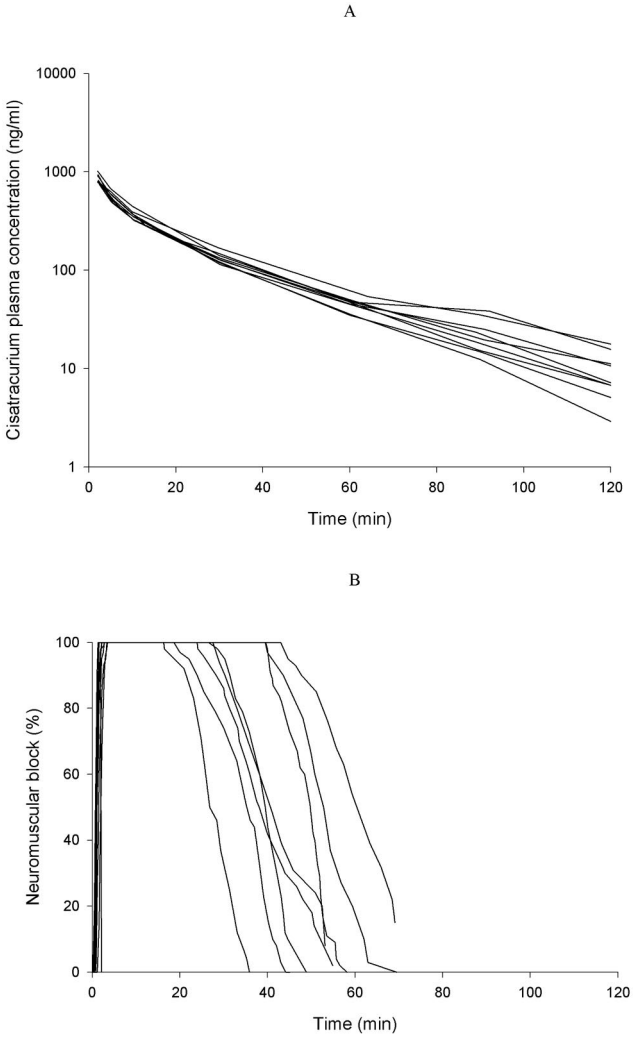

Figure 1. A. Individual cisatracurium plasma concentration-time curves in patients who received a bolus of 0.1 mg/kg of cisatracurium besylate. B. Individual neuromuscular block-time curves in patients who received a bolus of 0.1 mg/kg of cisatracurium besylate.

Table 2. Neuromuscular Response

Onset times (min)	
To 95% block	2.0 ± 0.7
To 100% block	2.5 ± 0.8
Recovery times (min)	
To 25%	37.6 ± 10.2
To 50%	43.1 ± 10.9
To 75%	48.5 ± 11.3
Recovery index (min)	
25% to 75%	10.9 ± 3.7

Values are mean ± SD; $n = 8$.

the response was the final T1 baseline. With the exception of two patients, the initial and final baselines were equal. The mean time from injection of cisatracurium to recovery of the TOF ratio to 0.4, 0.7, and 0.9 were 42.6 ± 8.3, 49.1 ± 9.2, and 56.6 ± 11 min, respectively. Pharmacokinetic data and results of the PK/PD analysis are presented in Table 3. The coefficients of variation were <20% for the PK/PD estimates. The values for the Akaike criterion were 14 ± 6.8 and 195 ± 41 for the PK and PK/PD data, respectively. Because of incomplete neuromuscular blockade data (technical failure), one patient was excluded from the PK/PD analysis.

Table 3. Analysis of Cisatracurium After an IV Bolus of 0.1 mg/kg Cisatracurium Besylate

PK parameters ($n = 9$)	
Exit-site-independent	
A (ng/mL)	824 ± 163
B (ng/mL)	334 ± 53
α (min^{-1})	0.209 ± 0.050
β (min^{-1})	0.031 ± 0.006
V_1 (L/kg)	0.087 ± 0.010
Cl_{tot} ($mL \cdot min^{-1} \cdot kg^{-1}$)	6.8 ± 0.7
Exit-site-dependent	
VD_{ss} (L/kg)	0.207 ± 0.031
K_{10} (min^{-1})	0.045 ± 0.016
K_{12} (min^{-1})	0.111 ± 0.033
K_{21} (min^{-1})	0.060 ± 0.022
PK/PD parameters ($n = 8$)	
K_{eo} (min^{-1})	0.115 ± 0.025
EC_{50} (ng/mL)	129 ± 27
γ	6.5 ± 1.3

Values are expressed as mean ± SD. A, B = coefficients; α= distribution rate constant; β = elimination rate constant; V_1 = volume of central compartment; Cl_{tot} = total body clearance; VD_{ss} = 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 transfer of drug from compartment 1 to compartment 2; K_{21} = first-order rate constant associated with the transfer of drug from compartment 2 to compartment 1; K_{eo} = effect compartment equilibration rate constant; EC_{50} = effect compartment concentration corresponding to 50% neuromuscular block; γ = slope factor.

Discussion

The relation between plasma concentration and effect for cisatracurium has not been characterized in children. Because propofol, with or without opioids, is a commonly used drug in pediatric anesthesia for both induction and maintenance, it is important to obtain PK/PD data of cisatracurium during this type of anesthesia.

Pharmacological studies have been performed in children with cisatracurium during inhaled (3,5–7,18) and opioid (3–5) anesthesia but not during propofol anesthesia. Using a similar dose, the effect data for our patients showed a comparable onset time (2.5 min) to that obtained during nitrous oxide/opioid anesthesia (2.3 min) (3) and halothane anesthesia (2.2 min or 2.5 min) (3,6), but the clinical duration (recovery time to 25% of baseline twitch height) was 38 ± 10 min in our patients, longer than that observed for the opioid group in Meretoja et al.'s (3) study (27 min; range, 24–33 min). In fact, it was comparable to that observed in Taivainen et al.'s study (19) (36 ± 5 min), in which a larger dose (0.15 mg/kg) was administered during N_2O/opioid anesthesia. Thus, in the light of our effect data alone, one would suggest that propofol has an enhancing effect on neuromuscular blockade, comparable to that seen in adults receiving inhaled anesthetics. However, in Meretoja et al. s' study, the clinical duration of cisatracurium in children during inhaled anesthesia (34 min; range, 22–40 min) was within the range observed for the opioid group (3). Because no comparative study was conducted, it is difficult to exclude the possibility that the longer clinical duration observed in our children is not merely the result of a different anesthetic setting.

In our patients, the recovery index from 25% to 75% of baseline twitch height (11 ± 4 min) was virtually identical to that reported in the abovementioned studies (3,6,19). This observation suggests that although the biological half-life of cisatracurium was not measured in other studies, it may not differ significantly among treatment groups. Moreover, spontaneous recovery rate seems independent of initial dosage and duration of infusion or the number of maintenance doses of cisatracurium administered. In one case report, a 7-kg infant received an overdose of 0.86 mg/kg and nevertheless obtained a recovery index between 10 and 15 min (20). This is also consistent with the previously demonstrated noncumulative effect of cisatracurium. Nonetheless, the overall recovery period to 75% of baseline twitch height in our patients remains clinically longer than that reported in previous pediatric studies.

Cisatracurium has a unique organ-independent elimination called Hofmann elimination that depends solely on pH and temperature and accounts for 77% of the Cl_{tot} (21). As expected with this type of elimination, the PKs of cisatracurium are linear up to 0.3 mg/kg (22). Only in adults have PK studies of cisatracurium been performed during propofol anesthesia (10). Our PK data indicate that both half-lives for the

distribution and elimination rate constants are similar to those reported in adults. This is consistent with previous observations made for atracurium in which the elimination half-life was shown to be similar in infants, children, and adults (23).

To calculate the apparent volume of distribution (an exit-site dependent parameter), the elimination rate from the peripheral compartment was assumed to be equal to the mean *in vitro* degradation rate in plasma published by Welch et al. (17). In a previous study (9), this value proved to be equal to or higher than the corresponding elimination rate from the central compartment in 4 of 48 patients, resulting in a null or negative organ clearance (model mis-specification). This limitation was not observed in our study. In our opinion, the difference in pH between plasma and tissue interstitial fluid is not large enough to significantly alter cisatracurium elimination.

In our patients, an almost twofold increase in the volume of distribution and Cl_{tot} of cisatracurium was observed when compared with adults (10). Parallel changes (approximately 20%) in the apparent V_{ss} and Cl_{tot} of atracurium have also been reported with increasing age (23); the progressive decrease in the extracellular fluid results in a proportional diminution of organ-independent elimination. These findings were corroborated in another PK study with atracurium in children and infants (24). Nonetheless, it remains that the increase in Cl_{tot} we observed in children versus adults is larger than that observed for atracurium. Many factors may explain this discrepancy. In contrast to its cis isomer, atracurium is eliminated by a dual mechanism: Hofmann degradation and metabolism by nonspecific esterases. In our study, venous concentrations were used, whereas other PK studies sampled arterial blood (10). Sampling site is often a confounding factor in PK studies. For example, the clearance of atracurium and mivacurium based on venous blood proved to be 25% and 50% larger, respectively, than that based on arterial levels (25,26). Arterial sampling was not clinically justified in our children.

Compared with adults (9,10), our PK/PD analysis revealed an almost twofold faster k_{eo} in children. Part of this difference is also attributable to the sampling site. For atracurium, a 47% increase in k_{eo} was observed when venous instead of arterial samples were used for modeling (26). However, physiological factors (increased heart rate, blood flow, and tissue permeability) certainly contribute to the large increase in k_{eo} observed in children. This observation is compatible with the shorter onset observed in children when compared with adults. The slope values were quite similar to those reported in adults (9,10). With regards to sensitivity, the EC_{50} observed in our children is quite similar (20% lower) to that observed in adults during propofol anesthesia (10). This is in agreement with previous findings for atracurium in which the steady-state plasma concentration resulting in 50% of neuromuscular blockade appeared independent of age-related changes (23).

In our institution the use of cisatracurium in pediatric anesthesia is predominantly in infants and children with metabolic, hepatic, or renal problems in whom administration of metabolized drugs may lead to unpredictable PK. It is particularly important to be able to predict dosage and duration in such patients. The finding of delayed onset of recovery in our patients (time to return to 25% of baseline twitch height) is of interest and of practical use because anticipating this will affect administration of relaxant and reversal drugs. In summary, we have demonstrated the safety and predictability of a $2 \times ED_{95}$ dose of cisatracurium during propofol anesthesia in children 1 to 6 years of age. The significant differences in PK values compared to adults are of use in predicting dosage and duration of action, and highlight, yet again, the need for pediatric pharmacological studies.

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