

Dose-Response Relationship and Infusion Requirement of Cisatracurium Besylate in Infants and Children during Nitrous Oxide-Narcotic Anesthesia

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Background: To determine the effect of age on the dose-response relation and infusion requirement of cisatracurium besylate in pediatric patients, 32 infants (mean age, 0.7 yr; range, 0.3-1.0 yr) and 32 children (mean age, 4.9 yr; range, 3.1-9.6 yr) were studied during thiopentone-nitrous oxide-oxygen-narcotic anesthesia.

Methods: Potency was determined using a single-dose (20, 26, 33, or 40 $\mu\text{g}/\text{kg}$) technique. Neuromuscular block was assessed by monitoring the electromyographic response of the adductor pollicis to supramaximal train-of-four stimulation of the ulnar nerve at 2 Hz.

Results: Least-squares linear regression analysis of the log-probit transformation of dose and maximal response yielded median effective dose (ED_{50}) and 95% effective dose (ED_{95}) values for infants ($29 \pm 3 \mu\text{g}/\text{kg}$ and $43 \pm 9 \mu\text{g}/\text{kg}$, respectively) that were similar to those for children ($29 \pm 2 \mu\text{g}/\text{kg}$ and $47 \pm 7 \mu\text{g}/\text{kg}$, respectively). The mean infusion rate necessary to maintain 90-99% neuromuscular block during the first hour in infants ($1.9 \pm 0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; range: $1.3-2.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was similar to that in children ($2.0 \pm 0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; range: $1.3-2.9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Conclusion: The authors conclude that cisatracurium is equipotent in infants and children when dose is referenced to body weight during balanced anesthesia.

PUBLISHED studies have reported that the dose-response relation of nondepolarizing neuromuscular blocking agents (NMBAs) is age dependent within the pediatric age range.¹ Cisatracurium besylate, the *R-cis* isomer of atracurium besylate, has been evaluated in adults² and children,³ but dose-response studies in different pediatric age groups are lacking. In the current study, we determined the neuromuscular dose-response relation and infusion requirement (for steady state 90-99% neuromuscular block) of cisatracurium in infants and children during nitrous oxide (N_2O)-oxygen-narcotic anesthesia.

Methods

Approval from the Research Ethics Board of the Hospital for Sick Children, Toronto, and informed parental

consent were obtained to study 32 infants (aged younger than 1 yr) and 32 children (aged 3-10 yr). All were classified as American Society of Anesthesiologists physical status I or II, not premedicated, and undergoing elective surgery that necessitated tracheal intubation. Children 7 yr of age or older gave verbal assent to participate in the study. Study subjects were excluded if difficulty with tracheal intubation was anticipated or if they had a history of neuromuscular disease or were prescribed medications known to affect neuromuscular blocking agents.

Nitrous oxide (66%) in oxygen was administered and an intravenous catheter was inserted. Standard intraoperative monitors were used. Anesthesia was induced with atropine (10 $\mu\text{g}/\text{kg}$), thiopentone (5 mg/kg), and fentanyl (5 $\mu\text{g}/\text{kg}$) intravenously and maintained with N_2O -oxygen, fentanyl, and midazolam. The trachea was intubated without the use of neuromuscular blocking agents. Intermittent positive-pressure ventilation was used to maintain normocapnia.

One forearm and one hand were washed with alcohol, allowed to dry, and immobilized using a splint for assessment of neuromuscular function by electromyography (Relaxograph; Datex-Ohmeda, Helsinki, Finland). Stimulating electrodes were applied to the skin over the ulnar nerve at the elbow, and recording electrodes were applied over the adductor pollicis and base of the thumb. Neuromuscular block was assessed by monitoring the evoked electromyographic response of the adductor pollicis to supramaximal train-of-four (2 Hz for 2 s) square-wave stimulation (0.1-ms duration) every 10 s. Axillary temperature was maintained 35.5°C or more.

The dose-response relation of cisatracurium was determined using a single-dose technique. Each child was assigned to receive one of four doses of cisatracurium (20, 26, 33, or 40 $\mu\text{g}/\text{kg}$) according to a randomization schedule that was derived from a table of random numbers. After at least 10 min of baseline supramaximal train-of-four stimulation, the dose of cisatracurium was administered as a rapid intravenous bolus. The maximum degree of neuromuscular block was determined from the reduction in the height of the first response of the train-of-four (T_1), expressed as a percentage of the control T_1 height.

To determine infusion requirement, we administered additional bolus doses of cisatracurium to achieve 90-99% neuromuscular block. A continuous infusion of cisatracurium was begun at $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and titrated at 5-min intervals to maintain the neuromuscular

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block within the target range of 90–99% for the duration of surgery. Individual and group mean infusion requirements were calculated. Data from 5-min intervals in which the neuromuscular block was outside the target range were not included in the calculation. Neuromuscular block was reversed at the end of surgery.

Statistical Analysis

Dose–response curves were plotted using micrograms per kilograms and micrograms per millimeter squared as dose units. Surface area was estimated from standard nomograms of height and weight. Median effective dose (ED₅₀) and 95% effective dose (ED₉₅) values were determined by log–probit transformation and least-squares linear regression analysis of dose and maximal response. Variance was calculated according to the method of Finney.⁴ The Mann–Whitney rank sum test was used to compare ED values and infusion rates. Data are presented as mean ± SD. *P* < 0.05 was considered to be statistically significant.

Results

Demographic data are presented in table 1. At each dose of cisatracurium, the maximum degree of neuromuscular block at the adductor pollicis and corresponding probit values in infants were similar to those in children (table 2). The ED values of cisatracurium calculated on the basis of body weight were independent of age. Least-squares linear regression analysis of the log–probit transformation yielded ED₅₀ and ED₉₅ values for infants (29 ± 3 μg/kg and 43 ± 9 μg/kg, respectively) that were similar to those for children (29 ± 2 μg/kg and 47 ± 7 μg/kg, respectively). Dose–response curves in infants and children had slopes of approximately 8.0 probits/log. In contrast, ED₅₀ and ED₉₅ values calculated for infants on the basis of body surface area (519 ± 35 μg/m² and 967 ± 151 μg/m², respectively) were significantly less than those in children (705 ± 64 μg/m² and 1166 ± 145 μg/m², respectively) (*P* < 0.01). The mean degree of neuromuscular block during infusion of cisatracurium was similar in infants and children (95 ± 2%). The infusion rate necessary to maintain this degree of neuromuscular block during the first hour in infants (1.9 ± 0.4 μg · kg⁻¹ · min⁻¹;

Table 1. Demographics

	Infants	Children
Age (yr)	0.7 ± 0.2 (0.3–1)	4.9 ± 1.8 (3.0–9.6)
Weight (kg)	8.5 ± 2.1 (6.0–12.6)	18.4 ± 5.2 (12.2–31.8)
Height (cm)	71 ± 4 (64–80)	107 ± 13 (86–146)
BSA (m ²)	0.4 ± 0.1 (0.3–0.5)	0.7 ± 0.2 (0.5–1.1)
Male/Female	24/8	20/12

Data are presented as mean ± SD (range) for 32 infants and 32 children. BSA = body surface area.

Table 2. Percent T1 Depression and Corresponding Probit Values (Mean ± SD) after Cisatracurium Besylate in Infants and Children during Nitrous Oxide–Narcotic Anesthesia

Dose (μg/kg)	Infants		Children	
	T1 Depression (%)	Probit	T1 Depression (%)	Probit
20	10 ± 6	3.7 ± 0.3	14 ± 11	3.8 ± 0.5
26	47 ± 30	4.9 ± 0.9	39 ± 32	4.6 ± 1.0
33	57 ± 27	5.2 ± 0.8	66 ± 27	5.5 ± 0.8
40	90 ± 8	6.4 ± 0.5	83 ± 11	6.1 ± 0.5

range: 1.3–2.5 μg · kg⁻¹ · min⁻¹) was similar to that in children (2.0 ± 0.5 μg · kg⁻¹ · min⁻¹; range: 1.3–2.9 μg · kg⁻¹ · min⁻¹). The mean infusion requirement in the first hour was approximately 2.5 times the ED₉₅ dose in infants and children. No adverse reaction or clinical evidence of histamine release was observed in any patient.

Discussion

We studied the dose–response relation of cisatracurium in infants and children during N₂O–oxygen–narcotic anesthesia. We found that the ED₅₀ of cisatracurium in infants and children was 29 μg/kg, which is approximately 25% greater than the value reported for children during halothane anesthesia³ and approximately one fourth the value for atracurium in infants during balanced anesthesia.^{5,6} The ED₅₀ and ED₉₅ values in the current study are similar to those reported for adults during N₂O–oxygen–narcotic anesthesia.²

The effective bolus dose of an NMBA can be calculated as the product of the effective plasma concentration and the apparent volume of distribution.⁷ During the first year of life, effective plasma concentration and volume of distribution relative to body weight undergo age-related changes: as age increases, the effective plasma concentration increases, whereas the volume of distribution decreases relative to body weight (but not relative to body surface area).¹ Age-related changes in these variables have been shown for atracurium, *d*-tubocurarine, and vecuronium^{8–11}; however, data for cisatracurium in infants and children are lacking. Based on the current data we can postulate that any increase in effective plasma concentration in children is probably offset by a proportionate reduction in volume of distribution relative to body weight. This has been shown to be the case for *d*-tubocurarine and vecuronium in pharmacokinetic studies^{10,11} that are supported by dose–response studies in the different age groups.^{12,13}

Our results show that ED values were similar in infants and children when calculated on the basis of body weight, but were significantly less in infants when calculated on the basis of body surface area. These data support our clinical practice of administering cisatra-

curium on the basis of body weight because the calculated doses are equipotent in the two age groups. The dose-response relation of other NMBAs has been investigated using body weight and body surface area as dose units in pediatric patients. Consistent with our results, the ED₅₀ for *d*-tubocurarine was significantly less in infants than in children only when calculated on the basis of body surface area.¹⁴ In contrast, the ED₅₀ of atracurium and vecuronium were significantly less in infants when either body weight or body surface area was used as a dose unit.^{5,15,16} Although methodological differences among the studies must be considered, it is likely that these differences result in part from variations among NMBAs in the magnitude and time course of changes in effective plasma concentration and volume of distribution.

The infusion rate of cisatracurium necessary to maintain a steady state 90–99% neuromuscular block was similar in infants and children, which is consistent with published data for atracurium.¹⁷ The infusion requirement for steady state neuromuscular block (and therefore the rate of drug removal from plasma at steady state) can be calculated as the product of the effective steady state plasma concentration and the clearance.⁷ In contrast to the effective plasma concentration, the total clearance of NMBAs either changes little during infancy and childhood, as in the case of *d*-tubocurarine¹⁰ and vecuronium,¹¹ or decreases as age increases, as in the case of atracurium.^{8,9} For atracurium, the net effect of the age-related changes in effective plasma concentration and clearance is that infusion requirement remains constant during infancy and childhood.¹⁷ Whether the similar infusion requirement of cisatracurium in infants and children also results from counteracting age-related changes in effective steady state plasma concentration and clearance is speculative.

Previous studies have investigated the neuromuscular potency of atracurium,¹⁵ pancuronium,¹⁸ or mivacurium¹⁹ in younger (2–6 months of age) and older infants (7–12 months of age). These studies showed consistently that the potency of these NMBAs is similar in infants older than 2 months of age. Therefore, it is unlikely that the results of the current study would differ had we studied a younger group of infants.

In conclusion, cisatracurium is equipotent in healthy full-term infants and children when dose is referenced to body weight during N₂O–oxygen–narcotic anesthesia. The current data suggest that cisatracurium can be administered in the same initial dose and infusion rate in infants and children.

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