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Comparison of Cisatracurium and Vecuronium by Infusion in Neonates and Small Infants after Congenital Heart Surgery

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Background: **Neonates and infants often require extended periods of mechanical ventilation facilitated by sedation and neuromuscular blockade.**

Methods: **Twenty-three patients aged younger than 2 yr were randomly assigned to receive either cisatracurium or vecuronium infusions postoperatively in a double-blinded fashion after undergoing congenital heart surgery. The infusion was titrated to maintain one twitch of a train-of-four. The times to full spontaneous recovery of train-of-four without fade, extubation, intensive care unit discharge, and hospital discharge were documented after drug discontinuation. Sparse sampling after termination of the infusion and a one-compartment model were used for pharmacokinetic analysis. The Mann–Whitney U test and Student *t* test were used to compare data between groups.**

Results: **There were no significant differences between groups with respect to demographic data or duration of postoperative neuromuscular blockade infusion. The median recovery time for train-of-four for cisatracurium (30 min) was less than that for vecuronium (180 min) ($P < 0.05$). Three patients in the vecuronium group had prolonged train-of-four recovery: Two had long elimination half-lives for vecuronium, and one had a high concentration of 3-OH vecuronium. There were no differences in extubation times, intensive care unit stays, or hospital stays between groups.**

Conclusions: **Our results parallel data from adults demonstrating a markedly shorter recovery of neuromuscular transmission after cisatracurium compared with vecuronium. Decreased clearance of vecuronium and the accumulation of 3-OH vecuronium may contribute to prolonged spontaneous recovery times. Cisatracurium is associated with faster spontaneous recovery of neuromuscular function compared with vecuronium but not with any differences in intermediate outcome measures in neonates and infants.**

CRITICALLY ill neonates and infants often require extended periods of mechanical ventilation facilitated by sedation and neuromuscular blockade. The use of neuromuscular blockade in neonates and infants remains controversial, but the incidence and severity of intraventricular hemorrhage may be decreased by neuromuscular blockade to prevent asynchronous breathing and barotrauma.[1]

Cisatracurium, a more potent isomer of atracurium, is devoid of histamine-releasing properties in clinical doses, has organ-independent Hofmann elimination, and has no breakdown products associated with neuromuscular blocking activity.[2–6] Hofmann elimination of cisatracurium results in low concentrations of laudanosine, a central nervous system stimulant, but these concentrations are well below those associated with seizures in an animal model.[7] Vecuronium is dependent mainly on hepatobiliary excretion, renal elimination, or both and has an active metabolite.[8–13] In adults, recovery from cisatracurium-induced neuromuscular blockade is markedly more rapid than recovery after vecuronium in patients from the intensive care unit.[14] Despite the lack of published data, vecuronium seems to have become the agent of choice for neuromuscular blockade in current pediatric intensive care practice.[15]

We hypothesized that cisatracurium would be associated with clinically improved neuromuscular recovery after prolonged infusions when compared with vecuronium for neonates and infants who required mechanical ventilation after congenital heart surgery. The purpose of the current investigation was to compare the infusion requirements, recovery characteristics, and pharmacokinetics of cisatracurium, vecuronium, and their metabolites in this patient population.

Materials and Methods

Institutional review board approval and patient recruitment occurred at one institution (Mount Sinai School of Medicine, New York, New York). After parental written informed consent was obtained, patients aged younger than 2 yr of age were studied after undergoing congenital heart surgery that necessitated postoperative mechanical ventilation. Patients were assigned to double-blinded treatment groups using a restricted randomization in clusters of four patients to minimize the effects of time and to maintain relative equality of the treatment groups.

After arrival in the pediatric cardiac surgical intensive care unit, the status of neuromuscular blockade was determined *via* standard train-of-four monitoring using a Datex NMT 221 monitor (Datex-Ohmeda, Tewksbury, MA) applied over the ulnar nerve and hand. In nearly all of the neonates, the magnitude of the electromyographic response in the adductor pollicis was too small to be

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detected by the monitor. Therefore, all determinations of train-of-four response were made by visual observation of thumb movement. When at least one out of four twitches was observed, the patients received an initial continuous infusion of either vecuronium or cisatracurium (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) according to group assignment. The study drug was provided to the intensivist by the hospital pharmacy as a "blinded" syringe containing 1 mg/ml of the appropriate drug.

Neuromuscular transmission was monitored every 15–60 min during initial titration of the infusion and at least once every 8 h for the duration of the infusion. The infusion rate of the study medication was adjusted upward or downward in 25–100% increments as necessary by one of the anesthesiologist investigators to achieve one twitch of a train-of-four. After the target degree of neuromuscular blockade was reached, monitoring continued at least every 8 h. The anesthesiologist investigators made adjustments to the infusion rate by 25% increments as necessary to maintain neuromuscular blockade in the target range during the remainder of the infusion. All patients were sedated with midazolam, and analgesia was provided with fentanyl according to standard intensive care unit protocols. Arterial blood samples (1.5 ml) were drawn for determination of concentrations of cisatracurium and laudanosine, or vecuronium and 3-OH vecuronium, as appropriate, once per day.

When patients had sufficiently recovered from surgery such that weaning from ventilatory support was considered appropriate, the train-of-four was recorded, and the infusion of the study drug was discontinued. The train-of-four was recorded every 15 min for the first 2 h and then at least hourly until complete spontaneous recovery of train-of-four without fade was present. After termination of the infusion, six arterial or venous blood samples (1.5 ml) were withdrawn at predetermined but randomly assigned intervals (*i.e.*, sparse sampling regimen) from each child. The blood samples were rapidly centrifuged (30 s), and the plasma supernatant was acidified and frozen. The times from discontinuation of the neuromuscular blocker infusion to extubation, intensive care unit discharge, and hospital discharge were recorded. The incidence of reintubation of the trachea was also recorded.

Cisatracurium was determined in human plasma by high-performance liquid chromatography analysis on a Regis C18 Spherisorb Little Champ column (Regis Technologies, Inc., Morton Grove, IL) (5 cm × 4.6 mm, 5 μm) using fluorescence detection. Plasma samples were spiked with the internal standard and extracted using solid phase extraction on C18 Bond Elut columns (Varian, Inc., Palo Alto, CA). The extracts were chromatographed on the Regis column. The mobile phase was 0.03 M sodium phosphate buffer, pH 3.0, containing 0.14% tetramethyl ammonium hydroxide and 40% acetonitrile. Laudanosine was analyzed on the same column connected in a series with fluorescence detection and similar solid phase extraction. The mobile phase was 0.03 M sodium phosphate buffer, pH 3.0, containing 0.14% tetramethyl ammonium hydroxide and 25% acetonitrile. The lower limit of detection for both compounds was 20 ng/ml.

Vecuronium and its metabolite (3-OH vecuronium) were determined in human plasma by high-performance liquid chromatography analysis on a Waters Nova-Pak CN column (Waters Corp., Milford, MA) with electrochemical detection. Plasma samples were spiked with internal standard and extracted through solid phase extraction using C1 Bond Elut columns preconditioned with methanol and water. After washing the cartridges with water, acetonitrile, and methanol, the compounds were eluted with 0.01 M sodium perchlorate in methanol. The extracts were evaporated in solvent, dissolved in 0.1 ml mobile phase. These were chromatographed on a Waters Nova-Pak CN column (3.9 × 150 mm, 4 μm). The mobile phase was 0.033 M phosphate buffer, pH 5.5, containing 40% acetonitrile. A sensitive electrochemical detector was used (ESA, Coulochem, model 5100A; ESA, Inc., Chelmsford, MA). The lower limit of detection for both compounds was 15 ng/ml.

The half-life and terminal disposition rate constant were determined from the declining drug concentration in the plasma-*versus*-time data collected after cessation of the intravenous infusion.[16] We assumed that the infusion was continued until steady state was achieved and that the distributive phase was reflected by the one-compartment model equation

$$Cp(t) = Cp(0) \cdot e^{-Kt},$$

where Cp(t) is the plasma concentration, Cp(0) is the plasma concentration at the zero time intercept (at termination of infusion), K is the elimination rate constant, and t is the time from termination of infusion.

Elimination half-life was calculated from the equation

$$t_{1/2} = 0.693/K,$$

where K is the elimination rate constant.

Clearance (Cl) was estimated for both cisatracurium and vecuronium from the following relation:

Cl = Infusion Rate (at termination of infusion)/Cp(0).

Clearance of 3-OH vecuronium and laudanosine cannot be estimated from this relation because we do not know the rate of formation of these metabolic products.

Data are expressed as median (range). The Mann–Whitney U test, chi square test, and Student *t* test were used, as appropriate, to compare data between groups. A two-tailed *P* value of less than 0.05 was considered significant.

Results

Twenty-three patients were originally entered into the study on arrival to the pediatric cardiac surgical intensive

Table 1. Demographics

Parameter	Cisatracurium	Vecuronium	*P* Value*
Age, days	6 (3–33)	7 (2–163)	NS
Weight, kg	3.7 (2.7–6.0)	3.9 (3.2–8.2)	NS
Height, cm	55 (35–65)	52 (49–76)	NS

Data are presented as median (range).

* Student unpaired *t* test.

NS = not statistically significant.

care unit. Four patients did not complete the study: Two patients died of underlying cardiac disease, one patient's parent withdrew consent after study initiation, and one patient had early termination of the study to facilitate tracheal extubation on the day of the surgery. Demographic data for the 19 patients who completed the study are summarized in table 1; 9 received vecuronium, and 10 received cisatracurium.

The median (range) infusion time for cisatracurium was 64.5 (25–157) h, whereas that for vecuronium was 46 (15–155) h (not statistically significant; table 2). The final dose of cisatracurium was higher than that of vecuronium, although no consistent pattern of tolerance over time was evident for either drug. Three patients had full train-of-four at the termination of infusion. One cisatracurium patient's intravenous line was determined to be nonfunctional at that time, and that patient was not included in the pharmacokinetic or neuromuscular recovery analysis. The two remaining patients with full train-of-four (one in each group) had functional intravenous lines and were included in the pharmacokinetic analysis. The goal of maintaining 0–1 twitches as determined by train-of-four monitoring was achieved in 16 of 19 patients.

The recovery time of spontaneous neuromuscular transmission (*i.e.*, normal train-of-four without fade) was 30 (0–45) min for cisatracurium and 180 (75–435) min for vecuronium ($P < 0.05$) after discontinuation of the infusion. Three of nine patients who received vecuronium took 4 h or longer to recover train-of-four without fade.

The intermediate outcomes after discontinuation of neuromuscular blocker infusion were not significantly different between the groups (table 2). Times to extubation, intensive care unit discharge, and hospital discharge were similar between the groups. Reintubation of the trachea occurred in 33% of cisatracurium patients and 11% of vecuronium patients (not statistically significant). Delays in extubation, reintubation, and adverse

Table 2. Infusion Characteristics and Patient Disposition

Drug	Duration Infusion, h	Final Dose, $\mu g \cdot kg^{-1} \cdot min^{-1}$	Twitches at End of Infusion	Extubation Time, min	Reintubated	ICU Post-NMB LOS, Days	Hospital Post-NMB LOS, Days	Comments
Cisatracurium	64	0.75	1	5,855	Yes	11	18	
	62	4.50	0			265	—	Died in ICU; never extubated
	66	3.50	0	7,337	No	2	38	Transferred to NICU, intubated
	25	2.00	0	1,600	No	4	12	
	65	2.00	1	1,640	No	6	8	
	38	2.00	4	3,070	No	6	11	
	157	4.00	4	388	Yes	2	31	Transferred to NICU, intubated
	132	11.5	0	2,840	Yes	220	—	Died in ICU
	64	4.00	0	285	No	2	25	
	67	4.00	0	5,935	No	5	26	
Median or %	64.5	3.75	0	2,840	33%	5.5	21.5	
Vecuronium	15	0.50	4	1,670	No	3	10	
	44	3.00	0	260	No	3	3	
	36	0.50	0	1,710	No	6	6	
	61	1.00	0	4,625	No	12	25	
	33	2.50	0	4,655	No	6	22	
	110	1.00	0	300	Yes	18	18	Required second operation
	155	1.00	0	4,575	No	7	13	
	46	3.00	0	2,545	No	4	6	
	67	1.00	0	1,415	No	4	10	
Median or %	46	1.00	0	1,710	11%	6	10	
P value	0.16	0.02	NS	NS	NS	NS	NS	

ICU = intensive care unit; NICU = neonatal intensive care unit; LOS = length of stay; NMB = neuromuscular blocker; NS = not statistically significant.

Table 3. Pharmacokinetic Parameters for Cisatracurium and Vecuronium

Parameter	Cisatracurium (n = 9)	Vecuronium (n = 7)	*P* Value*
Average rate, $\mu g \cdot kg^{-1} \cdot min^{-1}$	2.8 (0.6–4.9)	1.1 (0.9–2.9)	0.07
Plateau (steady state) plasma concentration, ng/ml	388 (154–743)	232 (42–498)	0.08
Elimination half-life, min	34 (15–468)	83 (31–185)	NS
Clearance, $ml \cdot kg^{-1} \cdot min^{-1}$	10.0 (1.2–16.3)	4.31 (2.4–71.4)	NS

Data are presented as median (range).

* Mann–Whitney U test.

NS = not statistically significant.

outcomes were not attributed to residual neuromuscular blockade in any of the patients. In all cases, the underlying cardiovascular disease was considered the etiology of these problems.

Pharmacokinetic Analysis

Blood from three patients could not be obtained for full data sets because of problems with vascular access or low hematocrits. The average infusion rate of cisatracurium was 2.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and that for vecuronium was 1.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P = 0.07$; table 3). The plateau concentrations of cisatracurium and vecuronium, their elimination half-lives, and their clearance rates are listed in table 3. After the infusion of cisatracurium was discontinued, a rapid decline in the plasma concentration was observed in six of the nine patients. In two of these patients, the sampling algorithm combined with the rapid decrease in plasma concentration precluded us from accurately estimating the half-life. We do not have measurements of acid–base balance or renal function in the three infants with a markedly prolonged half-life of cisatracurium.[17]

The observed plasma concentration of laudanosine (at termination of the infusion) averaged 334 ng/ml (table 4). The largest laudanosine concentration was 1.4 μg/ml. There was no correlation between the infusion rate or the clearance of cisatracurium and the initial plasma concentration of laudanosine. The median elimination half-life for laudanosine was 118 min. No side effects attributable to the continuous infusion of cisatracurium were observed in this study.

After the infusion of vecuronium was discontinued, a relatively slow decrease in the plasma concentration was observed in all patients. The concentration of 3-OH vecuronium at termination of the infusion was of the same order of magnitude as that of vecuronium (tables 3 and 4). The median half-life of 3-OH vecuronium was approximately fourfold that of vecuronium.

Table 4. Pharmacokinetic Parameters for Metabolites

Parameter	Laudanosine (n = 9)	3-OH Vecuronium (n = 7)
Initial concentration, ng/ml	339 (138–1,434)	226 (125–572)
Elimination half-life, min	118 (54–502)	354 (152–1,046)

Data are presented as median (range).

Discussion

In this study, critically ill neonates and small infants who had undergone repair of congenital heart lesions received ventilatory support facilitated by intense, prolonged neuromuscular blockade given by a continuous infusion of cisatracurium or vecuronium. The infusion rate of relaxant was based on monitoring of the adductor pollicis. The median infusion rate of cisatracurium was 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which is somewhat less than that needed in adults during comparable therapy[7,14] but similar to the dose needed in a pediatric critical care study of cisatracurium.[18] The median infusion rate of vecuronium (1.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was markedly less than that of cisatracurium. Recovery of neuromuscular transmission was ascertained by noting lack of fade after train-of-four. Although the electromyography device could not detect signals in these very small patients, visual observation confirmed that the train-of-four was in the range of 0.85 or greater.[19] The plateau plasma concentration of cisatracurium averaged less than 0.5 μg/ml, and that of vecuronium averaged less than 0.25 μg/ml.

Despite the more rapid spontaneous neuromuscular recovery with cisatracurium, there were no differences between the groups with regard to duration of mechanical ventilation, incidence of reintubation, duration of intensive care unit stay, or duration of hospital stay after termination of the neuromuscular blocker infusion. Therefore, there is no evidence in this small sample of patients that the more rapid neuromuscular recovery associated with cisatracurium leads to improved outcomes or reduction in costs.

We demonstrated markedly faster spontaneous recovery of neuromuscular function (*i.e.*, train-of-four) in patients receiving cisatracurium than in those receiving vecuronium. Cisatracurium is eliminated predominantly through Hofmann degradation (hydrolysis); metabolism of cisatracurium may occur from nonspecific esterases but has never been demonstrated. Organ elimination of cisatracurium has not been demonstrated. Hofmann degradation of cisatracurium (like that of atracurium) is both pH and temperature dependent (*i.e.*, lower pH, lower temperature, or both decrease Hofmann degradation). The elimination half-life and clearance of cisatracurium found in our patients are similar to those noted by others

in adults[5,7] and children.[18] Several infants had relatively prolonged elimination half-lives of cisatracurium that may have been caused by a metabolic acidosis (*e.g.*, lactic acidosis) associated with reduced cardiac output. The cisatracurium concentration decreased below the level of detection in 75 min (median); in all patients, cisatracurium was not detectable by 6 h.

Laudanosine, a tertiary amine analog of morphine, is the end product of both Hofmann elimination and ester hydrolysis.[2] Because cisatracurium is more potent than atracurium, less laudanosine is formed after clinically relevant infusions of the more potent drug. Laudanosine is metabolized in the liver and excreted through the kidney.[20,21] Organ failure or reduced cardiac output might reduce the elimination (clearance) of laudanosine. High plasma concentrations (> 20 μg/ml) have been associated with seizure activity in dogs[22] but not in cats.[23,24] No seizure activity, however, has been observed in patients.

The plasma concentrations of laudanosine observed in this study were markedly less than the plasma concentrations associated with seizure activity in animals.[22] The concentration of laudanosine averaged 0.34 μg/ml; the highest concentration noted was 1.4 μg/ml. These concentrations of laudanosine are comparable to those noted in adults.[5,7] Laudanosine has no known neuromuscular blocking effects.

Three of nine patients receiving vecuronium had spontaneous recovery times greater than 4 h. In two of these patients, we noted lower-than-average clearance of vecuronium; the highest measured concentration of 3-OH vecuronium was noted in the remaining patient. Although 25–50% of vecuronium is excreted *via* the hepatobiliary system, up to 25% of infused vecuronium is metabolized (hydrolyzed) in the liver by nonspecific esterases to form the 3-OH vecuronium metabolite. 3-OH vecuronium has half to equal the potency of the parent compound. Both compounds are dependent on organ elimination. During prolonged infusion, 3-OH vecuronium gradually accumulates because of both increased production and decreased elimination. Increased concentrations of 3-OH vecuronium may lead to prolonged neuromuscular blockade because its elimination half-life is fourfold that of vecuronium.[12] Therefore, it is not surprising that recovery of neuromuscular transmission after vecuronium was quite prolonged in this study. Our results parallel those of the adult patient multicenter study of Prielipp *et al.*[14] that was conducted in intensive care unit patients. In that study, there was a markedly shorter recovery of neuromuscular transmission after cisatracurium compared with vecuronium.

There may be other reasons why our neonates and infants in the current study would be prone to prolonged paralysis after vecuronium. All of these patients underwent cardiopulmonary bypass and therefore would likely experience deterioration in hepatic and renal function. The metabolism of vecuronium and the elimination of its active metabolite, 3-OH vecuronium, may have therefore been slower than in other subsets of critically ill pediatric patients. Because of the mortality rate in this patient sample, we chose to terminate our trial early based on the strong evidence of prolonged paralysis with vecuronium infusions in the preliminary analysis.

A comprehensive discussion of the merits and limitations of neuromuscular blockade in mechanically ventilated critically ill pediatric patients is beyond the scope of this article. The major advantages of neuromuscular blockade are the limitation of barotrauma, decreasing oxygen consumption and improving gas exchange,[15] and reducing requirements for sedative medications. Potential outcome improvement may occur if there is indeed a reduced incidence of intraventricular hemorrhage in preterm infants, but no trends toward differences in outcomes between groups were evident in the current study. Disadvantages include inability to assess neurologic function and the potential for overdose as manifested by prolonged neuromuscular blockade. Laudanosine accumulation is a theoretical disadvantage in cisatracurium infusions of long duration.

Limitations of this study include the inability to measure electromyography in the study sample. Although visual observation of train-of-four is a clinical standard and the blinded methodology ensured objectivity of this assessment with regard to drug administration, a more objective and quantitative measurement would have been desirable. In addition, the long times between neuromuscular recovery and extubation indicate that the clinical decision to extubate was based not on neuromuscular function but rather on hemodynamic and respiratory status.

In conclusion, the use of neuromuscular blockade remains controversial in critically ill neonates and infants. Based on our data, cisatracurium is associated with more rapid spontaneous recovery of neuromuscular function compared with vecuronium after postoperative neuromuscular blockade in neonates and infants. However, there is no evidence that this observed difference in neuromuscular recovery affects outcomes.

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