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Use of Cisatracurium in the Pediatric Intensive Care Unit

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Neuromuscular blockade is often necessary to ensure patient safety and optimize response to mechanical ventilation in critically ill children.[1,2] Cisatracurium, introduced in the United States in 1995, has become one of the most widely used neuromuscular blocking agents in the pediatric patient population. Its shorter duration of action, unique organ-independent elimination, and low incidence of adverse effects have made cisatracurium an appealing alternative to older agents such as pancuronium and vecuronium.[1,2]

Mechanism of Action

Cisatracurium besylate is a bisbenzyltetrahydro-isoquinolinium nondepolarizing neuromuscular blocking agent. It competitively binds to acetylcholine receptors on the motor end-plate, preventing neuromuscular transmission. This action can be antagonized by administration of acetylcholine inhibitors such as neostigmine or edrophonium. Cisatracurium is one of the three *cis*-isomers among the ten isomers of atracurium. While an effective neuromuscular blocking agent, atracurium use may produce clinically significant bradycardia and hypotension as a result of histamine release. In addition, laudanosine, one of the metabolites of atracurium, has been shown to cause central nervous system excitation in animal studies. Cisatracurium was developed to provide the same clinical benefits of atracurium while minimizing its adverse effects.[3]

Pharmacokinetics and Pharmacodynamics

Following IV administration, cisatracurium has a relatively small volume of distribution of 0.1-0.2 L/kg. It does not cross the blood brain barrier. Cisatracurium undergoes Hofmann elimination, a non-enzymatic chemical process which occurs at physiologic pH and temperature, to form two non-pharmacologically active metabolites: laudanosine and a quaternary monoacrylate. The resulting laudanosine concentration is approximately a third to a tenth that produced from atracurium metabolism. Laudanosine is further metabolized and excreted in the urine. Hofmann elimination is independent of both hepatic and renal function; however, a small percentage of a cisatracurium dose (< 10%) is excreted as unchanged drug. The clearance of cisatracurium in adults is approximately 4.5-5.7 mL/min/kg, with a terminal elimination half-life of 22-29 min.[1,3]

The pharmacokinetic profile of cisatracurium was evaluated in a study of 20 children undergoing surgery. Mean clearance was 5.89 mL/min/kg, slightly longer than that observed in adults.[3] In a study of nine children (1-6 years of age) given a cisatracurium dose of 0.1 mg/kg during anesthesia, Imbeault and colleagues found similar results, with a mean volume of distribution of 0.207 $\pm$ 0.031 L/kg, a clearance of 6.8 $\pm$ 0.7 mL/min/kg, and an elimination half-life of 22.9 $\pm$ 4.5 min.[4] In a study of 10 infants and children undergoing hypothermic cardio-pulmonary bypass (CPB), cisatracurium clearance was found to be significantly slower than expected. Mean clearance decreased from 5.47 $\pm$ 2.10 mL/min/kg to 1.10 $\pm$ 0.72 mL/min/kg during CPB. Clearance improved after CPB (7.50 $\pm$ 2.01 mL/min/kg, $p < 0.05$). The reduction in clearance during hypothermic CPB may reflect a slowing of Hofmann elimination at lower body temperatures.[5]

Cisatracurium is classified as an intermediate-acting nondepolarizing neuromuscular blocker. In studies conducted by the manufacturer, mean time to 90% blockade with cisatracurium ranged from 1.7 to 2.2 min following IV doses of 0.08 to 0.15 mg/kg in children 2-12 years of age. Time to maximum block was 2.8-3.3 min. Time to 25% recovery, considered the clinically effective duration of neuromuscular blockade, was 28-36 min. The 25%-75% recovery index ranged from 10.6-11.3 min. In infants 1-23 months of age, mean time to 90% blockade was 1.5 min after a dose of 0.15 mg/kg, similar to the results in older children. However, mean time to maximum block (2 min) in the infants was shorter than in the older children and mean time to 25% recovery (43 min) was longer, indicating a faster onset and longer duration of action in younger patients.[3] Similar results were reported

in the study by Imbeault, with a mean time to onset of 2.5 ± 0.8 min, a time to 25% recovery of 37.6 ± 10.2 min, and a 25%-75% recovery index of 10.9 ± 3.7 min.[4] In a study of 91 pediatric patients given 0.15 mg/kg cisatracurium in conjunction with either halothane or thiopental and fentanyl, intubating conditions were rated as excellent or good in 100% of patients 1-11 months of age, 92% of patients 1-4 years of age, and 97% of patients 5-12 years of age. Cisatracurium has not been studied in infants less than 1 month of age.[3]

Clinical Experience

Tobias published the first prospective study of cisatracurium in children in 1997.[6] The author evaluated 15 children, 10 months to 11 years of age, given cisatracurium during mechanical ventilation. All children received a 0.2 mg/kg cisatracurium bolus dose followed by a 3 mcg/kg/hr infusion along with an infusion of a benzodiazepine. Clinical response was evaluated with peripheral nerve stimulation and train-of-four (TOF) monitoring. This mode of assessment was performed by placing electrodes over the ulnar or peroneal nerve and monitoring response to four stimuli given over 2 seconds. The infusion was adjusted by increments of 1 mcg/kg/hr to maintain one out of four twitches, (indicating a 90% neuromuscular blockade). The duration of infusion ranged from 18 to 224 hrs, with an infusion rate of 1.4-22.7 mcg/kg/min (equivalent to 0.08-1.36 mg/kg/hr). The mean rate was 3.4 ± 1.4 mcg/kg/min. The mean infusion rate was significantly higher by the third day of therapy ($p < 0.01$). Infusion requirements continued to increase over time, with the highest requirements in patients treated for more than 6 days. Patients undergoing therapeutic hypothermia had the lowest dosing requirements, potentially the result of slower elimination.

In 2002, Odetola and colleagues described the results of a prospective open-label dose-finding study of cisatracurium in 11 infants and children (newborn to 2 years of age).[7] All patients received an initial bolus of 0.1 mg/kg, repeated as needed to achieve one twitch (90% blockade) with TOF monitoring. A continuous infusion of 2 mcg/kg/min was then started and adjusted to maintain a level of 0-1 twitches. The mean infusion rate required was 5.4 ± 3 mcg/kg/min. As in the Tobias study, there was a significant increase in the infusion rate over time, reflecting tachyphylaxis. Mean length of therapy was 65 ± 36 hrs. Mean time to complete recovery was 74.8 ± 32 min. One patient failed to achieve adequate neuromuscular blockade and was removed from the study after 18 hrs. No adverse hemodynamic effects were noted by the authors.

Two studies have compared cisatracurium and vecuronium in the pediatric intensive care unit. Reich and colleagues enrolled 23 children (0-2 years of age) after cardiac surgery in a double-blind comparison study.[8] The cisatracurium and vecuronium infusions were started at 1 mcg/kg/min and titrated to maintain 0-1 twitches on TOF monitoring. Sixteen children completed the study. The median infusion rates were 3.75 mcg/kg/min for cisatracurium and 1 mcg/kg/min for vecuronium. Duration of therapy was similar (64.5 hrs for cisatracurium, 46 hrs for vecuronium). Mean recovery time was significantly shorter with cisatracurium (30 min, range 0-45 min) compared to vecuronium (180 min, range 75-435 min, $p < 0.05$). Time to extubation, length of ICU stay, and length of hospitalization were not significantly different between groups. No adverse effects were noted.

Burmester and Mok conducted a prospective, randomized, double-blind trial comparing cisatracurium and vecuronium in 37 children.[9] The patients (ages 3 months-16 years) received either cisatracurium or vecuronium at 4 mcg/kg/min, along with infusions of midazolam and morphine. A bolus dose was given prior to the infusion if determined to be necessary by the patient's physician. The infusion was titrated to maintain one twitch on TOF monitoring. The mean infusion rate was 2.6 ± 1.3 mcg/kg/min for cisatracurium and 3.9 ± 1.3 mcg/kg/min. for vecuronium. Mean duration of infusion was not significantly different between groups. Median recovery time was significantly longer in the vecuronium group (123 min) than in the cisatracurium group (52 min, $p = 0.001$). No significant adverse effects were noted, including hypersensitivity or myopathy.

In 2007, Cooper and Bateman described the use of low-dose or "weakening dose" cisatracurium in a 4-year-old girl on mechanical ventilation.[10] The patient had received prolonged therapy with inhaled isoflurane during intubation for status asthmaticus and experienced withdrawal (choreoathetoid movements and agitation) when it was weaned. An infusion of 0.04 mg/kg/hr (equivalent to 0.68 mcg/kg/min) was started and titrated to response. At day 10, the infusion rate was 0.14 mg/kg/hr (2.4 mcg/kg/min), reflecting tachyphylaxis; however at this level of neuromuscular blockade the patient was able to be maintained on a spontaneous mode of ventilation and to make eye contact with her mother. Isoflurane was weaned, and the cisatracurium was discontinued after a total of 17 days. The authors suggest that low-dose cisatracurium may be of use in situations such as this to promote patient comfort and safety.

Warnings and Precautions

As with any neuromuscular blocking agent, cisatracurium should only be administered in a controlled setting with appropriate clinical monitoring. Clinical monitoring may include observation of response to stimulation from routine mouth or eye care, as well as peripheral nerve stimulation with TOF monitoring. A level of paralysis that maintains one or two twitches (reflecting 75% to 90% neuromuscular blockade) is recommended. Complete paralysis is rarely necessary.[1,11] Severe anaphylactic reactions have been reported with these agents. Administration of cisatracurium to a patient with a history of hypersensitivity to it or to any other depolarizing or nondepolarizing neuromuscular blocking agent should be accompanied by close monitoring by experienced clinicians. Cross-sensitivity has been reported with multiple agents in this therapeutic class.[3]

Nondepolarizing neuromuscular blocking agents should be used with caution in patients with neuromuscular diseases or acute intermittent porphyria. Use of a peripheral nerve stimulator to determine the depth of paralysis and use of the minimal effective dose is recommended. Potentiation of cisatracurium neuromuscular blockade may also occur in patients with acidosis, alterations in serum electrolytes (hyponatremia, hypokalemia, hypermagnesemia, or hypocalcemia), and renal or hepatic failure. In contrast, the effects of cisatracurium may be antagonized by the presence of alkalosis, hypercalcemia, or in patients with demyelinating lesions, peripheral neuropathies, infections, or diabetes mellitus. Trauma patients or those with recent extensive burns (> 30% body surface area burns within the past 5-70 days) may be resistant to the effects of cisatracurium.[3]

Adverse Effects

Use of nondepolarizing neuromuscular blocking agents can result in prolonged neuromuscular block, muscle weakness, and myopathy. Other adverse effects are relatively uncommon with cisatracurium. Bradycardia, hypotension, and flushing resulting from histamine release, bronchospasm, laryngospasm, rash and pruritus, have been reported in 0.1-0.4% of adults and children participating in premarketing studies.[3] No significant adverse hemodynamic effects have been reported in the pediatric clinical studies of cisatracurium published to date.[6-10]

Drug Interactions

Administration of many commonly used critical care drugs may enhance or potentiate the effects of cisatracurium (Table 1).[3]

Table 1. Drugs that Potentiate Cisatracurium

aminoglycosides	magnesium salts
bacitracin	polymixin b
calcium channel blockers	procainamide
clindamycin	quinidine
colistin	quinine
ketorolac	sod. colistiemethate
lincomycin	spironolactone
lithium	tetracyclines
local anesthetics	vancomycin
loop diuretics	

Administration of either isoflurane or enflurane with nitrous oxide/oxygen during surgery may prolong the duration of action of cisatracurium and necessitate a reduction in dose by as much as 30-40%. Concomitant administration of phenytoin or carbamazepine with cisatracurium may result in resistance to neuromuscular blockade and a shorter duration of effect. Cisatracurium doses may need to be increased in patients receiving these two antiepileptics. Cisatracurium may increase serum concentrations and/or the pharmacologic effects of digoxin, corticosteroids, or botulinum toxin.[3]

Availability

Cisatracurium is sold in the Unites States as the brand name product (Nimbex®, Abbott Laboratories) and as a generic from multiple manufacturers. It is available in 2 mg/mL 10 mL multi-dose vial as well as 2 mg/mL 5 mL and 10 mg/mL 20 mL single-dose vials. The 20 mL vial is intended for use in intensive care units. The 10 mL multi-dose vial contains 0.9% benzyl alcohol, which is contraindicated in neonates.[3]

Dosing Recommendations

The manufacturer's recommended initial dose of cisatracurium in infants 1-23 months of age is 0.15 mg/kg administered over 5 to 10 seconds. In clinical practice, an intermittent dose of 0.1 mg/kg is typically used. A dose of 0.1 to 0.15 mg/kg is recommended for children 2-12 years of age, with a dose of 0.15-2 mg/kg recommended for adults. Subsequent doses should be titrated to patient response. Cisatracurium infusions for patients receiving mechanical ventilation may be initiated at a rate of 0.2-1 mcg/kg/min and titrated to maintain the desired level of neuromuscular blockade. The usual range for cisatracurium infusions in children is 1-4 mcg/kg/min (0.06-0.24 mg/kg/hr), although dose escalation is often necessary with long-term use due to tachyphylaxis.[1,3,6-10]

Cisatracurium may be given undiluted for intermittent IV administration over 5-10 seconds. For continuous infusion, the manufacturer recommends that cisatracurium be diluted to a

concentration of 0.1 or 0.2 mg/mL with 5% dextrose, 0.9% sodium chloride, 5% dextrose and 0.9% sodium chloride. More concentrated infusions are often necessary in critically ill pediatric patients to minimize excessive fluid administration. Dilutions of 0.1, 2, and 5 mg/mL cisatracurium in 5% dextrose or 0.9% sodium chloride have been shown to be stable for up to 30 days at 4° C. Cisatracurium has been demonstrated to be compatible with many drugs used in the intensive care setting (Table 2).[3,12,13]

Table 2. Examples of IV Compatibility

amiodarone
cefazolin
corticosteroids (dexamethasone, hydrocortisone)
dexmedetomidine
gentamicin
inotropes (dopamine, epinephrine)
lidocaine
magnesium sulfate
midazolam
milrinone
ondansetron
opioids (fentanyl, hydromorphone, morphine)
piperacillin-tazobactam
potassium chloride
vancomycin
vasopressin

Cisatracurium is an acidic solution (pH 3.25 to 3.65) and is incompatible with alkaline solutions such as sodium bicarbonate. It is not compatible with ketorolac or propofol for Y-site administration. Concomitant infusion of cisatracurium and pantoprazole has been shown to produce turbidity suggesting drug precipitation. Simultaneous administration of these two drugs should be avoided, if possible, until additional information is available.[3,12, 13]

Summary

Cisatracurium is one of the most frequently used neuromuscular blocking agents in the pediatric intensive care setting. Its pharmacokinetic and pharmacodynamic characteristics, as well as its adverse effect profile, provide a rationale for choosing it over older agents in this therapeutic class. While a small number of studies support its use, more are needed to define optimal dosing and monitoring parameters.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their July meeting:

1. Polidocanol (Asclera®) was added to the Formulary with restriction to varicose vein clinics. Restrictions on sodium tetradecyl sulfate was amended to varicose vein clinics.
2. Nimodipine oral solution (Nymalize™) was added to the Formulary.

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