

Pediatric Pharmacotherapy

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Vecuronium: its role in the Pediatric Intensive Care Unit

LeAnn Prosniewski, Pharm.D. Candidate

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Formulary Update

Synthetic depolarizing and non-depolarizing neuromuscular blocking agents (NMBAs) have been used in the critical care setting since the 1970's. Non-depolarizing NMBAs are used primarily to induce skeletal muscle relaxation during surgery in conjunction with the use of general anesthetics, to facilitate endotracheal intubation, and to enhance pulmonary compliance in mechanically ventilated patients. This brief review will focus on the use of vecuronium bromide (Norcuron®), a non-depolarizing NBMA, in the pediatric intensive care population.

Mechanism of Action

Vecuronium is a bisquaternary nitrogen compound that acts by competitively binding to nicotinic cholinergic receptors, preventing conformational changes. The binding of vecuronium decreases the opportunity for acetylcholine to bind to the nicotinic receptor at the postjunctional membrane of the myoneural junction. As a result, depolarization is prevented, calcium ions are not released, and muscle contraction does not occur.^{1,2}

Indications

The Food and Drug Administration (FDA) has approved the use of vecuronium as an adjunct to general anesthesia, to facilitate endotracheal intubation, and to provide muscle relaxation during surgery or mechanical ventilation. According to FDA labeling, the safety and efficacy of vecuronium in children under 7 weeks of age have not been established.¹

Use in Children

Vecuronium has been administered to children by both continuous infusion and intermittent bolus injections. Eldadah and colleagues studied 12 pediatric intensive care unit (ICU) patients in a randomized, cross-over prospective trial.³ The mean age of the children was 35.5 months and the mean weight was 13.4 kg. Six patients received a continuous infusion of vecuronium, and six patients received bolus doses of vecuronium for a 12 hour period. After the initial 12 hours, patients were switched to the other administration technique for another 12 hours. During the bolus dosing period, subjects received vecuronium doses of 100 micrograms/kg intravenously (IV) every hour. Additional boluses of 100 micrograms/kg were available to maintain neuromuscular blockade if necessary. During the infusion phase, a bolus of 150 micrograms/kg of vecuronium was given, followed by an infusion of 1 micrograms/kg/min. The infusion was then titrated to maintain an adequate neuromuscular blockade.

The level of neuromuscular blockade was assessed peripherally using the train of four (TOF) method. Lack of the fourth twitch response in subjects was considered to be an adequate neuromuscular blockade. The amount of vecuronium needed to maintain this level of neuromuscular blockade was compared between the two methods of administration. The authors also evaluated the personnel time needed to prepare the doses.

Overall, patients receiving continuous infusions required significantly less ($p < 0.01$) vecuronium to maintain a similar neuromuscular blockade than when hourly boluses were used. The average dose for continuous administration was 0.79 micrograms/kg during the 12 hour study period (range 0.1-1.8 micrograms/kg) compared to an average dose for bolus administration of 1.34 micrograms/kg (range 1.0-2.55 micrograms/kg). Seven subjects needed additional boluses when they received a continuous infusion of vecuronium. Five

of those children also required additional boluses when they were receiving hourly bolus administration. The authors speculated that the children who required additional drug, regardless of administration method, were rapid metabolizers.

The personnel time required to administer vecuronium by continuous infusion was found to be significantly less ($p < 0.001$) than hourly bolus administration. The authors theorized that hourly dosing also may increase the possibility of human error, by increasing the need to prepare individual doses, and may increase the possibility of infection at the IV access site.

Another study of ICU patients involved 15 subjects (4 neonates, 11 infants and young children) who received a continuous infusion of vecuronium for paralysis during mechanical ventilation.⁴ The average age of the neonates was 5.3 ± 7.9 days and the average age of the older patients was 35.2 ± 38.7 months. A loading dose of 0.1 micrograms/kg was given followed by a maintenance dose of 0.1 micrograms/kg/hr. Rates were titrated to maintain a 90% neuromuscular blockade via TOF assessment. The neonates required a mean dose of 0.11 ± 0.05 micrograms/kg/hour, while the older children required a mean dose of 0.14 ± 0.05 micrograms/kg/hour. Only two subjects required additional bolus dosing to maintain the desired level of blockade. The average duration of infusion in this study was 51.2 ± 51.6 hours. On average, neonates recovered from the blockade within 46.8 ± 16.5 minutes, while it took the older children approximately 51.7 ± 17.6 minutes to recover. No cardiovascular or toxic adverse effects were observed. One subject died from complications of pneumonia and another subject died from complications of severe brain injury during the study. The authors concluded that continuous IV administration of vecuronium is feasible and effective in children.

Pharmacokinetics/Pharmacodynamics

The onset and duration of action of vecuronium is dose dependent, but varies among individuals. On average, an initial response occurs in 2.1 to 3.8 minutes, the peak response occurs within 2 to 5 minutes. The duration of a single dose is between 30 to 40 minutes.

Vecuronium is ionized and water soluble prohibiting passage through the blood brain barrier. It has a total protein binding capacity of 60% to 80% and has a distribution half-life of 4 to 11 minutes. The volume of distribution (V_d) of vecuronium is 0.2 to 0.4 L/kg. The V_d may be larger in infants when compared to older children, although no significant differences in body clearance or elimination half-life have been documented in these different age groups.

Thirty percent of an administered dose of vecuronium is metabolized in the liver, where it undergoes spontaneous deacetylation to three active metabolites. The elimination half-life is approximately 80 minutes. Renal excretion accounts for 15-20% of a dose of vecuronium and another 30-50% is excreted in the bile. Thus, it may take patients with cirrhosis or cholestasis longer to clear the drug.^{1,5-7}

Drug Interactions

The concomitant use of parenteral antibiotics such as aminoglycosides, tetracyclines, clindamycin, bacitracin, and polymixin B may intensify the neuromuscular blockade produced by vecuronium. Recurrent paralysis can occur for patients receiving quinidine after vecuronium use. The neuromuscular blocking effect and the duration of action of vecuronium also may be increased with the use of other NMBAs or calcium channel blockers. Conversely, the concomitant use of azathioprine or theophylline has been shown to decrease the neuromuscular blockade of vecuronium.^{1,6-7}

Adverse Effects

In general, vecuronium is well tolerated by most patients. Vecuronium lacks cardiovascular side effects such as tachycardia, hypertension, or hypotension (resulting from histamine release) that may be seen in conjunction with the use of other NMBAs.^{1,7} In 1988, a case report described a 14 year old male that experienced sinus node exit block twice approximately 5 minutes after receiving a 0.08 micrograms/kg intravenous dose of vecuronium. The block resolved spontaneously without sequelae.⁸

Bronchospasm occurs rarely with vecuronium administration. Anaphylaxis has also been documented after vecuronium administration. There appears to be a 66% cross-reactivity in patients with a history of anaphylaxis or allergy to a neuromuscular agent, with vecuronium and pancuronium having the highest cross-reactivity rate. Long-term use of vecuronium can result in prolonged muscle relaxation and weakness.^{1,9}

Vecuronium products containing benzyl alcohol should not be used in neonates due to the possible displacement of bilirubin from protein binding sites by benzoic acid, which may mask neonatal distress and result in a gasping syndrome.¹⁰

Dosing Recommendations and Monitoring

Vecuronium is available in 10 and 20 mg vials for IV administration. Intramuscular administration is not recommended due to lack of clinical studies with this route and due to potential erratic absorption intramuscularly during surgery or mechanical ventilation.^{1,6-7} Intraosseous administration of vecuronium has been successful in two children with doses of 0.1 to 0.15 micrograms/kg.¹¹ The onset of action (90 seconds in the 3 month old and 150 seconds in the 22 month old) with intraosseous administration did not vary significantly from that of IV administration.

Recommendations for dosing of vecuronium in children under the age of 10 years have come from clinical studies. A range of 0.05 to 0.1 micrograms/kg has been used in neonates. Older infants and children have received doses similar to adults, with initial doses between 0.08 to 0.1 micrograms/kg and maintenance

doses of 0.05 to 0.1 micrograms/kg. Children from the age of 1 to 9 years may need a slightly higher initial dose and more frequent supplemental dosing than children over the age of 10 years. For continuous infusion of vecuronium in children, doses in the range of 0.05 to 0.08 micrograms/kg/hour have been used safely and effectively.^{1,3-4,6-7,12}

Respiratory and cardiovascular status as well as level of neuromuscular blockade should be monitored in patients receiving vecuronium. Peripheral nerve stimulation using the TOF method has been successful in titrating adequate doses of NMBAs. The ulnar nerve is a common peripheral site to assess a subject's degree of paralysis. Upon electrical stimulation, three twitches are indicative of a 75 to 80% neuromuscular blockade, two twitches are indicative of a 80 to 90% blockade, and a single twitch is indicative of 90% of the acetylcholine receptors being blocked. Most ICU patients can be adequately paralyzed with a minimum of two twitches, however, some patients may require a greater degree of paralysis due to the possibility that any movement could be harmful. If a peripheral nerve stimulator device is not available, signs of decreased muscle relaxation such as movement of the diaphragm and/or an increase in jaw tone can be visualized. Since NMBAs do not alter a patient's state of consciousness, sedatives and analgesics are necessary adjuncts during neuromuscular blockade. Sedative agents that cause amnesia such as benzodiazepines can be used. Furthermore, long-term use of NMBAs requires deep vein thrombosis prophylaxis with either heparin or compression devices, as well as the use of artificial tears or ophthalmic ointment to prevent corneal damage. In addition, physical therapy and adequate nutrition are necessary to prevent skin and muscle atrophy.^{1,6-7,13}

Summary

Vecuronium is an intermediate-acting nondepolarizing neuromuscular blocking agent that can be used safely and effectively in children. The relative lack of adverse effects experienced with the use of vecuronium in comparison to other neuromuscular blocking agents make it an appealing alternative for children requiring pharmacologic paralysis during mechanical ventilation.

References

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Literature Review

Doxepin during breastfeeding

The authors present a single case of a nine day old term infant whose mother was being treated with low-dose doxepin therapy (35 mg/day). The infant developed symptoms of a poor suck and swallow, hypotonia, vomiting, and lethargy. The amount of doxepin and its active metabolite, N-desmethyldoxepin, ingested were estimated to be 10-20 mcg/kg/day. This value represents approximately 2.5% of the maternal dose. Despite the relatively small concentrations ingested, the authors believed the patient's symptoms to be related to doxepin ingestion and recommended discontinuing breastfeeding. All symptoms resolved within the next 2 days. Based on their experience, the authors recommend that doxepin should not be used in breastfeeding mothers. Other antidepressants less likely to cross into breastmilk, such as amitriptyline, nortriptyline, desipramine, or sertraline, may be preferable. Frey OR, Scheidt P, von Brenndorff AI. Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. *Ann Pharmacother* 1999;33:690-3.

Ibuprofen-associated pyloric channel stricture

This case report describes a 12 year old child with cystic fibrosis (CF) who developed a pyloric channel stricture after ibuprofen use. The patient was taking ibuprofen at a dose of 56 mg/kg/day as part of an investigational protocol designed to evaluate the effects of long-term anti-inflammatory use on the pulmonary manifestations of CF. Approximately 2 months after starting therapy, the patient developed symptoms of food intolerance and emesis. Conservative management of her symptoms did not cause improvement, and the diagnosis of pyloric channel stricture was made 3 months later. The patient slowly recovered after pyloric channel dilation and discontinuation of ibuprofen. Follow-up one year later revealed no long-term sequelae. The authors suggest that the stricture resulted from undiagnosed peptic ulcers caused by high-dose ibuprofen. Bell EA, Grothe R, Zivkovich V, et al. Pyloric channel stricture secondary to high-dose ibuprofen therapy in a patient with cystic fibrosis. **Ann Pharmacother** 1999;33:693-6.

Sertraline-erythromycin interaction

A 12 year old boy receiving sertraline who developed serotonin syndrome after starting erythromycin is described in this brief case report. The patient had been on sertraline therapy 4 months for severe obsessive-compulsive disorder and simple phobia. Within 4 days of starting erythromycin for a presumed infection, he developed nervousness, escalating over the next 10 days to signs and symptoms associated with serotonin syndrome: panic, agitation, paresthesias, and confusion. Discontinuation of the drugs resulted in resolution of most symptoms within 72 hours. The authors hypothesize that the patient's symptoms resulted from the inhibition of cytochrome P450 3A4 enzyme function by erythromycin, allowing accumulation of sertraline to toxic concentrations. Lee DO, Lee CD. Serotonin syndrome in a child associated with erythromycin and sertraline. **Pharmacotherapy** 1999;19:894-6.

Zidovudine pharmacokinetics in infants

Although zidovudine has become a standard therapy in infants exposed to HIV in utero, there is still much to learn about zidovudine elimination in this age group. The authors of this study used population analysis to determine bioavailability, volume of distribution, and the elimination rate constant from 698 serum samples taken from 83 infants. Analysis revealed a slow zidovudine elimination shortly after birth, that increased rapidly to achieve adult values by the first two months of life. Gender, race, or previous exposure to didanosine or nevirapine had no impact on elimination. Bioavailability was increased during the first two weeks of life, likely the result of a decrease in hepatic first-pass effect. Mirochnick M, Capparelli E, Connor J. Pharmacokinetics of zidovudine in infants: A population analysis across studies. **Clin Pharmacol Ther** 1999;66:16-24.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 8/27/99:

1. Recombinant factor VIIa (NovoSeven[®]) was added to the formulary, restricted to use by the adult and pediatric hematology.
2. Isoetharine was removed from the formulary because of lack of use.

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