PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 6 Number 10 October 2000

Rocuronium for Tracheal Intubation

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Neuromuscular blockade is an essential component of caring for the critically ill child. Potential situations requiring neuromuscular blockade include: tracheal intubation and mechanical ventilation, certain diagnostic and therapeutic procedures, surgery requiring immobility or relaxation of abdominal muscles, and agitation unresponsive to sedation and analgesia. Succinylcholine has long been used for tracheal intubation due to its quick onset of action and short duration. However, in an effort to avoid the adverse reactions associated with succinylcholine, such as arrhythmias and malignant hyperthermia[1-4], non-depolarizing agents have been investigated for their efficacy during intubation. This review will focus on rocuronium bromide (Zemuron®), an intermediate acting nondepolarizing neuromuscular blocker and its role in pediatric intubation.

Mechanism of Action

In general, neuromuscular blockers prevent the transmission of electrical impulses to the muscle by altering the normal interaction of acetylcholine with the postsynaptic cholinergic receptor. Rocuronium, an analog of vecuronium, is an aminosteroid neuromuscular blocker which exerts its action through competitive inhibition of the cholinergic receptor at the motor end-plate of the myoneural junction. Rocuronium blocks the effect of both the small quantities of acetylcholine that maintain muscle tone and the large quantities of acetylcholine that produce voluntary muscle contraction, but does not alter the resting electrical potential of the motor end-plate or cause muscle contraction.[1-3,5]

Indications

Rocuronium is approved by the Food and Drug Administration (FDA) as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. Use in children less than three months of age has not been studied.[2,5]

Use in Children

Since rocuronium was approved by the FDA in 1994, there have been numerous trials evaluating its use in children.[6-11] Scheiber and colleagues[6] evaluated 60 children aged 18 to 72 months undergoing elective surgical procedures requiring intubation. The children were randomized to receive rocuronium 0.6 mg/kg, vecuronium 0.1 mg/kg, or atracurium 0.5 mg/kg after induction of anesthesia with etomidate and fentanyl. Endotracheal intubation was attempted every 30 seconds, beginning 30 seconds after administration of the neuromuscular blocker, until intubation was achieved under good or excellent conditions. Intubating condition grades were based on jaw relaxation, closing of the vocal cords, and diaphragmatic response.

Rocuronium produced acceptable intubating conditions significantly faster than vecuronium or atracurium. All children in the rocuronium group were intubated by 60 seconds (60% intubated at 30 seconds), compared to 120 seconds for complete intubation of the vecuronium group and 180 seconds for the atracurium group. The adductor pollicus muscle was electrically stimulated in order to assess a train-of-four every twenty seconds. Onset of 95% blockade at the adducter pollicis muscle was not significantly different between the groups and the peripheral muscle block was not complete in all groups at the time of successful intubation. Based on these results, the authors speculated that rocuronium may have a faster onset at laryngeal muscle compared with peripheral muscle.

Woolf and colleagues[7] completed a two-part study to evaluate the potency of rocuronium in children. They compared the time course of action at doses up to three times the effective dose for 95% neuromuscular block (ED_{95}) with that of succinylcholine. Forty-eight children aged 2 to 10 years were randomized to intravenous rocuronium 120, 160, 200 or 240 mcg/kg after being anesthetized with nitrous oxide, fentanyl, and propofol. Neuromuscular

block was assessed by monitoring train-of-four stimulation of the ulnar nerve every 2 seconds for 10 seconds. This initial study yielded ED_{50} and ED_{95} values of 210±24 and 404±135 mcg/kg, respectively.

In the second part of the study, 30 children were randomized to receive 2.0 mg/kg of succinylcholine, 0.8 mg/kg, or 1.2 mg/kg of rocuronium (two and three times the ED_{95}). Time to 90 and 100% block was not significantly different between succinylcholine (30±7 seconds) and 1.2 mg/kg of rocuronium (33±5 seconds); both were significantly less than the 0.8 mg/kg group (46±8 seconds). Time to 25% recovery from 1.2 mg/kg of rocuronium was nearly 8 times longer than after succinylcholine (41±13 compared to 5.2±1.9 minutes).

Another study by Mazurek and coworkers[8] compared 1.2 mg/kg of rocuronium with 1.5 mg/kg of succinylcholine in 26 children aged 2 to 15 years. All children received 5 mg/kg of thiopental. Intubation was attempted after 30 seconds. No difference was noted in time to completion of intubation (41.8±2.9 seconds for rocuronium compared to 40.2±4 seconds for succinylcholine) or in the number of patients receiving excellent intubating scores. Time to recovery of 25% of train-of-four was significantly longer for patients receiving rocuronium, 46.3±23.4 compared to 5.8±3.3 minutes for succinylcholine.

Rocuronium appears to be an acceptable alternative to succinylcholine in providing adequate intubating conditions within 60 seconds of administration. The use of rocuronium is limited by its long duration of action. It should only be used when a rapid return to spontaneous respiration is not required.

Pharmacokinetics/Pharmacodynamics

Rocuronium is structurally related to vecuronium, and has a similar pharmacokinetic profile with the exception of a more rapid onset of action. On average, maximal neuromuscular block following an intravenous dose occurs within one minute. Following intramuscular (IM) administration into the deltoid, plasma concentrations peak at 13 minutes. Approximately 80% of the drug is absorbed systemically after an IM dose.[12]

Clinical duration of action for rocuronium ranges from 30 minutes to 1 hour. Mean duration in children aged 3 months to 1 year is reported to be 41 minutes, significantly longer than the mean of 27 minutes found in children aged 1 to 12 years.[3,5]

Rocuronium is a polar molecule and distributes into extracellular fluid; protein binding has minimal effect.[13,14] In a pharmacokinetic study by Vuksanaji and Fisher of children ages 4 to 11 years, the clearance (Cl) of rocuronium varied inversely with body weight. Volume at steady state (Vss) did not vary, resulting in an increase in half-life with age and weight.[15] The impact of these changes is relatively small. The average half-life for an infant between 3 and 12 months of age is 1.3±0.5 hrs, compared to 0.8±0.3 hrs for a child between 3 and 8 years of age.

Several studies have found that newborn infants demonstrate an increased Vss, a slower Cl, and an increased mean recovery time for rocuronium compared to older infants and children.[14] Several factors may be responsible for these differences. The neuromuscular junction changes during the first two months of life. The immature receptor remains open for a longer period of time, allowing for easier depolarization, but may have a decreased affinity for nondepolarizing agents. Infants have a smaller muscle mass to fat ratio resulting in a decreased number of cholinergic receptors that need to be inhibited to allow for muscle relaxation.[1,13] In addition, the infant diaphragm has fewer type I fibers (slow-twitch) which are more sensitive to neuromuscular blockade than type II fibers (fast-twitch). As a result, the diaphragm may remain more active than peripheral muscles.[1] While these sometimes opposing physiologic factors are not yet fully understood, they may explain the variation in response observed in newborns given neuromuscular blockers.

Rocuronium is primarily eliminated via hepatic reuptake and biliary excretion. After a 0.6 mg/kg dose, 12 to 22% is excreted unchanged in the urine. Rocuronium has one metabolite, 17-desacetylrocuronium, which is unlikely to contribute to its neuromuscular blocking action. While there is no documented evidence that renal dysfunction adversely affects the clearance of rocuronium, recovery parameters tend to be longer and more variable in the elderly and those with some degree of renal impairment. Patients with hepatic dysfunction, particularly cirrhosis, demonstrate increased volume of distribution, decreased clearance, and increased half-life.[5,14]

Drug Interactions

Concurrent administration of inhalational anesthetics causes a nondepolarizing block and can potentiate the effects of rocuronium. This effect is often used therapeutically to allow a lower dose of the neuromuscular blocker. Aminoglycosides are also known to prolong skeletal muscle relaxation. Other antibiotics such as clindamycin, tetracycline and the polymyxins potentiate the blockade, but to a lesser extent. Potassium-wasting drugs such as thiazide and loop diuretics, amphotericin B, and corticosteroids may also prolong neuromuscular blockade. Other agents that may contribute to a longer duration of action for rocuronium include: calcium channel blockers, magnesium, beta-blockers, lithium, and procainamide.

Phenytoin and carbamazepine can antagonize the neuromuscular blockade produced by rocuronium. Sympathomimetic drugs, such as epinephrine, may also reverse neuromuscular blockade. Neostigmine and other acetylcholinesterase inhibitors are used to reverse the effects of nondepolarizing neuromuscular blockers when there is no further need for pharmacologic paralysis.[1,2,5]

Adverse Effects

Rocuronium is generally well tolerated. According to the manufacturer, there are no adverse events that occur in greater than 1% of the patients studied.[5] Rocuronium is notable for cardiovascular stability and lack of histamine release. Slight increases in heart rate and blood pressure may occur, and arrhythmias have been reported in <1% of treated patients. Other rare events include bronchospasm, rash, pruritis and injection site edema. As with all neuromuscular blockers, rocuronium has the potential to cause anaphylactic reactions.[1,3,5,16]

Dosing Recommendations and Monitoring

Rocuronium is available in 10 mg/mL vials containing 50 mg for injection. While intravenous administration is preferred[4-14], IM administration has also been reported. Intramuscular injection of rocuronium has been compared to intramuscular succinylcholine with conflicting results. Reynolds and colleagues found that deltoid injections of 1 mg/kg in infants and 1.8 mg/kg in children permitted intubation within 3 minutes with a time to recovery of greater than 60 minutes.[17] However, Kaplan found that after administering the same doses, adequate tracheal conditions were not reached until 7 minutes, and time to recovery was extended to 80 minutes.[18]

Recommendations for intravenous dosing in children have been derived from the results of several clinical studies. In infants and children, doses that have been evaluated range from 0.6 mg/kg to 1.2 mg/kg given as intravenous boluses in conjunction with either inhalational or intravenous anesthetics. These doses typically produce neuromuscular blockade within 60 seconds.[6-11] The usual dose for tracheal intubation in adults is 0.6 mg/kg. Continuous infusions of 0.01 to 0.012 mg/kg/min have been used to prolong paralysis after bolus dosing, once neuromuscular blockade has returned to 10% of control.[3] Tachyphylaxis can occur within 48 to 72 hours of continuous administration, requiring dosage adjustment to maintain the desired level of paralysis.[1]

Cardiovascular and respiratory status should be monitored in all patients receiving rocuronium. Heart rate and blood pressure may slightly increase while respiratory drive may decrease. Level of neuromuscular blockade should also be monitored. This can be achieved by electrically stimulating the ulnar nerve and assessing the train-of-four response or evaluating signs of muscle relaxation such as diaphragm response or decrease in jaw tone. It is important to remember that peripheral nerve stimulation may not reflect the response of the diaphragm or larynx.[1,5]

As with all nondepolarizing neuromuscular blockers, analgesics and sedatives must be administered during rocuronium use. If the patient is to be paralyzed for a prolonged period of time, other preventative measures should be taken. Deep vein thrombosis prophylaxis should be considered in older children. Artificial tears or ointment should be used to prevent corneal damage. Physical therapy and adequate nutrition should be used to prevent skin breakdown and muscle atrophy.[1-3,5]

Summary

Intravenously administered rocuronium has been safely and effectively used in infants and children to provide adequate neuromuscular blockade for tracheal intubation. Because of its quick onset of action and low incidence of adverse effects, rocuronium appears to be an acceptable alternative to succinylcholine.

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Pharmacology Literature Review

Antiepileptic Review

A concise, but very interesting review of the impact of physical development on antiepileptic use has been published in a recent supplement to *Pharmacotherapy*. The author addresses the susceptibility of the immature brain, the effects of genetic alterations and perinatal illness, and the impact of maturation on antiepileptic response. Moshe SL. Special considerations in treating children with epilepsy. **Pharmacotherapy 2000:20(8 Pt 2):171S-177S.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 9/22/00:

1. Quetiapine (Seroquel®) was added to the Formulary for the management of patients with psychotic disorders.
2. Rivastigmine (Exelon®) was added for the management of patients with Alzheimer's disease. Tacrine (Cognex®) was removed from the Formulary.
3. Docetaxel (Taxotere®) was added as a second-line therapy for non-small cell lung cancer and metastatic breast cancer.
4. Gemtuzumab ozogamicin (Mylotarg®) was also added, restricted to use in patients with CD33-positive AML who have relapsed.
5. The following agents were removed from the Formulary because of lack of use: aminophylline tablets, cycloserine capsules, ethionamide tablets, fluoxymesterone, guanethidine tablets, kanamycin capsules, metaproterenol tablets, metocurine injection, methoxamine injection, methysergide tablets, norethynodrel/mestranol tablets, and xylometazoline for intranasal use.

**** Correction**********

In the September issue (Vol. 6, No. 9), the equation for a PGE_1 infusion was incorrect. The correct equation should determine the amount of drug in **mg**, rather than mcg.

0.15 x wt (in kg) = ___ **mg** of PGE_1 added to 50 ml fluid to run at 1 ml/hr = 0.05 mcg/kg/min

Please make this change in your copy. We apologize for this error.

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