PEDIATRIC PHARMACOTHERAPY

University of Virginia Children's Hospital

Volume 20 Number 5 May 2014

Use of Atropine in Infants and Children

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Atropine, an alkaloid found in *Atropa belladonna* (deadly nightshade), *Datura stamonium* (Jimson weed or thornapple), or *Hyoscyamus niger* (black henbane), was first isolated in the 1831 by George Mein, and separately in 1833 by Philipe Lounz Geiger and Germain Henri Hes. The name atropine was derived from Atropos, the oldest of the three Fates of Greek mythology, who cut the thread of life. Long before the isolation of atropine, these plants were known for both their medicinal and toxicological effects.[1,2]

Mechanism of Action

Atropine is a racemic mixture of d- and l-hyoscyamine. Its pharmacologic activity is due primarily to the l-hyoscyamine isomer. While it is typically considered an anticholinergic, it is more accurately classified as an antimuscarinic agent. Atropine is a non-selective competitive acetylcholine antagonist at muscarinic receptor subtypes M1, M2, M3, M4, and M5.[1-3]

The cardiac effects of atropine result from binding at M2 muscarinic receptors located in the sinoatrial (SA) and atrioventricular (AV) nodes. By blocking activity at these sites, atropine blocks vagal nerve activity on the heart and increases heart rate. In addition to its use in treating symptomatic bradycardia, atropine may be useful in the treatment of second degree heart block (Wenckebach block) and third degree heart block with a high Purkinje or AV-nodal escape rhythm. The parasympathetic effects of atropine also include inhibition of salivary and mucus glands, making it a useful tool for reducing secretions during intubation. Other uses for atropine include the treatment of hyperhidrosis, ocular administration to produce cycloplegia and mydriasis for ophthmologic exams, and use in conjunction with pralidoxime (2-PAM) for organophosphate poisonings.[1-3]

Pharmacokinetics and Pharmacodynamics

Atropine may be administered by a variety of routes, including intravenous (IV), intraosseous (IO), and endotracheal administration for resuscitation, as well as by intramuscular and subcutaneous administration for other uses. Atropine is widely distributed throughout the body after IV administration, reaching the central nervous system within 30-60 minutes after dose administration. It is 44% protein bound, primarily to alpha-1-acid glycoprotein. Approximately 60% of an atropine dose is excreted in the urine as unchanged drug. The remainder undergoes hepatic metabolism to inactive metabolites, including noratropine, atropine-n-oxide, tropine, and tropic acid. The elimination half-life of atropine in adults is approximately 2 hours. There is little information available on the pharmacokinetics of atropine in the pediatric population.[2,3]

Resuscitation

Atropine was first recommended for the treatment of pediatric bradycardia in the 1950s. Although atropine is no longer considered a primary component of the management of pediatric cardiac arrest, it remains an option in the guidelines from the International Liaison Committee on Resuscitation (ILCOR) and its affiliate in the United States, the American Heart Association (AHA), for treatment of bradycardia caused by increased vagal tone, primary atrioventricular (AV) block, or cholinergic drug toxicity. It is also considered a second-line therapy for bradycardia refractory to epinephrine.[4,5] The 2010 ILCOR and AHA guidelines recommend an atropine dose of 0.02 mg/kg, with a minimum dose of 0.1 mg for all pediatric patients to prevent paradoxical bradycardia. The use of a minimum dose regardless of patient weight or age has come under question over the past decade.[6]

The source most often cited for the 0.1 mg minimum atropine dose is the study by Dauchet and Gravenstein published in a 1971 issue of *Clinical Pharmacology and Therapeutics*.[7] The authors studied the effects of atropine, given in four divided doses up to a total of 1 mg/70kg in 79 patients undergoing elective surgery. The patients (6 weeks to 79 years) were grouped by age: 6 weeks-2.9 years, 3-6.9 years, 7-12.9 years, 13-19.9 years, 20-39.9 years, 40-59.9 years, and

60-79 years. Atropine was administered as two 1.8 mcg/kg doses, a 3.6 mcg/kg dose, and a 7.1 mcg/kg dose.

The authors noted that after the initial small doses, the heart rate was either normal or lower than normal. It was only after the higher doses that the patients had clear tachycardia. The authors noted that the initial paradoxical bradycardia was not substantially different in infants and young children than in adults when baseline heart rate was taken into account. At the conclusion of the article, the authors suggested a dose of 0.1 mg for newborns (although no newborns were included in the study) and a dose of 0.6 to 0.8 mg in adults; there were no specific guidelines for children or weight-based recommendations provided. Despite the clear limitations of this study, the 0.1 mg dose was adopted as the minimum recommended atropine dose in the belief lower doses were more likely to produce paradoxical bradycardia. In a 2011 article in *Pediatrics*, Barrington reviewed the data from the Dauchet study and concluded that the assumption that a 0.1 mg minimum dose would prevent paradoxical bradycardia reflected an inaccurate interpretation of the data.[6]

The use of a standard 0.1 mg minimum dose means that patients weighing less than 5 kg are potentially exposed to an excessive dose. Adverse effects from using a standard 0.1 mg atropine dose in neonates have now been reported by several authors.[8,9] In one recent report, a 1-day-old neonate (3.3 kg) was given 0.1 mg atropine during resuscitation after rapid blood loss during the surgical resection of a sacral teratoma.[8] The patient survived, but failed to exhibit spontaneous movement for more than 24 hours. The medical team, based on the possibility of central anticholinergic syndrome, gave the patient 0.5 mg pyridostigmine and within minutes, the patient had spontaneous purposeful movement. While the authors did not comment on the atropine dose, based on a weight of 1.8 kg (the patient's weight after removal of the 1.5 kg tumor) it was 0.06 mg/kg, well above the recommended weight-based dose.

In addition, several recent studies of preterm and term neonates given weight-based atropine doses of 0.01-0.02 mg/kg have shown no evidence of paradoxical bradycardia.[10-12] As a result of these reports, the use of weight-based dosing for patients less than 5 kg has become adopted by many pediatric healthcare providers and is noted in several reference texts and clinical guidelines.[13,14]

Intubation

Vagolytics are given prior to intubation to minimize bradycardia and reduce bronchial and salivary secretions. Premedication for neonatal or pediatric rapid sequence intubation typically includes a sedative (remifentanil, fentanyl, or morphine), a short-acting neuromuscular blocking agent (rocuronium or succinylcholine) and a vagolytic (atropine or glycopyrrolate).[15] Current guidelines for intubation of neonates from the American Academy of Pediatrics and the Canadian Paediatric Society recommend the use of atropine, at a dose of 0.02 mg/kg given IV or IM, if a vagolytic is desired.[14-16] Although considered a standard premedication, both guidelines acknowledge the lack of evidence supporting the efficacy of atropine in this setting.

In a 2004 retrospective cohort study of 143 children (newborn to 19 years of age) undergoing intubation, Fastle and Roback found bradycardia in only six patients (4%): three who were given atropine and three who were not.[17] There were, however, more hypoxic events in the children given atropine (28% versus 16% in the untreated patients, $p = 0.046$). The authors concluded that their results suggest that the overall incidence of clinically significant arrhythmias during intubation is low and does not merit the use of atropine. In the correspondence following publication of this study, Rothrock and Pagane recommended limiting atropine use to infants, based on a greater likelihood for stress-induced arrhythmias, and patients receiving ketamine or more than one dose of succinylcholine.[18]

In contrast, a 2013 2-year prospective single-center observational study identified a clinically significant benefit from atropine administration.[19] A total of 322 neonatal and pediatric intubations (newborns to 8 years of age) were included in the analysis, including 152 cases (47%) in which atropine (0.02 mg/kg) was used. All patients were evaluated with an electrocardiogram (ECG) prior to and during intubation. Patients with an abnormal baseline ECG were excluded from receiving atropine. In the patients given atropine, the mean heart rate prior to intubation increased from 153 to 171 beats/min ($p < 0.001$). The development of intubation-related ECG abnormalities, primarily bradycardia, was significantly less common in the group given atropine (4.5% versus 26.5%, OR 0.14 [95% CI 0.06-0.35], $p < 0.001$). Based on their findings, the authors concluded that atropine may contribute to the safety of pediatric intubation. While this single study does not resolve the question of atropine's utility during intubation, it provides useful information gathered in a large number of patients using more standardized methods for patient assessment.

Procedural Sedation

The benefit of atropine in minimizing the hypersalivation associated with ketamine has been documented in two recent studies. In 2012, Kye and colleagues conducted a randomized double-blind placebo-controlled trial of atropine in 140 children (1-10 years of age) requiring sedation in the emergency department.[20] All patients received ketamine 2 mg/kg given IV and were randomized to receive 0.01 mg/kg atropine or placebo. The degree of salivation was assessed on a 100-point analog scale by a nurse. There were significantly fewer secretions in the atropine group (16.5 $\pm$ 9.9 versus 27.0 $\pm$ 15.9, $p < 0.05$). Salivation scores of 50 or more were assigned in only 1 of the 68 atropine patients (1.5%), compared to 7 of the 72 controls (9.7%). In spite of the increased salivation in the controls, few patients required repositioning or suctioning. Heart rate was significantly higher in the atropine group ($p < 0.05$), but there was no difference in adverse effects. The authors concluded that while atropine administration reduced hypersalivation, it may not be necessary for children receiving ketamine for procedural sedation without intubation.

Asadi and colleagues conducted a similar double-blind randomized controlled trial of atropine in 200 children (ages 2-15 years) receiving ketamine for procedural sedation in the emergency department.[21] The number of patients rated as having hypersalivation was significantly lower in the group given 0.01 mg/kg atropine than the group who was not treated (12% versus 28%, OR 0.37, 95% CI 0.18-0.74). Rates of nausea and vomiting were less in the atropine group, but the results were not statistically significant.

The potential for atropine or metoclopramide to reduce ketamine-associated vomiting was investigated by Lee and colleagues in an open-label randomized controlled study.[22] A total of 338 infants and children (4 months-5 years) undergoing wound repair were randomized to one of three groups: ketamine (4 mg/kg IM) alone, ketamine plus atropine (0.01 mg/kg IM), or ketamine plus metoclopramide (0.4 mg/kg IM). The rates of vomiting were 28.4%, 27.9%, and 31.2% in the three groups, respectively ($p = 0.86$). Time to resumption of a normal diet was similar among the groups (ranging from 7.5 to 8 hours). The authors concluded that neither adjunctive medication was useful in this setting.

Contraindications and Precautions

Administration of atropine is contraindicated in patients with glaucoma, pyloric stenosis, or prostatic hypertrophy because of the potential to precipitate sudden profound worsening of their underlying disease. Use of a single low dose prior to anesthesia or intubation is typically considered acceptable in patients with these contraindications. Atropine should be used with caution in patients with chronic lung disease because of the risk for producing mucous plugs.[3]

Drug Interactions

Atropine may decrease the rate of mexiletine absorption, but does not alter its oral bioavailability.[3]

Adverse Effects

The adverse effects most frequently reported with atropine administration are related to its antimuscarinic properties: tachycardia, dry mouth, difficulty swallowing, and relaxed lower esophageal sphincter tone, posing a risk for aspiration, as well as urinary retention, constipation, and blurred vision or photophobia due to mydriasis,. Atropine-induced anhidrosis may lead to heat intolerance and elevated body temperatures, particularly in young children and the elderly. Hypersensitivity reactions to atropine are rare, but cases of rash and exfoliation have been reported.[3]

In the setting of an atropine overdose or repeated administration of high doses over a short period of time, atropine may produce dizziness, ataxia, disorientation, agitation, hallucinations, delirium, tremor, or seizures. In addition, patients may experience hypotension, respiratory failure, paralysis, and circulatory collapse. In addition to supportive therapies, physostigmine, an acetylcholinesterase inhibitor, may be given at a dose of 0.5-1 mg in children or 1-4 mg in adults to reverse the effects of atropine. Repeated doses may be required.[3]

Availability and Dosing Recommendations

Atropine injection is available from several manufacturers in the U.S., and comes in a variety of strengths: 0.05 mg/mL, 0.1 mg/mL, 0.4 mg/mL, 0.8 mg/mL, and 1 mg/mL. It is sold in single-dose vials and pre-filled syringes. The more than 10-fold variation in concentration requires close attention during product selection, dose preparation, and administration. In a 2012 retrospective analysis of medication errors in children treated by emergency medical services prior to being seen in the emergency department of a tertiary care children's hospital, 20 of the 41 (48.8%) atropine doses administered over a 2-year period were incorrect, with eight overdoses and 12 underdoses. The use of dosing tools such as the Broselow-Luten tape or weight-specific dosing cards were associated with significantly fewer errors.[23]

The recommended dose for the treatment of bradycardia or to reduce secretions in infants and children is 0.01-0.03 mg/kg. Current AHA and

ILCOR guidelines recommend a dose of 0.02 mg/kg given IV or IO.[4,5] In adolescents and adults, a dose of 0.5-1 mg may be given every 3-5 minutes up to a maximum 3 mg dose for antisialagogue or antivagal effects. For endotracheal administration during cardiac arrest, a dose of 1-2 mg is recommended, diluted up to a volume of 10 mL with sterile water or normal saline.[3]

Summary

The role of atropine in pediatric medicine continues to evolve over time. While no longer a primary medication for pediatric resuscitation, atropine still serves as a second-line therapy for selected arrhythmias. It remains a frequent part of premedication for neonatal and pediatric intubation, and is still used as adjunctive therapy during procedural sedation by many clinicians, although recent studies have questioned its utility in these settings.

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Formulary Update

The following actions by the Pharmacy and Therapeutics Committee at their April 2014 meeting:

1. Posaconazole injection and delayed-release tablets (Noxafil®) were added with restriction to Antimicrobial Category A and an Infectious Diseases consult for adult patients.
2. The restriction on collagenase clostridium histolyticum (Xiaflex™) was amended to use by registered prescribers at the Urology Clinic and Outpatient Hand Center.
3. Neomycin-containing irrigation solutions were removed from the Formulary due to the risks associated with compounding.
4. Vitamin A injection was removed from the Formulary due to lack of use.

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