PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

Volume 14 Number 8 August 2008

Adenosine for the Management of Neonatal and Pediatric Supraventricular Tachycardia

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Supraventricular tachycardia (SVT) is the most common symptomatic arrhythmia of childhood, occurring in 1 in 250 to 1,000 children.[1,2] In October 1989, adenosine was approved by the Food and Drug Administration (FDA) for the conversion of paroxysmal supraventricular tachycardia (SVT) to sinus rhythm.[3,4] Even before approval by the FDA, adenosine was studied in the management of infants and children with SVT.[5,6] Some of the initial studies were conducted at the University of Virginia by John DiMarco and colleagues, who were also involved in its development.[6] Twenty years of accumulated experience have substantiated the efficacy of adenosine and revealed a relatively low incidence of serious adverse effects in patients who undergo treatment. This issue of *Pediatric Pharmacotherapy* will provide an overview of adenosine and provide recommendations for its use in infants and children with SVT.

Mechanism of Action

Adenosine is an endogenous purine nucleoside present in cells throughout the body. It is formed by breakdown of adenosine triphosphate (ATP) or 5-adenosylhomocysteine. While the multiple roles of endogenous adenosine are still being investigated, it is known to aid in maintaining the balance between oxygen delivery and demand by dilating the coronaries and slowing heart rate. These effects result from binding to adenosine A_1 receptors in the sinoatrial (SA) node, the atrioventricular (AV) node, atrial myocytes, and coronaries.[2,3,7,8]

Binding at cardiac A_1 receptors results in direct activation of an outward potassium current ($I_{K,Ado}$) and inhibition of cyclic adenosine monophosphate (cAMP), resulting in hyperpolarization of atrial myocardial cell membranes and a shortened action potential duration in the sinus node which impairs conduction. Adenosine also has an indirect effect through antagonism of the β-adrenergic system, resulting in inhibition of β-adrenergic-mediated increases in the inward calcium current and slowing of the pacemaker current.[2,3,7,8] These same mechanisms result in the ability of exogenous adenosine to slow conduction through the SA, AV node, and atrial tissue. Adenosine is effective in terminating SVT associated with AV nodal re-entry, AV re-entry tachycardia associated with an accessory pathway, sinus node re-entry, and automatic atrial tachycardia. It has also been shown to produce cardioversion in patients with Wolff-Parkinson-White (WPW) syndrome. In addition to its use in cardioversion of SVT, adenosine has been used to induce arrhythmias during electrophysiologic (EP) studies to aid in the diagnosis and evaluation of patients with intermittent tachycardias.[2,3,7-9]

Pharmacokinetics

Following an intravenous (IV) dose, adenosine is rapidly taken up by erythrocytes and vascular endothelial cells. Intracellular adenosine is metabolized to adenosine monophosphate (AMP) by phosphorylation via adenosine kinase and to inosine by deamination via adenosine deaminase. The resulting AMP formed by phosphorylation is incorporated into the body's high-energy pool. The elimination half-life of adenosine is less than 10 seconds.[3,4]

Use in Infants and Children

In 1987, Clarke and colleagues at Brompton and St. George's Hospitals in London published the first study of adenosine in pediatric patients.[5] They treated four children, three with paroxysmal SVT who were in cardiac failure, and one who was undergoing an elective EP study. They ranged in age from 7 days to 10 years. The patients were treated initially with an adenosine dose of 0.05 mg/kg given by IV and followed by a normal saline flush. If there was no response, the adenosine dose was increased by 0.05 mg/kg increments and repeated every 2 minutes until tachycardia was eliminated. Tachycardia resolved in all four children within 20 seconds. Three of the patients responded to a total dose of 0.1 mg/kg; the remaining patient required a dose of 0.25 mg/kg. Based on these initial cases, the authors concluded that adenosine may be a useful agent for termination of SVT in children and should undergo further study.

The following year, Overholt and colleagues at the University of Virginia published their experience with adenosine in 25 infants and children.[6] The patients ranged in age from 6 hours to 17 years. Eleven of the patients had sustained SVT, and 14 were undergoing an EP study. Adenosine was administered at an initial IV dose of 37.5 mcg/kg (0.0375 mg/kg). The dose was increased by 37.5 mcg/kg increments until a response was seen. Adenosine produced either termination of the arrhythmia or AV block in all patients. The average effective dose ranged from 114 to 165 mcg/kg (approximately 0.1 to 0.2 mg/kg), depending on the underlying arrhythmia. Six patients (24%) had minor adverse effects. One patient had bradycardia requiring temporary pacing. As in the Clarke study, the authors concluded that adenosine was a safe and effective agent for the evaluation and treatment of SVT in children.

In 1989, Till and colleagues from London, the same investigators from the 1987 study, published the largest pediatric adenosine series to date.[10] They reviewed 117 episodes of SVT in 50 children ranging in age from 1 day to 17 years. Adenosine was administered at an initial IV dose of 0.05 mg/kg, with subsequent doses increased by 0.05 mg/kg increments every 2 minutes until the arrhythmia was controlled or a maximum single dose of 0.25 mg/kg was reached. Adenosine was successful in terminating 90 (77%) of the 117 episodes. The median effective dose was 0.15 mg/kg, with a range of 0.05 to 0.25 mg/kg.

The most common adverse effects reported after adenosine administration in this patient series were flushing and transient changes in respiration. One child developed nausea and a headache. One infant experienced a period of sinus bradycardia lasting less than 40 seconds. Two patients developed transient heart block, resolving in less than 10 seconds. One child developed a transient junctional rhythm and six had ventricular couplets or extrasystoles immediately after adenosine administration. Re-emergence of SVT occurred in 13 of the successfully treated patients. Based on the results of this study, as well as their earlier work, the authors concluded that adenosine was an effective treatment for SVT in infants and children, as well as a useful diagnostic tool.[10]

In 1994, Ralston and colleagues reviewed their experiences with adenosine in 24 children with narrow-complex tachycardias.[11] The median age of the patients was 4 years. Four patients were neonates. The initial dose of adenosine was 0.1 mg/kg; this was doubled (up to 12 mg) and repeated if there was no response within 5 minutes. Adenosine produced AV block in 21 (88%) of the patients. The patients who failed to respond included two cases of atrial flutter and one patient with ectopic atrial tachycardia. Complete termination of tachycardia was achieved in 11 of the 21 patients who responded. In 17 cases, adenosine was useful in determining the underlying cause of the tachycardia.

Sherwood, Lau, and Sholler published an additional retrospective review in 1998.[12] They described the use of adenosine in 43 children with SVT. The median patient age was 1 year, with a range from 1 day to 16 years. Conversion to normal sinus rhythm occurred in 75% of the patients, including 96% of the children with re-entrant SVT. In a quarter of the patients, their arrhythmia resumed after the dose had been cleared. Sixteen percent of the patients responded to an initial dose of 0.05 mg/kg. Another 35% responded to a dose of 0.1 mg/kg, Adenosine was well tolerated. Six patients experienced transient bradycardia. Transient sinus arrest, Wenckebach phenomenon, and complete AV block were reported immediately after adenosine administration, but resolved without treatment. Fifteen patients had other transient adverse effects, most often facial flushing. Children old enough to respond to questions regarding adverse effects frequently described chest discomfort, and less commonly, light-headedness, abdominal pain, tiredness, nausea, and arm discomfort at the injection site. None of the patients discontinued treatment because of adverse effects.

The cumulative results of these case series and retrospective studies have established the efficacy of adenosine in the treatment of SVT in infants and children. Adenosine is typically not effective in converting atrial flutter or fibrillation, although it may slow ventricular response to atrial arrhythmias. It is not effective in the treatment of most ventricular arrhythmias, however there are reports of adenosine-sensitive ventricular tachycardias arising from the right ventricular outflow tract.[13] There are also reports of its use in the management of junctional tachycardia occurring after surgery to correct congenital heart disease, although it is not considered routine therapy for any arrhythmias other than SVT.[14]

Precautions

Administration of adenosine is contraindicated in patients with pre-existing second or third degree heart block or sinus node disease (including sick sinus syndrome and symptomatic bradycardia). All patients receiving adenosine should be

closely monitored for the development of first, second, or third-degree heart block, asystole, or torsades de pointes immediately after dose administration. Although these arrhythmias are generally transient and require no treatment, there are reports of patients developing prolonged arrhythmias.[3,4]

Fatalities have occurred in adult patients who developed prolonged asytole or ventricular fibrillation after receiving adenosine.[3,4] Serious arrhythmias have also been reported in children treated with adenosine. In 1995, Kipel and colleagues reported a case of malignant wide complex tachycardia in a 10 year old boy who received adenosine two days after he had undergone a Fontan procedure.[15]

Adenosine is a respiratory stimulant and may produce severe bronchoconstriction and bronchospasm as a result of mast cell degradation and histamine release.[16] It should be used with caution in patients with obstructive lung disease and should be avoided in those with severe asthma or bronchospasm. Administration of adenosine should be immediately discontinued in patients who develop respiratory compromise.

Adverse Effects

The most frequent adverse effects reported after adenosine administration include transient arrhythmias at the time of cardioversion (reported in up to 55% of patients in clinical trials), facial flushing (18%), shortness of breath (12%), a feeling of pressure in the chest (7%), nausea (3%), headache and dizziness (both in 2%). Less common effects include: chest pain, transient alterations in blood pressure, sweating, numbness and tingling in the arms, apprehension, hyperventilation, blurred vision, a burning sensation, as well as neck, back, groin and arm pain, a metallic taste in the mouth, and tightness of the throat (all reported in < 1% of patients). Isolated cases of seizures occurring after adenosine administration have been reported to the manufacturer.[3,4]

Drug Interactions

In several of the fatalities reported after adenosine administration in adults, the patients were receiving digoxin and/or verapamil prior to being treated with adenosine. Although no definitive drug interaction has been identified, there may be an additive or synergistic effect on slowing AV node conduction. Adenosine should be used with caution in patients receiving either digoxin or verapamil. In addition, patients given adenosine who are already taking carbamazepine may be at greater risk of heart block.[3,4]

Dipyridamole potentiates the effects of adenosine by blocking its degradation.[3,4] Some resources consider adenosine contraindicated in patients receiving dipyridamole, due to the increased risk of heart block.[1] If adenosine is attempted in these patients, the dose should be reduced.

Methylxanthines (caffeine, aminophylline, and theophylline) antagonize the effects of adenosine. Larger adenosine doses may be required in order to achieve cardioversion in infants receiving a methylxanthine for apnea or in children receiving theophylline for asthma.[3,4] Berui described a premature infant being treated with aminophylline for apnea of prematurity and bronchopulmonary dysplasia who required high-dose adenosine.[17] When she developed SVT on day of life 16, the patient was treated with adenosine, with an initial dose of 0.05 mg/kg and subsequent dose titration to achieve response. Conversion to sinus rhythm did not occur until a dose of 0.4 mg/kg was given. Subsequent episodes of tachycardia required doses of 0.4 to 0.8 mg/kg for termination.

Dosing Recommendations

Adenosine should be administered by rapid IV bolus over 1-2 seconds. It may be delivered directly into a vein or given through IV access in the port closest to the patient. The dose should be immediately followed by a rapid saline flush.[3,4] In patients without IV access, adenosine may be delivered through an intraosseous catheter.[18,19] Intraosseous administration has been shown in animal models to produce a rate of cardioversion similar to IV administration.[18]

In adults and children weighing 50 kg or more, the recommended initial adenosine dose is 6 mg. If the patient does not convert to normal sinus rhythm, a 12 mg dose may be given within 1-2 minutes. A subsequent 12 mg dose may be administered if needed. In children weighing less than 50 kg, the manufacturer recommends an IV adenosine dose of 0.05 to 0.1 mg/kg. If there is no response, subsequent doses may be increased by 0.5 to 0.1 mg/kg increments up to a maximum single dose of 0.3 mg/kg.[3,4]

Several consensus papers and policy statements, including the 2005 American Heart Association guidelines for pediatric cardiopulmonary resuscitation, recommend an initial adenosine dose of 0.1 mg/kg in infants and children, with an increase to 0.2 mg/kg for subsequent doses.[1,20] This recommendation has been based on the lack of response frequently observed with the 0.05 mg/kg dose.[6,11,12] In their retrospective study of 23 infants, Dixon and colleagues found that a dose of 0.05 mg/kg was effective in only 9% of

their patients.[21] The recommended initial dose for intraosseous administration is also 0.1 mg/kg.[19]

Availability and Cost

Adenosine is available as Adenocard® (Astellas Pharma US, Inc.) and as a generic product from several manufacturers. It is available in a 3 mg/mL concentration in both 2 mL and 4 mL preservative-free prefilled syringes and vials. Adenosine should be stored at room temperature. Refrigeration will result in crystal formation.[3,4] The average wholesale price (AWP) of adenosine injection is approximately $14 for a 2 mL vial and $35 to $40 for a prefilled syringe. The AWP is $28 for a 4 mL vial and $78 for a 4 mL prefilled syringe.[22]

Summary

Twenty years of clinical experience have shown that adenosine is a valuable tool in the management of SVT in infants and children. At an initial dose of 0.1 mg/kg, with titration as needed, adenosine is both effective and safe for most patients. Although rare, adenosine can produce severe heart block or asystole. Careful patient evaluation and close monitoring both during and after adenosine administration are necessary to ensure optimal patient response.

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The editors wish to thank Dr. George McDaniel, UVA Division of Pediatric Cardiology, for reviewing this article prior to publication.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/25/08:

1. Nitazoxanide (Alinia®) was added for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum* or treatment of *Clostridium difficile* colitis.
2. Conivaptan (Vaprisol®), a vasopressin V_{1A} and V_2 antagonist, was added for the treatment of euvolemic and hypervolemic hyponatremia.
3. The restrictions on the use of argatroban and fondaparinux (Arixtra®) were removed.

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