

Adenosine for the Cardioversion of Supraventricular Tachycardia during General Anesthesia and Open Heart Surgery

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Adenosine (Adenocard[®], Fujisawa), a rapidly acting endogenous purine nucleoside with an ultrashort duration of action, was recently approved by the Food and Drug Administration for the treatment of paroxysmal supraventricular tachycardias. We describe the use of adenosine to terminate SVT in an infant undergoing general anesthesia for open heart surgery.

CASE REPORT

An 8-day-old, 3.2-kg girl was transferred to the Hospital for Sick Children, Toronto, with a diagnosis of multiple intracardiac rhabdomyomas made on prenatal fetal echocardiography. Echocardiography on day 3 of life demonstrated large intracavitary masses in both ventricles, with a 45-mmHg systolic pressure gradient caused by a 1-cm mass in the subaortic position in the left ventricular outflow tract. Biventricular function was normal.

In the operating room, after the ECG, blood pressure (BP), and pulse oximeter monitors were applied, anesthesia was induced with N₂O/O₂ and halothane. Intravenous access was established, and fentanyl and pancuronium were administered. Surgery proceeded uneventfully; the patient had a stable sinus rhythm of 130 beats/min and BP of 85/45 mmHg until sternotomy. Following the first application of electrocautery to the pericardium, the patient's heart rhythm changed to a supraventricular tachycardia (SVT) at a rate of 240 beats/min and the systolic BP decreased from 70 to 55 mmHg, with cannon A waves visible on the central venous pressure (CVP) tracing. Ten milliliters of colloid was administered, and then a bolus of phenylephrine was given in order to precipitate hypertension and increase vagal tone. Although the BP increased to 72 systolic, the heart rate remained unchanged (240 beats/min). Since the patient's BP had stabilized, cardioversion was withheld while adenosine was obtained from the pharmacy.‡ Within the next few minutes, following pericardial dissection, clamping of the atrial appendage for the pursestring cannulation suture caused reversion to sinus rhythm (SR) at a rate of 130 beats/min. One more episode of SVT occurred prebypass, which, though again un-

responsive to phenylephrine, converted to SR upon direct mechanical stimulation of the atrial appendage.

The remainder of the prebypass and bypass period was unremarkable. A 1-cm friable mass was excised from the left ventricular outflow tract, the aorta closed, and the patient separated from cardiopulmonary bypass (CPB) without difficulty. The postbypass period was uncomplicated until skin closure, when the SVT recurred (rate of 220 beats/min). With adenosine now in the operating room, a rapid bolus dose of 50 µg/kg was administered intravenously. After 30 s with no effect, a dose of 100 µg/kg was given. This was also without effect, and a second 100-µg/kg dose of adenosine was administered, followed 15 s later by termination of the arrhythmia and an increase in BP and loss of the cannon A waves (fig. 1). Ten minutes later, while the infant was prepared for transfer to the stretcher, the SVT recurred, this time with a decrease in the systolic BP from 85 to 45 mmHg. A bolus of adenosine 100 µg/kg was given, with conversion to SR within 15 s and recovery of the systolic BP to 80 mmHg. The patient was then transferred to the intensive care unit in stable condition. Approximately 15 min later, the arrhythmia recurred and was again converted with a 100-µg/kg bolus of adenosine. No additional arrhythmias occurred, and the remainder of the patient's hospital course was uneventful.

DISCUSSION

Electrophysiologic effects of adenine compounds, including heart block, were first described in 1929,¹ and in 1955 Somló² reported on three series, comprising nearly 500 patients with paroxysmal tachycardias who were successfully treated with adenosine triphosphate (ATP). The action of ATP in this regard has subsequently been shown to be mediated primarily *via* hydrolysis to adenosine.³ It was not until 1983, however, that the therapeutic use of adenosine itself for terminating paroxysmal SVT was described.⁴ The nucleoside acts by binding to adenosine A₁ receptors on atrioventricular (AV) nodal cell surfaces,⁵ causing activation of adenylate cyclase, intracellular cyclic-AMP production,⁶ and depression of the action potential of nodal cells, probably *via* an increase in potassium conductance.^{3,6} This prolongs the nodal-to-His-bundle portion of the atrial-to-His-bundle interval and, hence, conduction time through the AV node, resulting in slowing or block of AV nodal conduction and termination of tachyarrhythmias involving the AV node. This also explains adenosine's lack of efficacy in treating atrial supraventricular reciprocating tachycardias not involving the AV node, such as atrial flutter and atrial fibrillation. Of note, there is good evidence that ischemia-induced sinus slowing and AV block are mediated by adenosine released from myocardial cells rendered hypoxic. In fact, in the setting of inferior wall myocardial infarction, aminoph-

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‡ Prior to our use in this patient, one of us had used adenosine twice to convert SVT in an adult during general anesthesia for placement of an automatic implantable cardioverter defibrillator.

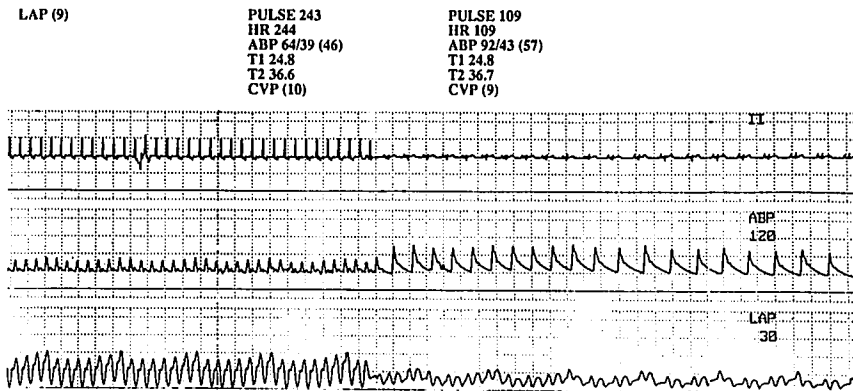


FIG. 1. The three-channel recording shows the rapid supraventricular tachycardia on the upper rhythm strip with corresponding cannon A waves on the lower left atrial pressure (LAP) tracing. There is an abrupt termination of the arrhythmia after adenosine, resulting in slowing of the heart rate (HR), an increase in blood pressure (middle tracing), and loss of the cannon A waves. ABP = arterial blood pressure.

ylline, a known adenosine antagonist, has been reported to restore SR in patients with atropine- and isoproterenol-resistant complete AV block.^{3,6}

Adenosine also directly depresses sinus node activity and ventricular automaticity^{1-3,6}; thus, 2-4-s sinus pauses, with and without ventricular or nodal escape, may occur during treatment for supraventricular arrhythmias.^{2,4,6-8} These effects seem to occur primarily at larger doses; DiMarco⁴ found that the dose needed to produce sinus slowing or higher levels of AV block was approximately 180 $\mu\text{g}/\text{kg}$, more than twice the $82 \pm 35 \mu\text{g}/\text{kg}$ necessary to convert SVT. Rankin *et al.*⁹ independently reported nearly identical findings, and Overholt *et al.*¹⁰ reported a similar experience in children. In all reports, the transient nature of these pauses and escape rhythms (lasting no more than a few seconds or three to five complexes) has been such that they are without clinical import in both adults and children.^{2,4,6-8,10-12} Somló's² report described the use of as much as 70 mg of ATP (equivalent potency to approximately 42 mg^{11,13} or 500 $\mu\text{g}/\text{kg}$ of adenosine), with a similar lack of clinically significant conduction sequelae.

Bolus doses of adenosine have a rapid onset of action of less than 20 s,^{2,4,7,8,10,11} and a duration of action of less than 1 min. The latter reflects an elimination half-life of adenosine from human blood on the order of seconds,^{3,8} due to rapid intracellular transport and enzymatic deamination.³ The rapid inactivation and the lack of tachyphylaxis allows repeated administration and rapid escalation of dose over short intervals (minutes) without cumulative effect, thereby facilitating individual dose titration.³ Although paroxysmal arrhythmias may recur after adenosine, repeated treatments at the dose previously terminating the arrhythmia are generally effective.

In recent years, verapamil has been the principal pharmacologic agent used to treat SVT, with an average 87% reported efficacy rate,¹⁴ but with relatively long lasting, potentially deleterious vasodilator and negative inotropic side effects. These can be particularly deleterious in hemodynamically unstable patients and in those receiving β -blockers, patients with impaired LV function, patients undergoing general anesthesia, or any patients in the immediate postbypass period after open heart surgery, when impaired ventricular function is the rule even in patients with preoperatively good ventricular function.¹⁵ Verapamil also has an increased incidence of serious hemodynamic consequences in neonates, infants, and children,¹⁰ with the potential for cardiovascular collapse in infants less than 1 yr of age.^{8,12}

An equally important problem is the administration of verapamil to patients with wide complex tachycardia, misdiagnosed as SVT with aberrancy.¹⁶ In cases with an actual underlying rhythm of ventricular tachycardia, verapamil has precipitated hypotension and even cardiac arrest.

Adenosine, in contrast, has not been reported in any patient to cause hemodynamic deterioration. Hypotension, specifically, has not been reported as a side effect of the dosages used to treat SVT, even in Somló's report,² in which large bolus doses were administered. Adenosine's use in hypotensive patients without adverse sequelae is, in fact, noted as one of the drug's major advantages compared to verapamil.^{3,8,10,12} Adenosine has also been used safely in patients in heart failure,^{4,7,8,10,12} patients on β -blockers,^{6,8,9} and patients with wide complex tachycardia, including ventricular tachycardia.^{6,9,17}

Clinical trials have proven adenosine to be highly effective in converting reentrant AV nodal tachyarrhythmias when administered as an intravenous bolus at a dose of 50-250 $\mu\text{g}/\text{kg}$.³ Adenosine (Adenocard[®]) is marketed in 6-mg vials, and this is the usual starting dose in adults. Some patients require as much as 12 mg, although this may reflect the route of administration (see below). In a

§ Moser GH, Schrader J: Half-life of adenosine in human blood: Effects of dipyridamole (abstract). Pflugers Archiv. European Journal of Physiology (Berlin) 1986, 407:S37.

recent randomized, multicenter, comparative trial in adults,¹³ both adenosine and verapamil, at their highest dose levels of 12 and 7.5 mg respectively, had a greater than 91% success rate in terminating acute episodes of paroxysmal SVT. Of note, many studies have reported that patients whose arrhythmias did not convert to SR with verapamil, converted to sinus rhythm after adenosine.^{7,8,10-13,18} This may reflect a greater efficacy of adenosine in patients with an already partially blocked AV node. Other studies report a near 100% efficacy in termination of SVT with adenosine, significantly better than verapamil in some comparisons.^{7,9,10,15,19,20}

As Clarke⁷ further noted, since most cases of SVT in children are due to atrioventricular reentry, adenosine would also be expected to be efficacious in these patients. Four studies^{7,8,10,12} reported the rapid (< 20 s, shorter if administered centrally) termination of supraventricular tachyarrhythmias by adenosine in neonates, infants, and children, at doses of 35-350 $\mu\text{g}/\text{kg}$, without adverse hemodynamic side effects even in those critically ill. These reports include term and preterm neonates, infants with severe heart failure, children with severe congenital heart disease (both pre- and postoperatively, including one patient with hypoplastic left heart following Norwood stage I repair), and infants receiving infusions of catecholamines. Adenosine was successful also in patients hypotensive from their arrhythmia and in patients with SVT resistant to other drugs such as digoxin, verapamil, atenolol, quinidine, amiodarone, flecainide, and disopyramide. Identical microgram-per-kilogram doses and rapid efficacy led Overholt to suggest that the neonatal and adult AV node have a similar sensitivity to adenosine.¹⁰ Also, as in adults, transient high-grade AV block, sinus bradycardia, and ventricular asystoles occurred but were of such brief duration (seconds) as to not require intervention. No decrease in BP occurred in any patient.

Because of its AV-blocking effects, adenosine has also been noted in adults and children to expose underlying junctional and preexcited arrhythmias and atrial activity in other arrhythmias, thereby facilitating diagnosis.^{4,8-10,12,17} Its potent but ultrashort action makes it particularly useful as a diagnostic agent in this regard. Since the above-described case in our neonatal patient, we have used adenosine in a 17-yr-old patient with asymmetric septal hypertrophy undergoing septal myomectomy. In the post-bypass period, this patient had what appeared to be an atrial tachycardia resistant to all efforts to treat it, including β -adrenergic blockers, edrophonium, and large additional doses of fentanyl and diazepam. Administration of a 6-mg dose of adenosine (86 $\mu\text{g}/\text{kg}$) caused, in 20 s, a transient slowing of AV conduction lasting three beats that exposed an underlying rhythm of atrial flutter. Electrical cardioversion was followed by improvement in the hemodynamics.

Because of the short half-life in the circulation, on the order of a few seconds, the efficacy of a given dose of adenosine depends on rapid delivery to the site of action. This is influenced by infusion time,¹¹ circulation time from the site of injection, and mixing volumes.¹³ Thus, a rapid bolus injection of adenosine into as centrally located a vein as possible would be expected to enhance efficacy.^{8,13,19} Indeed, the aforementioned factors may account for the varying efficacy rates reported, although all rates approach 100%. DiMarco *et al.*,¹³ in fact, noted that maximum doses may have been necessary in their study because all doses of adenosine were administered peripherally.

Side effects of adenosine most commonly reported are chest discomfort, dyspnea, and facial flushing,¹³ occurring in about one third of patients, and have been attributed to combined end-organ, vascular, and autonomic responses.¹³ Because of the ultrashort half-life, however, side effects are transient with the bolus doses used to treat SVT, lasting a median duration of 50 s, and none lasting more than 2 min.¹³ Thus, they are usually not bothersome to patients and are of minor clinical significance.

On the other hand, there are a number of important interactions with commonly used drugs. Dipyridamole blocks cellular adenosine uptake and potentiates adenosine-induced conduction delay. In one study, the effective dose producing an electrophysiologic effect was 8-fold lower in two patients taking dipyridamole.¹⁸ Theophylline antagonizes the effect of adenosine on AV conduction *via* blockade of the A_1 receptor, at concentrations well below that required for phosphodiesterase inhibition.³ The ability of adenosine to terminate SVT in patients receiving theophylline, however, has not been studied, although SVT in one patient taking theophylline was reportedly converted following administration of a low dose (50 $\mu\text{g}/\text{kg}$) of adenosine.⁸ Because inhaled adenosine has been reported to cause bronchoconstriction,²¹ most studies have not included patients with asthma.^{4,19}

Supraventricular arrhythmias occur commonly during open heart surgery. In patients dependent on the atrial contribution to ventricular filling, these arrhythmias may seriously compromise cardiac output. When pharmacologic treatment of paroxysmal SVT is indicated in these and other situations, available evidence indicates that adenosine is highly effective, causing rapid conversion to sinus rhythm. Equally important, it is safe and well tolerated without significant adverse side effects in virtually any setting (including patients with arrhythmias classically unresponsive to adenosine to whom it is diagnostically or mistakenly given). The reports cited and our experience above suggest that adenosine would be safe and efficacious in cardioverting SVT in patients undergoing general anesthesia and in patients undergoing open heart surgery, even in the postbypass period. Adenosine may become

the drug of choice for treating SVT in hemodynamically compromised children.^{3,12} Adverse reactions are very brief and do not limit therapy.

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