Safety and Efficacy of Central Intravenous Bolus Administration of Adenosine for Termination of Supraventricular Tachycardia

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Objectives. This study was done to quantify the dosing differences between central and peripheral adenosine administration for treatment of supraventricular tachycardia.

Background. Earlier studies that evaluated the safety and efficacy of adenosine primarily utilized a peripheral site of administration. Although it has been recommended that lower doses should be given centrally, dosing recommendations have not been provided.

Methods. Thirty adults with supraventricular tachycardia underwent invasive electrophysiologic study and were treated with central and peripheral intravenous administration of adenosine. Peripheral injections were administered through a venous catheter in an upper extremity and central infusions were accomplished by means of a catheter positioned in or near the right atrium. The site of administration was randomized and each subject received adenosine by both routes. Adenosine was administered every minute in increasing increments of 3, 6, 9 and 12 mg until the tachycardia terminated. Peripheral responses were compared with those obtained centrally.

Results. The minimal effective peripheral dose was distributed among the four doses: Tachycardia was terminated in 11 patients with 3 mg (37%), in 10 (33%) with 6 mg, in 4 (13%) with 9 mg and in 5 (17%) with 12 mg. In contrast, after central administration, 23 episodes of tachycardia (77%) were terminated with 3 mg, 6 (28%) with 6 mg and 1 (3%) with 9 mg; none required 12 mg. Lower doses of adenosine were more effective after central than after peripheral administration, with 63% of the subjects requiring a lesser dose. There was no difference between the two routes of drug administration in the incidence of side effects or transient arrhythmias at the time of tachycardia termination.

Conclusions. Adenosine can be safely given centrally for termination of supraventricular tachycardia. The initial dose should be 3 mg.

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Since its release in 1989, adenosine has become a popular therapeutic agent for immediate termination of supraventricular tachycardia involving the atroventricular (AV) node (1,2). Adenosine acts directly on the nodal cells, resulting in negative chronotrophic and dromotrophic activity (3). At the time of tachycardia termination, a brief episode of bradycardia or sinus pause is common. Although these conduction disturbances are usually transient, they may be more pronounced when higher doses are used (4) or in instances where a higher concentration of the drug reaches the receptors (that is, injection through a large proximal vein). We have observed rare instances of ventricular standstill lasting >12 s when recommended (6 or 12 mg) doses of adenosine were administered through the right atrial port of a pulmonary artery catheter. The therapeutic usefulness of bolus doses of adenosine for termination of supraventricular tachycardia was determined primarily by utilizing an upper extremity access site for drug administration (5-8). In the few pilot studies conducted where adenosine was administered through a femoral or iliac vein (4,9-11), investigator noted that the mean effective dose was significantly less than that for an extremity access site. Subsequently, although it has been suggested that a smaller dose should be given when using a central port (6,7), dosing recommendations have not been provided. Because central access is often available in critically ill patients in intensive care units, this study was designed to compare central versus peripheral administration of adenosine with a specific focus on dose ranging.

Methods

Subject selection and setting. The study was designed as a prospective randomized study in patients with supraventricular tachycardia who underwent an electrophysiologic study. Patients <18 years of age, pregnant and allergic or sensitive to adenosine were not considered for entry into the study. Between February and August 1991, 34 adults agreed to participate. All subjects were studied in a fasting state and were mildly sedated with Versed (midazolam hydrochloride) or morphine, or both. No subject was taking agents known to potentiate or inhibit the actions of adenosine (theophylline, dipryridamole or carbamazepine) and none had a history of asthma. All antiarrhythmic agents were discontinued for

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≈5 drug half-lives in all but one patient, who had inadvertently taken a dose of propafenone and diltiazem on the morning of the study.

As is routine in our electrophysiology laboratory, a peripheral intravenous catheter was inserted into an upper extremity for fluid and drug administration. Intracardiac electrodes for monitoring and pacing were inserted through a large vein by means of a 7F Cordis sheath with a side port for central bolus injections. When a side port was not available, central administration was performed with a Zucker catheter, through the groin, with an infusion that exited directly into the right atrium.

**Protocol.** Written informed consent as approved by the Institutional Committee on Human Research was obtained by each patient before the study. The electrophysiologic protocol for supraventricular tachycardia, previously described in detail (12), involves insertion of electrode catheters into the coronary sinus, high right atrium and His bundle region in the right ventricle. In 10 subjects, an isoproterenol infusion (0.5 to 4.0 \( \mu \)g/min) was required to initiate sustained tachycardia and the dose remained constant throughout the study. The protocol began after the mechanism of the supraventricular tachycardia was determined. Two episodes of tachycardia (spontaneous or induced) were needed to complete the protocol. The duration of the tachycardia before adenosine administration varied from 30 s to minutes. Each individual received peripheral and central doses of adenosine and the order of the administration site was randomly determined. During episodes of supraventricular tachycardia, sequential doses of 3, 6, 9 and 12 mg of adenosine (Adenocard, Fujisawa Pharmaceutical Company) were given. If the subject's tachycardia failed to terminate within 1 min with the first dose, the next higher dose was given. When the maximal dose (12 mg) failed to terminate the rhythm, overdrive pacing was used and the protocol was terminated. The tachycardia was considered terminated when sinus rhythm was restored.

All infusions of adenosine were given as a rapid bolus injection (<2 s), followed by a 10-ml flush of normal saline solution. Continuous 12-lead electrocardiograms (ECGs) with a Marquette electrocardiograph were obtained before, during and after all injections of adenosine. The ECGs were analyzed for the following indices: the time necessary for conversion to sinus rhythm after the minimal effective dose, the longest RR interval at the time of tachycardia termination and any associated arrhythmias. Subjective complaints after central and peripheral adenosine administration were also documented.

**Data analysis.** Demographic data were analyzed using the mean value or were reported with frequency lists. Subjects served as their own control, with measurements obtained from central administration compared with those after peripheral administration. The minimal effective doses for peripherally and centrally administered adenosine were compared using the Student paired \( t \) test. The longest RR interval in ms was compared between administration sites using the Student paired \( t \) test. A \( p \) value < 0.05 was considered statistically significant. Arrhythmias and subjective adverse effects were expressed with frequency lists.

### Results

Subject characteristics. Of the 34 patients initially enrolled in the study, 4 were excluded from the final analysis for the following reasons. One patient had only one of the two required episodes of tachycardia. Another had antiodromic tachycardia that failed to respond to adenosine. A 66-year old woman with hemodynamic instability during the tachycardia was also excluded because the tachycardia could not be maintained for the duration of the protocol. A fourth patient developed sustained atrial fibrillation after 6 mg of centrally administered adenosine. Early termination of the study was required in this patient and peripheral administration was not attempted. A total of 30 patients (56% male) with a mean age of 38.4 years completed the protocol. The majority had no associated cardiac disease and presented with orthodromic AV reentrant tachycardia (Table 1). The supraventricular tachycardia mechanism and rate were similar for both the central (174 ± 25.5 beats/min) and peripheral (175 ± 24.6 beats/min) routes. The remaining 60 episodes of tachycardia were successfully terminated after both central and peripheral adenosine administration.

**Dose response.** Figure 1 compares the efficacy of sequential doses of central versus peripheral adenosine. The tachycardia was terminated with a 3-mg dose administered centrally in 77% of the subjects. In contrast, the minimal effective peripheral dose was distributed among the four doses. Of note, five patients required 12 mg peripherally, whereas the maximal dose required with central administration was only 9 mg. When the two routes were compared for mean effective dose, the central dose (3.8 ± 1.6 mg) was significantly lower than the peripheral dose (6.3 ± 3.3 mg) (\( p < 0.0001 \)). Nineteen patients (63%) responded to a lesser dose when adenosine was injected through the central line, whereas 9 (30%) responded with the same dose (3 mg). However, two subjects (7%) required a higher dose with central (6 mg) than with peripheral (3 mg) administration.

<table>
<thead>
<tr>
<th>Table 1. Cardiac History in the 30 Study Patients</th>
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</tr>
<tr>
<td>AV node reentrant tachycardia</td>
<td>12</td>
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**AV** = atrioventricular.
The individual responses for the two routes are listed in Table 2. The time from adenosine injection to termination of tachycardia was shorter (12.7 ± 5.1 s, range 6 to 29) after central than after peripheral (19.2 ± 7.9 s, range 8 to 35) drug administration (p < 0.0001). When the central route was compared with the peripheral route for all doses, there was no significant difference (p = 0.88) in the mean pause (1,186 ± 323 and 1,173 ± 407 ms, respectively) after tachycardia termination. When similar doses were compared, no difference was noted between central (1,185 ± 333.8 ms) and peripheral administration (1,094 ± 228.4 ms) in the mean cycle length with a 3-mg dose or with a 6-mg dose (1,267 ± 250.3 ms and 1,247 ± 525.6 ms, respectively). Moreover, in the nine patients given the same dose (3 mg) for both routes, there was no significant difference (p = 0.66) in the mean pause after tachycardia termination between peripheral (1,155 ± 200 ms) and central (1,215 ± 288 ms) administration. Of note, the longest RR interval measured was 2,560 ms after a peripheral dose of 6 mg.

Termination arrhythmias. Various arrhythmias were observed at the time of tachycardia termination and many patients experienced a combination of irregularities. The most frequently observed arrhythmia was premature ventricular beats, which occurred either at or after termination of tachycardia in nine patients (30%) after both peripheral and central injections. Premature atrial beats were also observed in equal frequencies (13%) for both routes. Sinus bradycardia developed in four patients with peripheral injections and in two patients after central administration of adenosine. With the initial 3-mg bolus injection one patient had a brief episode (8 and 22 s), respectively, of atrial fibrillation after both peripheral and central injections. Early recurrence of the supraventricular tachycardia was observed in five patients and was usually preceded by either sinus bradycardia or premature beats. Twelve episodes of reflex sinus tachycardia after tachycardia termination were recorded after peripheral administration of adenosine and 14 after central dosing. In all instances, the arrhythmias were of brief duration and none required intervention.

Adverse effects. Subjective adverse effects were common after adenosine regardless of the route of administration. There was no significant difference in the total frequency of complaints comparing central (67%) and peripheral (60%) administration. Flushing occurred more often, followed by dyspnea and chest discomfort. Eight patients (27%) complained of flushing after both routes of adenosine administration. Although dyspnea was also experienced equally (26%) in the two groups being analyzed, chest pain was experienced more frequently after central injections. Five patients (17%) noted chest discomfort after the central dose compared with 3 (10%) with the peripheral dose.

When patients were evaluated on an individual basis, interesting trends were noted. For instance, three patients whose tachycardia was terminated with a 3-mg dose by both routes reported no side effects when the drug was adminis-
tered through the peripheral line but experienced symptoms when the drug was given centrally. Two other patients reported dyspnea when higher doses were administered by the peripheral route but had no complaints when a lesser dose was given centrally. In all but one instance, the side effects lasted <30 s and were self-limiting. A 68-year-old woman who received isoproterenol (1 μg/min) concurrently during the protocol complained of nausea and severe chest pain for 10 min after a 3-mg central bolus injection. When the symptoms subsided, she received the same dose peripherally without recurrence of symptoms. No patient refused to continue the study as a result of the adverse reactions.

**Discussion**

**Dose response.** The results generated from this study confirm the hypothesis (4,10) that lower doses of adenosine are effective when given by a central route. A more significant finding was that when adenosine was injected through a central line, a more homogeneous response resulted, with nearly 80% of the tachycardias terminating after a 3-mg dose. This finding is congruent with the pharmacokinetic properties of this agent. Adenosine is rapidly metabolized within the blood vessels, where it is taken up by erythrocytes and vascular endothelium or enzymatically degraded (13,14). The longer adenosine remains in the peripheral circulation, the greater the amount that will be metabolized before it reaches the heart. However, by administering adenosine through a central route, the circulation time is decreased and more drug reaches the cardiac adenosine receptors. As in previous reports (8,9), this study displayed marked variability among patients in the minimal effective dose after peripheral administration. In a large multicenter dose-ranging study (7), investigators noted that the individual effective doses after peripheral administration ranged from 3 to 12 mg. Other studies (4,6,13) using peripheral access reported a 10-fold range of values, with effective doses ranging from 2 to 30 mg.

**Termination arrhythmias.** Premature ventricular beats often occur at the time of tachycardia termination with adenosine. In this study, the overall incidence of 30% was the same for the two routes and comparable to the findings of an earlier study (7). However, after dose stratification, there was a tendency for the frequency of ventricular extrasystoles to increase as the dose increased. A larger sample would be necessary to support this finding.

The association of adenosine administration and development of atrial fibrillation has been previously reported (16). Dimarco et al. (6) also noted that atrial flutter and fibrillation occurred when higher than necessary doses were given to two patients with supraventricular tachycardia. Two patients in the current study developed atrial fibrillation after adenosine. One developed sustained atrial fibrillation after a 6-mg central bolus injection. Because this patient demonstrated frequent spontaneous degeneration of his tachycardia into atrial fibrillation, a cause and effect relation is difficult to prove. The other developed nonsustained atrial fibrillation before tachycardia termination after he received 3 mg of adenosine by both routes; therefore, it is unlikely that the administration site was the key issue for development of this arrhythmia.

**Adverse effects.** Although adverse effects after adenosine are common (7), the severity as well as the frequency of the subjective complaints appear to be dose dependent (1,17,18). In this study, there was the beginning of a trend for the frequency of dyspnea to increase as the dose increased regardless of the site of drug administration; however, a larger sample is needed to prove whether a trend indeed exists. Biaggioni et al. (17) described a similar dose-dependent trend with dyspnea and with other adverse effects as well. Angina-like chest pains have also been initiated when larger doses were administered to healthy persons (18).

**Study limitations.** Side effects in this study were assessed by determining the presence or absence of a complaint and no effort was made to grade the severity. In a few instances, adverse effects were difficult to elicit because of the mental changes the patients experienced with sedation. However, the overall incidence of adverse effects in this study was similar to that reported by others (4,7,9). Additionally, only healthy patients with hemodynamically stable arrhythmias were enrolled into this study. Patients with underlying sick sinus syndrome or those taking dipyridamole may have enhanced conduction defects at the time of termination of tachycardia, and these may be further exaggerated if adenosine was administered centrally.

**Conclusions.** Adenosine can safely be administered through a central intravenous catheter for termination of supraventricular tachycardia. On the basis of our observations, we recommend an initial bolus injection of 3 mg for central administration because nearly 80% of our patients responded to this dose.

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**References**

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