Termination of Paroxysmal Supraventricular Tachycardia by Tecadenoson (CVT-510), a Novel A1-Adenosine Receptor Agonist

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OBJECTIVES The aim of this study was to evaluate tecadenoson safety and efficacy during conversion of paroxysmal supraventricular tachycardia (PSVT) to sinus rhythm.

BACKGROUND Tecadenoson (CVT-510), a novel adenosine receptor (Ado R) agonist, selectively activates the A1 Ado R and prolongs atrioventricular (AV) nodal conduction at doses lower than those required to cause A2 Ado R-mediated coronary and peripheral vasodilation. Unlike adenosine, which non-selectively activates all four Ado R subtypes and produces unwanted effects, tecadenoson appears to terminate AV node-dependent supraventricular tachycardias without hypotension and bronchoconstriction.

METHODS In this open-label, multicenter, dose escalation study, tecadenoson was administered to 37 patients (AV node re-entrant tachycardia, n = 29; AV re-entrant tachycardia, n = 8) with inducible PSVT sustained for ≥1 min during an electrophysiology study. Seven regimens (0.3 to 15 μg/kg) of up to two identical tecadenoson intravenous bolus doses were administered. After the first or second bolus, PSVT converted to sustained sinus rhythm for ≥5 min in 86.5% (32/37) of the patients, with 91% (29/32) of the conversions occurring after the first bolus (most within 30 s), coincident with anterograde conduction block in the AV node. No effects on sinus cycle length (SCL) or systolic blood pressure were observed. The atrial-His (AH), but not the His-ventricular (HV) interval was prolonged up to 5 min after the final tecadenoson bolus, returning to baseline by 10 min. Tecadenoson was generally well tolerated.

RESULTS In this study, tecadenoson rapidly terminated sustained PSVT by depressing AV nodal conduction without causing hypotension. After sinus rhythm restoration, there was minimal AH interval prolongation without HV interval or SCL prolongation. (J Am Coll Cardiol 2003;42:1098–102) © 2003 by the American College of Cardiology Foundation

The cardiac actions of adenosine include slowing of sinus rate, depression of atrioventricular (AV) nodal conduction, depression of atrial, but not ventricular contractility, shortening of atrial but lengthening of the AV nodal refractory period, and attenuation of the stimulatory effects of catecholamines on the myocardium (1,2). These actions of adenosine are mediated by the A1 adenosine receptor (Ado R) subtype and are, for the most part, due to the direct activation of the inward rectifying potassium current and inhibition of catecholamine-stimulated ion currents such as the pacemaker current and the L type calcium currents (2,3).

The Ado R-mediated negative dromotropic effect of adenosine is the basis for the use of this nucleoside to interrupt transiently AV nodal conduction during paroxysmal supraventricular tachycardia (PSVT) (4,5). This results in conversion of PSVT to sinus rhythm in a majority of cases of AV node-dependent tachycardia such as AV nodal re-entry and AV re-entry (6). Although adenosine is effective in terminating PSVT, significant limitations to its use include a high incidence of subjective symptoms and arrhythmias at the time of conversion (55%) (7). Shortening of the atrial action potential and refractory period may promote the development of atrial flutter or fibrillation (5,6,8).

Tecadenoson (6-[(N-3’-(R)-tetrahydrofuranyl)-amino-purine riboside or CVT-510) is a novel selective A1 Ado R agonist. The functional selectivity of tecadenoson for an A1 Ado R has been demonstrated in an anesthetized, atrial-paced guinea pig heart model (9). In these studies, intravenous (IV) tecadenoson prolonged the PR interval without...
Abbreviations and Acronyms

Ado R = adenosine receptor
AH = atrial-His
AV = atrioventricular
AVNRT = atrioventricular node re-entrant tachycardia
AVRT = atrioventricular re-entrant tachycardia
C\(_{\text{max}}\) = maximum plasma level
HV = His-ventricular
IV = intravenous
PSVT = paroxysmal supraventricular tachycardia
SCL = sinus cycle length
S-H = stimulus-to-His bundle interval
SNRT = sinus node recovery time

Reducing systemic blood pressure (9). Additionally, in guinea pig isolated hearts, tecadenoson was approximately five-fold more potent in prolonging the stimulus-to-His bundle (S-H) interval, an A\(_1\) Ado R effect, than in increasing coronary conductance, an A\(_{2A}\) Ado R-mediated effect (9). In the same model, tecadenoson was three-fold more potent in prolonging the S-H interval than in shortening the atrial action potential. In contrast, adenosine has a greater effect on the A\(_{2A}\) rather than the A\(_1\) Ado R-mediated effects, and is equipotent in prolonging the S-H interval and in shortening the atrial action potential (10,11). Thus, a selective A\(_1\) Ado R agonist such as tecadenoson may offer an advantage over adenosine for conversion of PSVT to sinus rhythm, while minimizing the incidence of atrial proarrhythmias, hypotension, or bronchoconstriction.

In a previous study, the electrophysiologic effects of tecadenoson were determined in 32 patients with normal AV nodal function (12). Tecadenoson administered in IV bolus doses of 0.3 to 10 \(\mu\)g/kg caused rapid and transient dose-dependent increases in the atrial-His (AH) interval without affecting blood pressure, sinus cycle length (SCL), or His-ventricular (HV) interval (12). At doses of 15 and 30 \(\mu\)g/kg, transient second- and third-degree AV block in sinus rhythm was observed (12). The purpose of the present study was to determine the safety and efficacy of bolus doses of tecadenoson to convert PSVT induced during electrophysiology study to sinus rhythm in patients with a history of tachycardia.

**METHODS**

**Study design.** This was a multicenter, dose-escalation study in which patients with a history of spontaneous PSVT were dosed with tecadenoson in an open-label fashion during the course of a routinely scheduled clinical electrophysiology study. The protocol and informed consent forms for this study were approved by the institutional review committees at all the respective study centers. All patients gave written informed consent before enrollment. All anti-arrhythmic medications were withheld for five half-lives before the electrophysiology study. Standard electrophysiologic techniques were employed (6). In brief, three to four multipolar electrode catheters were inserted intravenously and positioned in the right atrium, right ventricle, His bundle area, and coronary sinus. Programmed atrial and ventricular stimulations were performed, PSVT was induced, and the diagnosis of atrioventricular node re-entrant tachycardia (AVNRT) or atrioventricular re-entrant tachycardia (AVRT) was made using standard criteria. Tecadenoson was administered via a peripheral vein after PSVT had been sustained for at least 1 min. After the first bolus, if PSVT had not converted to sustained sinus rhythm, a second identical bolus of tecadenoson was administered. The shortest time between consecutive doses of tecadenoson was 2 min. The effects of the following dose regimens were studied in 37 patients: up to two identical bolus doses of 0.3 \(\mu\)g/kg (n = 1); 3 \(\mu\)g/kg (n = 4); 5 \(\mu\)g/kg (n = 9); 7.5 \(\mu\)g/kg (n = 4); 10 \(\mu\)g/kg (n = 5); 12.5 \(\mu\)g/kg (n = 4); and 15 \(\mu\)g/kg (n = 10).

Cycle length, blood pressure, AH and HV intervals, atrial effective refractory period, ventricular effective refractory period, sinus node recovery time (SNRT) were determined, and a 12-lead electrocardiogram was recorded at defined time points throughout the study (baseline and after administration of tecadenoson). In instances where isoproterenol was needed for initiation of PSVT, electrophysiologic measurements before and after tecadenoson administration were obtained without a change in isoproterenol dose. Blood samples for determination of plasma levels of tecadenoson were also obtained.

**Statistical methods.** The rate of conversion of PSVT to sustained sinus rhythm was calculated for all patients and is expressed as a percentage of the total number of patients dosed. All other results (blood pressure, cycle length, intracardiac intervals and refractory periods, as well as SNRT) are expressed as mean ± SEM. Two sample t-tests were performed to compare patients who did and did not receive isoproterenol. Paired t tests were performed to compare baseline with post-dose values. Fisher exact tests were performed to compare rates of conversion. A value p ≤ 0.05 was considered to be statistically significant.

**RESULTS**

**Patient characteristics.** All 37 patients, 14 male, had a history of symptomatic PSVT that was due to AVNRT in 29 (78%) patients and AVRT in 8 (22%) patients. The mean age was 45 years (range 19 to 81 years). The PSVT episodes were more than 10 per year in 14 (38%) patients, and overall 19 of 37 patients had previously received adenosine, 16 of whom responded to it. The mean cycle length of sustained PSVT was 323 ms (range 240 to 460 ms) for all patients and was not different between patients with AVNRT (328 ± 10 ms) and AVRT (306 ± 12 ms). The PSVT cycle length was significantly shorter in the 19 patients who received isoproterenol (298 ± 8 ms) compared...
with 18 patients who did not receive isoproterenol (349 ± 12 ms; p = 0.0013) for induction of PSVT.

Effect of tecadenoson on PSVT conversion. Paroxysmal supraventricular tachycardia of at least 1 min duration was converted to sustained (≥5 min) sinus rhythm in 32 of 37 patients (86.5%) after administration of one or two boluses of tecadenoson. Conversion to sinus rhythm occurred after the first bolus of tecadenoson in 29 of 32 patients (91%), and 66% of these conversions (19 of 29 patients) occurred within 30 s after administration of the bolus. There were 26 of 29 (90%) patients with AVNRT who converted with tecadenoson. In the 24 patients in whom the site of block was documented, 23 converted with anterograde block in the slow pathway and 1 with anterograde block in the fast pathway. Tarcadenoson caused termination of PSVT in 6 of 8 (75%) patients with AVRT. The PSVT termination site was documented in five patients, and the AV node was the site of block in all patients. One patient had transient termination with anterograde block in the AV node, but PSVT resumed within a few seconds. The number of patients tested at each dose level was too small to detect any dose-related trends in the conversion rate of PSVT to sinus rhythm (Fig. 1). The success rate of conversion to sinus rhythm was lower in patients requiring isoproterenol to sustain their PSVT (15 of 19 patients; 79%) than in the cohort of patients who did not require isoproterenol to sustain their PSVT (17 of 18 patients; 94%); however, this difference was not significant (p = 0.34). The single patient dosed at 0.3 μg/kg failed to convert to sinus rhythm; however, tachycardia transiently slowed after each bolus in this patient.

Effect of tecadenoson on SCL, blood pressure, AH and HV intervals. There were no significant effects of tecadenoson on the SCL or systolic blood pressure after conversion of PSVT to sinus rhythm (Table 1). There was a minimal increase in mean diastolic blood pressure from 69 to 74 mm Hg 1 min after dosing (p = 0.01). The AH interval, but not the HV interval, was transiently and significantly prolonged (p < 0.005) at the 1- and 5-min time points after the final dose of tecadenoson, returning to baseline by 10 min post-dose.

Pharmacokinetics and pharmacodynamics of tecadenoson. The pharmacokinetic profile of tecadenoson determined using a two-compartment model showed that peak plasma levels were achieved immediately (<30 s) after IV bolus administration, with a rapid decline within 2 min due to distribution. The terminal elimination half-life was approximately 30 min. The second bolus produced a peak plasma level that was only marginally higher than that observed after the first bolus owing to the rapid distribution of tecadenoson after IV bolus injection. The overall pharmacokinetic results did not indicate any deviation from dose proportionality. The peak plasma levels were independent of body weight or gender, implying that uniform (non–weight-based) dosing could be used to minimize variability between patients receiving the same dose. The conversion of PSVT occurred approximately at the maximum plasma level (Cmax) in all instances. This is consistent with the observation that the mean time to conversion was within 30 s after completion of the bolus.

Adverse events. Nine patients (24%) had 15 adverse events on the day of tecadenoson administration (Table 2). Eight

Table 1. Hemodynamic and Electrophysiologic Effects of Tecadenoson in Patients Who Converted After Study Drug Administration

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 Min After Bolus</th>
<th>5 Min After Bolus</th>
<th>10 Min After Bolus</th>
<th>20 Min After Bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128.5 ± 3.9</td>
<td>136.2 ± 4.9</td>
<td>130.6 ± 3.7</td>
<td>130.7 ± 4.3</td>
<td>ND</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>68.7 ± 2.3</td>
<td>73.9 ± 2.2*</td>
<td>70.4 ± 2.6</td>
<td>71.1 ± 2.7</td>
<td>ND</td>
</tr>
<tr>
<td>SCL (ms)</td>
<td>718.6 ± 27.3</td>
<td>715.3 ± 40.7</td>
<td>731.7 ± 31.9</td>
<td>684.4 ± 26.8</td>
<td>ND</td>
</tr>
<tr>
<td>A-H interval (ms)</td>
<td>82.8 ± 3.8</td>
<td>96.6 ± 4.3*</td>
<td>88.3 ± 3.6*</td>
<td>83.4 ± 4.0</td>
<td>ND</td>
</tr>
<tr>
<td>H-V interval (ms)</td>
<td>40.1 ± 2.0</td>
<td>42.2 ± 2.7</td>
<td>42.6 ± 2.4</td>
<td>42.4 ± 2.4</td>
<td>ND</td>
</tr>
<tr>
<td>SNRT (ms)</td>
<td>959.2 ± 43.5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>860.0 ± 46.8*</td>
</tr>
<tr>
<td>AERP (ms)</td>
<td>209.3 ± 7.5</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>209.6 ± 8.6</td>
</tr>
<tr>
<td>VERP (ms)</td>
<td>218.9 ± 4.9</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>214.8 ± 5.4</td>
</tr>
</tbody>
</table>

*Statistically different (p < 0.05).

AERP = atrial effective refractory period; A-H = atrial-His; H-V = His-ventricular; ND = not determined; SCL = sinus cycle length; SNRT = sinus node recovery time; VERP = ventricular effective refractory period.
Table 2. Adverse Events Reported After Treatment With Tecadenoson

<table>
<thead>
<tr>
<th>Adverse event listing</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any adverse event</td>
<td>17 (46)</td>
</tr>
<tr>
<td>Patients with any adverse event post dose on the day of dosing</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Allergic reaction to concomitant medication</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Complete AV block after radiofrequency ablation</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Hypotension (after withdrawal of central venous access sheaths in 1 case)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Asthenia (heaviness in arms and legs)*</td>
<td>1 (3)</td>
</tr>
<tr>
<td>2:1 AV block during recurrent tachycardia after PSVT conversion with tecadenoson*</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Bradycardia (after withdrawal of central venous access sheaths)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pain (burning sensation in wrists and legs)*</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Recurrent tachycardia after PSVT conversion with tecadenoson*</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

*Events considered probably or possibly related to administration of tecadenoson by the investigator.

AV = atrioventricular; PSVT = paroxysmal supraventricular tachycardia.

DISCUSSION

The key new observations from this study are demonstration of: 1) the efficacy rate of tecadenoson, a novel selective A<sub>1</sub> Ado R agonist, to terminate PSVT with minimal recurrence (3%), and 2) the relatively prolonged elimination half-life of 30 min for tecadenoson, in contrast to a few seconds for the currently available adenosine. Further, the selectivity of tecadenoson for the A<sub>1</sub> Ado R, at least in part, may have accounted for the lack of hypotension or other side effects even with the sustained effects (up to 5 min after dosing) on prolongation of AV conduction.

Rapid IV boluses of tecadenoson were associated with the conversion of programmed electrical stimulation-induced PSVT to sustained sinus rhythm in a majority (86%) of patients, with conversion occurring within 30 s (close to t<sub>Cmax</sub>) in over one-half of the patients. Conversion of PSVT to sinus rhythm after administration of tecadenoson was not associated with hypotension and pro-arrhythmic effects such as the induction of atrial fibrillation. The sample size in this study was too small to detect any dose-related differences in the effects of the drug in converting PSVT to sinus rhythm. Conversion of PSVT to sinus rhythm was noted across a wide range of doses, but there was no clear dose-related trend in the incidence of drug-related adverse events.

The longer duration of effect of tecadenoson (minutes) relative to that of adenosine (seconds) is consistent with the observation that the AH interval remained prolonged for at least 5 min after dosing. The persistent negative dromotropic effect of tecadenoson on AV nodal conduction after termination of PSVT had terminated following tecadenoson administration, in contrast to a few seconds for the currently available adenosine. Further, the selectivity of tecadenoson for the A<sub>1</sub> Ado R, at least in part, may have accounted for the lack of hypotension or other side effects even with the sustained effects (up to 5 min after dosing) on prolongation of AV conduction.

A potent A<sub>1</sub> agonist could be relatively selective for the AV node by slowing AV conduction at doses that do not cause sinus bradycardia and/or marked shortening of the atrial action potential. This is due, at least in part, to the fact that A<sub>1</sub> Ado R reserve is greater in the AV node than either the atria or the sinus node (18,19). Consequently, tecadenoson would have to activate significantly fewer A<sub>1</sub> Ado R in the AV node than in either the atria or the sinus node to produce its effects. Whereas the A<sub>1</sub> Ado R-selective properties of tecadenoson have been shown in the guinea pig.
isolated heart and whole animal models, the present study has demonstrated for the first time in humans that the undesirable A2 and A3 Ado R-mediated effects of adenosine during conversion of PSVT can be avoided by an A1 receptor subtype-selective agonist. Furthermore, this study supports the concept that a selective A2 Ado R agonist can be used for “smooth” uneventful termination of PSVT with restoration of sustained sinus rhythm and minimal occurrence of atrial fibrillation. This is in contrast to adenosine, which often terminates PSVT with the occurrence of high-grade, albeit, transient AV block accompanied by unpleasant symptoms and atrial fibrillation. For example, the reported incidence of atrial fibrillation and/or flutter after IV bolus injection of adenosine (<12 mg) varies from 1% to 12% (20–23). The most common adverse reactions after an IV bolus of adenosine are flushing, dyspnea, and chest discomfort. These side effects have been reported to occur in approximately 18%, 12%, and 7%, respectively, of the patients treated with doses of adenosine ≤12 mg (20). Further studies are needed to determine whether tecadenoson administered by constant infusion will be useful to control ventricular rate in atrial fibrillation.

In this study, tecadenoson rapidly terminated PSVT by prolonging AV nodal conduction without causing hypotension. After restoration of sinus rhythm there was minimal prolongation of AH interval without prolongation of HV interval, or SCL. These features make tecadenoson a potentially advantageous alternative to current therapies for the acute management of PSVT.

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