Trial to Evaluate the Management of Paroxysmal Supraventricular Tachycardia During an Electrophysiology Study With Tecadenoson

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Background—Tecadenoson is a potent selective A1-adenosine receptor agonist with a dose-dependent negative dromotropic effect on the AV node. Tecadenoson terminates induced paroxysmal supraventricular tachycardia (PSVT) without the clinically significant side effects caused by stimulation of other adenosine receptors. This trial was designed to determine a safe and effective tecadenoson bolus for termination of electrophysiologically induced PSVT.

Methods and Results—Patients with a history of symptomatic PSVT and inducible PSVT at the time of a clinically indicated electrophysiology study were randomized into a multicenter, double-blind, placebo-controlled trial. Five 2-dose tecadenoson bolus regimens were evaluated versus placebo (75/150, 150/300, 300/600, 450/900, 900 μg/900 μg). The second bolus was administered only if PSVT persisted for 1 minute after the first bolus. Each tecadenoson regimen resulted in a significant therapeutic conversion rate compared with placebo (range, 50.0% to 90.3%; analysis of all patients dosed; n=181; P<0.0005). Conversion by the first bolus was dose related (range: placebo, 3.3% to 86.7% for 900 μg/900 μg). Time to conversion was dose dependent, with a median time of <1 minute for the 3 highest dose regimens. Postconversion arrhythmias were transient, requiring no additional treatment in 4 regimens (including placebo). Transient second- and third-degree heart block occurred at higher doses (300/600, 450/900, 900 μg/900 μg) and was supported with backup pacing when needed. No effect on blood pressure was observed. Ten patients with a history of asthma or chronic obstructive pulmonary disease tolerated tecadenoson without bronchospasm.

Conclusions—We identified an optimal tecadenoson regimen (300 μg/600 μg) that effectively and rapidly converted 90% (28 of 31) of PSVT patients to normal sinus rhythm with no significant adverse effects. (Circulation. 2005;111:3202-3208.)

Key Words: adenosine • drugs • electrophysiology • tachyarrhythmias • tecadenoson

A cute paroxysmal supraventricular tachycardia (PSVT) has an annual estimated incidence of 89 000 cases and a prevalence of 570 000 cases.1 PSVT often presents with other comorbid conditions; notably, 90% of men and 48% of women with PSVT are reported to have concurrent cardiovascular disease.1 PSVT can be benign and self-limiting; however, patients may also experience serious complaints or symptoms, including angina, dyspnea, hypotension, or congestive heart failure.2,3

In symptomatic rapid PSVT, intervention with AV nodal blocking drugs is often required. β-Blockers or calcium channel blockers can be used to terminate acute PSVT; however, because of their side effects and long duration of action, the ultra-short-acting and potent adenosine is often preferred.4,5 Myriad adenosine-induced side effects such as flushing, dyspnea, chest pain, transient hypotension,2,5 and arrhythmias4 are mediated by the nonselective activation of adenosine on multiple adenosine receptor subtypes: A1, A2A, A2B, and A3. Although activation of the A1 receptor results in the desired termination of PSVT,6 activation of the remaining adenosine receptors presumably is the cause of the adverse effects described above.7

This study evaluated tecadenoson (6-[(N-3’-(R)-tetrahydrofuranyl)-amino-purine riboside, formerly CVT-
510), a selective A1-adenosine agonist, for the acute termination of PSVT. In the atrial-paced guinea pig heart model,5 tecadenoson was 5-fold more potent in prolonging the stimulus-to-His bundle (S-H) interval, an A1-adenosine receptor–mediated effect, than in increasing coronary conductance, an A2A-adenosine receptor–mediated effect.

In phase 1 and 2 clinical studies, tecadenoson caused an A1-adenosine receptor–mediated negative dromotropic effect on the AV node and lengthening of the AV nodal refractory period, leading to termination of reentrant PSVT at doses that did not affect blood pressure (BP), sinus cycle length, or the His-ventricular interval.7,8 Side effects mediated by the A2A, A2B, and A1-adenosine receptors such as flushing, chest pressure, hypotension, and bronchospasm were infrequent, consistent with the A1-adenosine receptor selectivity of the drug.

The primary objective of this phase 3 trial was to determine the optimal therapeutic tecadenoson bolus regimen for PSVT termination by comparing the frequency of therapeutic PSVT conversion with each of 5 regimens of tecadenoson versus placebo. A secondary objective was to evaluate tecadenoson safety during PSVT conversion.

Methods

Study Design

This randomized, double-blind, placebo-controlled study compared 5 different tecadenoson regimens with placebo in patients with a history of PSVT who required an electrophysiology (EP) study. To demonstrate a 50% increase in the PSVT conversion rate for any of the 5 tecadenoson dose regimens compared with placebo, a minimum of 23 patients in each of the tecadenoson dose groups and 23 in the placebo group were required; the sample size calculations were based on an overall α of 5% and power of 90% with an assumed placebo conversion rate of 20%. Thirty patients were targeted for enrollment in each group. Thirty-four investigational sites across the United States and the United Kingdom enrolled patients after institutional review board or independent ethics committee approval of the protocol; all patients gave written informed consent.

Exclusion Criteria

Patients were excluded for the following reasons: current treatment for reactive airway diseases, including asthma; presence of atrial fibrillation; heart rate (HR) in sinus rhythm ≥50 or ≥130 bpm; second- or third-degree AV block on the screening ECG; NYHA class IV congestive heart failure; chronic illness likely to impede follow-up evaluations; allergy to tecadenoson or its components; or use of antiarrhythmic medications (including β-blockers, amiodarone, calcium channel blockers, or digoxin) within 5 half-lives before dosing with the investigational agent.

Randomization and Study Drug

Blinded study drug was withdrawn into syringes for administration as an intravenous bolus dose. A centralized randomization schedule was used at the study level. Each patient was randomly allocated to 1 of the 10 treatment types (active A, B, C, D, and E, and placebo A, B, C, D, and E) with a 5:5:5:5:5:1:1:1:1:1 ratio. The blocks contained 30 entries each. The pharmacist was blinded to study drug assignment (ie, tecadenoson versus placebo) but not to the dose regimens. The investigator and patient remained blinded to both study drug assignment and dosing regimen.

Five active tecadenoson regimens were studied (first dose/second dose [regimen]: 75 μg/150 μg [A], 150 μg/300 μg [B], 300 μg/600 μg [C], 450 μg/900 μg [D], 900 μg/900 μg [E]) versus placebo (Figure 1). The first dose was administered as a single rapid intravenous bolus (≤10 seconds) via a peripheral intravenous catheter. If PSVT persisted after 1 minute, the second dose was administered as 2 rapid, sequential intravenous boluses.

Evaluations

Predose screening evaluations included medical history, physical examination with BP and HR, and 12-lead ECG. On the day of the EP study, medical history, 12-lead ECG, BP, HR, hematology, serum chemistry, and urinalysis were done. A physical examination, BP, HR, and repeated laboratory measures were completed at study termination. Patients were contacted for follow-up and any possible adverse events 14 days after dosing. Adverse events reported by the patient or determined through physical examination, cardiac monitoring, or laboratory testing were recorded throughout the study period.

PSVT Induction

Standard intracardiac electrodes, including a ventricular pacing catheter, were placed before dosing; ventricular capture was demonstrated during ventricular pacing before PSVT induction. Dyspnea, dizziness, chest pain, and palpitations were assessed before study drug administration, during PSVT, and 2 minutes after the first study drug dose. PSVT was initiated and sustained for ≥2 minutes before the first dose of study drug. If PSVT persisted 1 minute after the first dose, the second dose of study drug was administered. If study drug–related conversion was not achieved after either the first or second dose, then PSVT was converted by overdrive pacing or by cardioversion at the physician’s discretion. Other nonstudy antiar-
rhythms were administered only if overdrive pacing and cardioversion failed to convert PSVT.

Definitions of Conversion
Therapeutic conversion was defined as a return to normal sinus rhythm by 1 minute after the final dose without the occurrence of second- or third-degree AV block. Study drug–related conversion was defined as any rhythm other than PSVT at 1 minute after study drug administration without subsequent overdrive pacing or cardioversion during the intervening minute or the administration of another AV nodal blocking drug. Non–study drug–related conversion was defined as the termination of persistent PSVT to any other rhythm >1 minute after the final dose of study drug spontaneously or by overdrive pacing, cardioversion, or use of another AV nodal blocking drug. Persistent PSVT was PSVT 1 minute after the last study drug dose. Recurrent PSVT was defined as any episode of ≥10 consecutive beats of PSVT that occurred ≥5 minutes after successful conversion.

Pharmacokinetics
Blood samples for pharmacokinetic analyses were collected at baseline, at 30 and 90 seconds, and at 3, 5, 10, and 30 minutes after the first dose of study drug. Plasma levels of tecadenoson were analyzed by high-performance liquid chromatography with danem mass spectrometry (LC/MS/MS) using positive-ion ray ionization as described previously.7 The dose concentration at each time point was averaged by the number of full doses.

Statistical Analysis
All dosed patients were included in the safety and efficacy analyses. All statistical tests were 2 sided at the 0.05 level of significance. All statistical computations were performed with SAS version 8.1 software.9 Bivariate relationships between dose regimens and baseline characteristics were evaluated with frequency tables and χ² tests of independence. The primary efficacy endpoint was the frequency of therapeutic conversion of PSVT after the final dose. The rate of therapeutic conversion of each of 5 tecadenoson regimens was compared with placebo through the use of Pearson’s χ² test. Multiple comparisons were addressed by a multiple-stage step-up procedure.10 Secondary efficacy analyses were as follows: The rate of therapeutic conversion after the first dose of each of 5 tecadenoson regimens was compared with placebo through the use of Pearson’s χ² test; the distribution of time from initiation of treatment to study drug–related conversion was estimated by the Kaplan-Meier method, and dose regimens were compared by use of log-rank tests; the frequency of PSVT recurrence and conversion arrhythmias after conversion following treatment with each tecadenoson regimen was compared with that following placebo through a χ² test; and the overall mean score of relief from symptoms associated with PSVT (eg, dyspnea, dizziness, chest pain, and palpitations) of each tecadenoson regimen was compared with the placebo mean by the exact Cochran-Mantel-Haenszel test without stratification. Safety was evaluated by listing and summarization of adverse events, serious adverse events, vital signs, ECG measurements (PR, QRS, and QTc; and abnormalities). Vital signs and ECG measurements were summarized descriptively at each time point over study.

Results
Patients and Treatment
Thirty-four centers in the United States and United Kingdom enrolled 341 patients, 181 of whom met inclusion criteria and were randomized to study drug or placebo (Figure 1). The remaining 160 patients were excluded because of noninducible PSVT (n=153), failure to give consent (n=2), or other reasons (n=5). Patient demographic and baseline characteristics by treatment group were summarized in Table 1. Ten patients in the tecadenoson group and 4 in the placebo group had a history of chronic obstructive pulmonary disease (COPD)/asthma for which they were receiving no acute bronchodilator or other treatment at the time of the study; none had an exacerbation during the trial. At induction of sustained PSVT, 136 patients (75.1%) had AV nodal reentrant tachycardia, and 45 (24.9%) had AV reentrant tachycardia.

Efficacy
Of the 181 dosed patients, 151 received tecadenoson, and 30 received placebo. The overall therapeutic conversion to normal sinus rhythm was 62.4% (113 of 181; 111 tecadenoson subjects, 2 placebo subjects). Four additional patients who received tecadenoson had a study drug–related conversion. Each tecadenoson regimen resulted in significantly higher therapeutic conversion rates compared with placebo (n=181; P<0.0005; Figure 2). Therapeutic conversion rates were as follows: placebo, 6.7% (2 of 30); A, 50.0% (16 of 32); B, 58.6% (17 of 29); C, 90.3% (28 of 31); D, 82.8% (24 of 29); and E, 86.7% (26 of 30). A dose-dependent relationship in therapeutic conversion rate was observed after both the first and final doses of study drug (Figure 2). After the first bolus, tecadenoson terminated PSVT (82 of 151, 54.3%) more effectively than placebo (1 of 30, 3.3%). Except in regimen E, a second bolus recruited more therapeutic conversions in the remaining PSVT patients. The Kaplan-Meier estimate of the median time to tecadenoson-related conversion was also dose dependent: <1 minute for regimens C, D, and E and >2 minutes for regimens A and B after the final dose (Figure 3). Four patients had study drug–related conversion but converted to a rhythm other than normal sinus
rhythm: complete AV block (group E; duration, 23 seconds), 2:1 AV block (group E; duration, 17 seconds), second-degree AV block (group C; duration, 72 seconds), and atrial fibrillation (group B).

Of the 64 patients (tecadenoson or placebo) with a non-study drug–related conversion, 14 had a spontaneous PSVT conversion by 5 minutes after the final dose, 44 patients required overdrive pacing to convert, 1 was externally cardioverted, 1 received adenosine, 1 had a premature ventricular contraction introduced into tachycardia, 1 had an atrial extrastimulus introduced into tachycardia, and 2 had slow pathway ablation.

Recurrent PSVT after study drug–related conversion occurred in a few patients (0%, 0%, 6%, 7%, 12%, and 7% in placebo, A, B, C, D, and E, respectively). Conversion arrhythmias were determined by an ECG core laboratory as any arrhythmia 2 seconds before through 30 seconds after conversion (excluding patients who had overdrive pacing). Most conversion arrhythmias were atrial or ventricular ectopic beats, which were benign and transient. Postconversion AV block (Table 2) was dose dependent (P<0.0001). There were 2 patients with second-degree AV block in regimen C, 4 in regimen D, and 6 in regimen E. Second-degree AV block was Wenckebach (Mobitz I) except in regimen E, in which 1 of the 6 had Mobitz II and 2 had a 2:1 AV block. Complete or third-degree AV block was observed only with regimen E. Atrial flutter and atrial fibrillation occurred with regimen D and E; they were self-limited (eg, spontaneously terminated).

**Pharmacokinetics**

The time to peak plasma concentration for a single tecadenoson bolus was <2 minutes (range, 1.2 to 1.86 minutes). Mean maximum plasma concentration (Cmax) ranged from 1.96 ng/mL (regimen A) to 41.66 ng/mL (regimen E) among patients who received 1 dose. Both Cmax and the area under the concentration curve (AUC and AUClast) increased proportionally with tecadenoson dose. The initial Cmax correlated with the rate of PSVT conversion. For those who did not convert after the initial bolus, the second tecadenoson bolus resulted in a higher Cmax to increase the probability of conversion.

**Safety**

Tecadenoson was well tolerated as assessed by both objective and subjective (symptom) standards. The average HR was 169 bpm during PSVT. At 1 and 10 minutes after conversion...
and at study termination, the average HR returned to about 85 to 89 bpm (Figure 4). During tachycardia, most patients had ≥1 symptoms (dyspnea, dizziness, chest pain, and palpitations) (data not shown) that abated after conversion (P<0.05). The BP measurements at baseline and before, during, and after PSVT conversion were similar (Figure 5). After the tecadenoson bolus and during rapid PSVT, clinically insignificant increases in PR intervals (22 ms) were observed. QT interval corrected by both Bazett’s and Fridericia’s formulas showed no significant treatment effect. There were no significant changes in laboratory parameters or physical examination findings observed during the study.

A total of 101 tecadenoson-dosed patients (66.9%) experienced an average of 1.5 adverse events each compared with 17 of 30 (56.7%) patients receiving placebo (P=0.28). Most of these adverse events, regardless of the cause, were considered mild or moderate in severity. However, the frequency of adverse events considered by the investigator to be probably related to study drug was 23.8% (36 of 151) for tecadenoson versus 6.7% (2 of 30) for placebo (P=0.035) (Table 3). Overall, adverse events related to the cardiovascular system occurred in 15.2% (23 of 151) of tecadenoson subjects compared with 3.3% (1 of 30) of placebo subjects (P=0.32). These included tachycardia, atrial fibrillation, first- and second-degree AV block, flushing, and dyspnea. There was a correlation between increasing doses of tecadenoson and the incidence and severity of AV block.

There were 4 serious adverse events: syncope, deep vein thrombosis, cardiac arrest, and pericardial effusion. The syncopal episode, pericardial effusion, and deep vein thrombosis were deemed by the investigator to be probably not related to study drug. The pericardial effusion and tamponade were attributed to anticoagulation and multiple radiofrequency ablation lesions delivered during the EP study. The cardiac arrest occurred in an 84-year-old man 22 hours after dosing; the terminal elimination half-life of tecadenoson is 30 minutes.

About 65% of patients reported any symptoms during PSVT at baseline; this rate was lower than expected. It is likely the anxiolytic sedative given during the EP procedure contributed to an underreporting of symptoms. Nevertheless, there is a positive correlation between symptomatic relief with tecadenoson before and after PSVT conversion compared with placebo (P<0.05). No symptomatic relief was noted in the placebo group because most patients remained in tachycardia.

**Discussion**

In this trial, tecadenoson bolus regimen C (300 μg/600 μg) converted 90% of PSVT patients and was well tolerated. Regimen C was selected as optimal over regimen D (450 μg/900 μg) because of a greater safety margin, even though regimen D had a slight advantage in conversion rate after the first bolus. However, the overall PSVT conversion rate in regimen C (90.3%) was higher than regimen D (82.8%). Successful conversion after the first bolus correlated with the tecadenoson dose, thus suggesting that the plasma peak concentration plays an important role. A second tecadenoson bolus recruited more conversions in all regimens except in E, perhaps representing a saturation of the AV nodal receptors.

**TABLE 2. Arrhythmias at Conversion**

<table>
<thead>
<tr>
<th>Atrial ectopy</th>
<th>Ventricular ectopy</th>
<th>Second-degree AV block</th>
<th>Third-degree AV block</th>
<th>Atrial flutter</th>
<th>Atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>A B C D E</td>
<td>Total (A–E)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Placebo, n (%)</td>
<td>Placebo, n (%)</td>
<td>14 14 28 23 23 102</td>
<td>14 14 28 23 23 102</td>
<td>2 (14)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Aisle, n (%)</td>
<td>Aisle, n (%)</td>
<td>2 (14) 4 (14) 5 (22)</td>
<td>2 (14) 4 (14) 5 (22)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Regimen C</td>
<td>Regimen D</td>
<td>3 (11) 5 (22) 5 (22)</td>
<td>3 (11) 5 (22) 5 (22)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Regimen E</td>
<td>Total (A–E)</td>
<td>23 23 18 18 16 16</td>
<td>23 23 18 18 16 16</td>
<td>14 (14)</td>
<td>14 (14)</td>
</tr>
</tbody>
</table>

*All overdrive pacing was excluded. Study drug–related conversion was analyzed for tecadenoson. Any conversion was analyzed for placebo.

**Figure 4.** Change in HR. Each bar represents mean HR for each group at baseline and at subsequent intervals during study. Mean HR returned to ~85 to 89 bpm by 1 minute after conversion.
after the first tecadenoson dose in regimen E. The rate of conversion of PSVT in tecadenoson regimen C is close to what has been reported with adenosine (85% to 96%).11–13 The median time to tecadenoson-related conversion was also dose dependent. Conversion occurred in <1 minute with the 3 highest dose regimens (300/600, 450/900, and 900 μg/900 μg) but was >2 minutes for the 2 lower dose regimens (75/150 and 150 μg/300 μg).

The clinically desirable duration of tecadenoson effect on the human AV node is ≈5 minutes, and its measurable negative dromotropic effect on the AV node disappears by 20 minutes.7 The types of AV block associated with tecadenoson in regimen C were primarily first degree and Wenckebach. Postconversion arrhythmias such as atrial and ventricular ectopics were observed but without any clinical consequences. Because tecadenoson would be administered in a medically monitored setting, the risk related to the development of Wenckebach or atrial arrhythmias would be expected to be small, because these arrhythmias rarely cause hemodynamic compromise and medical personnel are immediately available to treat potential complications.

Tecadenoson was well tolerated in this trial, and selective activation of the A1-receptor appears to result in no side effects related to stimulation of the other adenosine receptors that can cause vasodilatation in the coronary and peripheral arteries and increased pulmonary vessel reactivity.6,7,14 An earlier preclinical study showed that tecadenoson delays guinea pig AV nodal conduction to the same degree as diltiazem but without negative hemodynamic effects.6 Although the guinea pig study showed that tecadenoson specifically acts on the AV node through A1-adenosine receptor, it has no effect on BP because it never triggered the other adenosine receptors. Subsequent clinical phase 1 and 2 trials with tecadenoson also demonstrated and confirmed successful conversion of induced PSVT without affecting BP.7,8 In this study, tecadenoson had no effect on BP compared with placebo. Ten patients with a history of COPD/asthma but not on active treatment were enrolled and received tecadenoson in this study. T...
atrial refractory period, atrial fibrillation after conversion is not unexpected.\textsuperscript{19,20} Compared with adenosine, however, tecadenoson is less potent in shortening the atrial action potential than in depressing the AV node. The incidence of atrial fibrillation after a central venous intravenous adenosine bolus is reported to be 11\% to 15\%, and both were higher than the incidence of atrial fibrillation reported in this study.\textsuperscript{21,22} The question of the safety of tecadenoson relative to adenosine will have to await a direct prospective comparative trial.

Tecadenoson, a novel selective A\textsubscript{1}-adenosine receptor agonist, shows promise for the treatment of PSVT conversion. In this trial, we identified a dose for further clinical investigation. It appears to be a highly efficacious and well-tolerated agent for PSVT conversion. Comparative studies between tecadenoson and adenosine are needed to further evaluate adenosine receptor selectivity.

Acknowledgments

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References

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