Drugs of the Future 2002, 27(9): 846-849

CCC: 0377-8282/2002

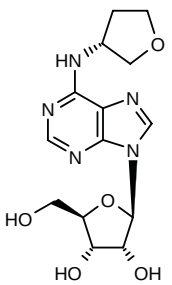
Tecadenoson

USAN

Antiarrhythmic
Adenosine A_1 Agonist

CVT-510

N^6-[3(*R*)-Tetrahydrofuranyl]adenosine



$C_{14}H_{19}N_5O_5$

Mol wt: 337.3341

CAS: 204512-90-3

CAS: 204512-89-0 (as undefined isomer)

EN: 252682

Abstract

Adenosine has been shown to be a clinically effective antiarrhythmic agent. However, because it acts on all 4 adenosine cell surface receptors (AdoRs), in addition to the cardiovascular effects beneficial for treating arrhythmias (*i.e.*, negative chronotropic, negative dromotropic, negative inotropic, anti-β-adrenergic effects) occurring via activation of the A_1 AdoR, adenosine also exerts positive coronary vasodilatory effects via A_{2A} AdoR. Thus, clinical use of the agent is associated with unwanted side effects including hypotension. Selective activation of A_1 AdoR would eliminate induction of hypotension from the possible cardioprotectant effects of adenosine and/or adenosine agonists. Tecadenoson is an agent that has been shown to be highly selective for A_1 AdoR over A_{2A} AdoR. It was selected for further development in controlling heart rate during acute atrial arrhythmias, including conditions of atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardias (PSVT), without lowering blood pressure.

Synthesis

The reaction of 3-tetrahydrofuroic acid (I) with diphenyl phosphoryl azide (DPPA) in refluxing dioxane gives the isocyanate intermediate (II), which is treated with benzyl alcohol (III) to yield carbamate (IV). Subsequent hydrogenolysis in the presence of Pd/C affords racemic amine (V), which is resolved by treatment with (*S*)-(+)-10-camphorsulfonyl chloride (VI) in pyridine, followed by column chromatography and recrystallization of the resulting sulfonamide (VII) in acetone. Finally, hydrolysis of compound (VII) in HCl/AcOH provides the (*S*)-amine (VIII), which is condensed with 6-chloropurine riboside (IX) in the presence of triethylamine in refluxing MeOH (1). Scheme 1.

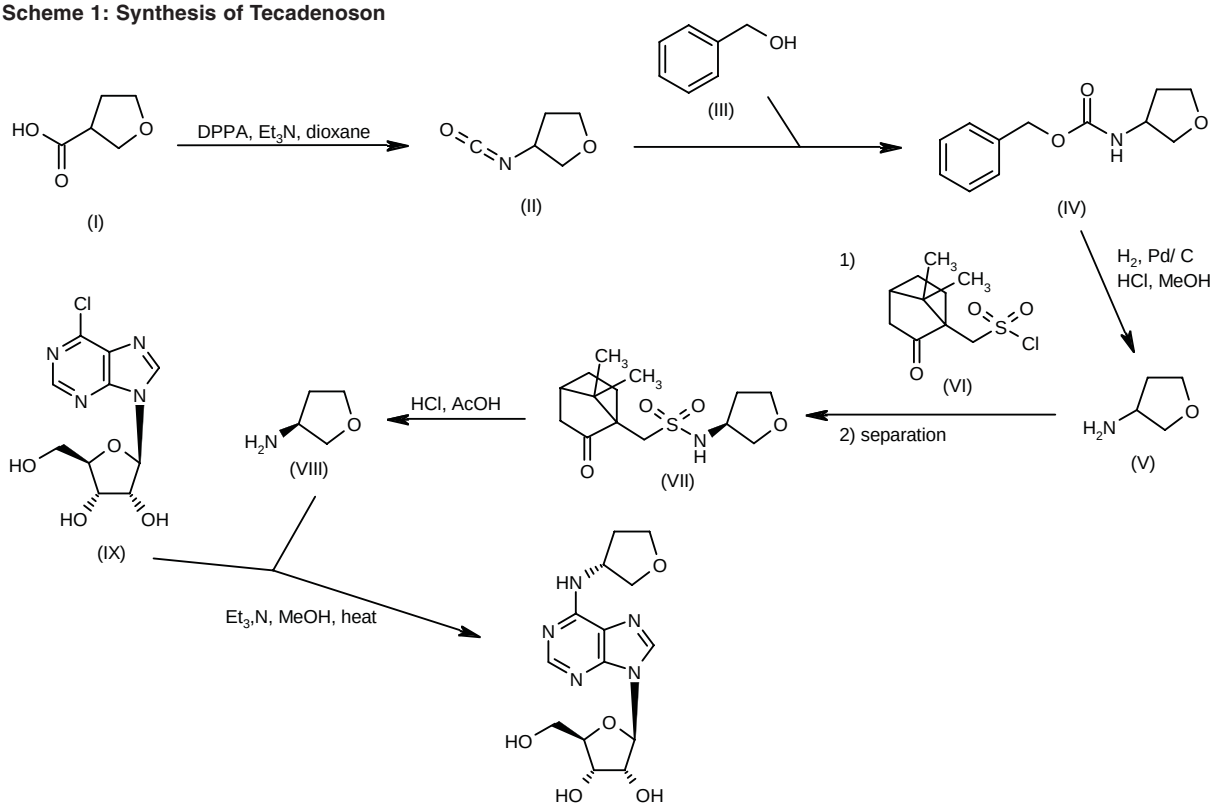
Introduction

Extracellular endogenous adenosine exerts several cardiovascular effects via action on cell surface adenosine receptors (AdoRs). These effects include slowing of heart rate (negative chronotropic effect), prolongation of atrioventricular (AV) nodal conduction (negative dromotropic effect), reductions in atrial contractility (negative inotropic effect), attenuation of the stimulatory actions of catecholamines on the heart (anti-β-adrenergic effects) and increases in coronary artery blood flow. Four AdoRs subtypes have been identified and cloned (A_1, A_{2A}, A_{2B} and A_3) and research has demonstrated that the A_1 subtype is responsible for the chronotropic, dromotropic, inotropic and anti-β-adrenergic effects of AdoRs on cardiac myocytes. In contrast, adenosine-mediated coronary vasodilation occurs mainly via stimulation of A_2 AdoRs (2-6).

A_1 AdoR activation has been shown to be responsible for several cardioprotective effects, including reductions in infarct size, improvements in postischemic function and decreases in arrhythmias. These cardioprotective effects are due to the effects described above, in addition to other possible cellular metabolic actions such as

L.A. Sorbera, J. Castañer, L. Martín, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Tecadenoson



attenuation of ATP depletion and cellular acidosis and inhibition of lipolysis resulting in a reduction in free fatty acid levels that are linked to postischemic damage, increased arrhythmia and death in patients (7-11). Atrial arrhythmias in particular are responsible for 2.6 million hospitalizations in the U.S. every year and have been linked to an increased risk of stroke. Through its negative dromotropic effect of depression of AV node activity, adenosine and adenosine agonists can convert supraventricular tachycardias to sinus rhythm. Adenosine is considered to be an effective antiarrhythmic agent due to it short duration of action. On the other hand, adenosine is a full agonist acting on all 4 adenosine receptor subtypes and thus its clinical use is associated with several side effects (particularly hypotension) (2, 12). A selective A_1 AdoR agonist appears to be a clinical solution for the treatment of atrial arrhythmias. One such selective agent, tecadenoson (CVT-510), has shown potent negative dromotropic effects and a high selectivity for the A_1 AdoR over the A_{2A} AdoR. Tecadenoson has been selected for further development for the sustained control of heart rate during acute atrial arrhythmias, including conditions of atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardias (PSVT), without lowering blood pressure.

Pharmacological Actions

The selectivity of tecadenoson for the A_1 AdoR over the A_{2A} AdoR was demonstrated in radioligand binding studies with pig forebrain (A_1 AdoR) and striatum (A_{2A} AdoR) membrane preparations using [^{3}H]-8-cyclopentyl-1,3-dipropylxanthine (CPX) and [^{3}H]-CGS-21680, respectively. Although tecadenoson binding was dose-dependent and complete in both types of membranes, the agent was 356-fold more potent in competing for [^{3}H]-CPX than [^{3}H]-CGS-21680. K_i values obtained for the A_1 and A_{2A} AdoRs were 6.5 ± 1.4 and 2315 ± 650 nM, respectively (13).

In a study using isolated atrial-paced guinea pig hearts, tecadenoson was 5 times more potent in prolonging the stimulus-to-His bundle (S-H interval), indicating a slowing of AV nodal conduction (EC_{50} = 40.6 nM), than it was in increasing coronary conductance (EC_{50} = 200.5 nM). The negative dromotropic effect of tecadenoson was completely reversed by addition of the selective A_1 AdoR antagonist CPX (60 nM), while the A_{2A} AdoR receptor antagonist ZM-241385 (100 nM) had no effect. Although both tecadenoson (40 nM) and diltiazem (1 μM) prolonged the S-H interval by about 10 ms, only diltiazem significantly decreased left ventricular developed pressure (LVP) and increased coronary conductance.

Moreover, tecadenoson shortened atrial monophasic action potentials (MAPs; EC_{50} = 73 nM) but had no effect on ventricular MAPs. This suggests that tecadenoson would not cause proarrythmic effects in the ventricular myocardium. Further experiments *in vivo* in anesthetized atrial-paced guinea pigs comparing the effects of tecadenoson (0.75-1 μg/kg/min) with diltiazem (200-400 μg/kg/min), showed that i.v. boluses of both agents increased the P-R interval in a similar manner but only diltiazem significantly reduced mean arterial blood pressure. Together these results indicate that although both agents slowed AV nodal conduction, only tecadenoson did so without the negative inotropic vasodilator effects seen with diltiazem (14).

The induction of sinus bradycardia by tecadenoson was further characterized in an *in vivo* study using both anesthetized and awake rats. The heart rate of anesthetized rats was dose-dependently slowed from baseline by 30-40% and > 50% with tecadenoson doses of 0.5-1 mg/kg and > 1.5 μg/kg i.v., respectively. The decreases in heart rate were correlated with stepwise increases in plasma tecadenoson levels. Heart rates returned to normal levels upon completion of infusion. Dose-dependent bradycardia was observed in awake rats administered repeated i.p. boluses (50 μg/kg) or chronic (4 days) s.c. doses (33.7 and 50.6 μg/kg/ h via an osmotic minipump). An i.p. bolus of 50 μg/kg i.p. resulted in bradycardia of greater than 100 bpm, while continuous s.c. administration of 100 nmol/kg/h slowed the heart rate by 80-60 bpm throughout the 4-day infusion period. Results show that tecadenoson-induced bradycardia is not desensitized by repeated dosing and persists with chronic administration (15).

Clinical Studies

A multicenter, open-label, single-dose, dose-escalation phase I study characterized the pharmacokinetics and effects of tecadenoson (0.3-30 μg/kg i.v. bolus) on AV nodal conduction in 32 healthy volunteers, of whom 29 had no structural heart disease, 2 had coronary artery disease and 1 had mild aortic stenosis. A two-compartment pharmacokinetic model was found to fit all dose groups. In groups receiving 0.3-15 μg/kg, the initial half-life indicating the distribution phase ranged from 1.3-2.9 min, while the terminal half-life ranged from 21-27 min. The overall pharmacokinetics were generally dose-proportional. Dose-dependent increases in the A-H intervals were observed so that at 1 min a 10 μg/kg bolus significantly increased the interval from 93 ± 23 to 114 ± 37 ms and from 114 ± 31 to 146 ± 44 ms during atrial pacing at 600 ms. Intervals returned to baseline after 20 min. No effects on sinus rate, H-V interval or systemic blood pressure were seen with doses of 0.3-10 μg/kg. However, after dosing with 15 and 30 μg/kg, 4 patients experienced transient high-degree (second/third) AV block. One of these patients also experienced a prolonged sedative effect that was reversed with aminophylline. Other adverse events seen were consistent with stimulation of AV nodal and atrial A_1 AdoRs such as slowing of AV conduction and shortening of the atrial refractory period, respectively. Two patients given 10 μg/kg and 1 patient given 30 μg/kg developed transient (> 8 min) atrial fibrillation during atrial pacing. However, atrial fibrillation was well tolerated and not accompanied by a decrease in systolic blood pressure. Results suggest that tecadenoson may be effective as an antiarrhythmic when atrial fibrillation or flutter or termination of PSVT involving the AV node must be controlled (16). The results of this clinical study and the two that follow are summarized in Table I.

Table I: Clinical studies of tecadenoson (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Tachy-arrhythmia	Open, multicenter	Tecadenoson, 0.3 μg/kg i.v. bolus s.d. Tecadenoson, 1 μg/kg i.v. bolus s.d. Tecadenoson, 3 μg/kg i.v. bolus s.d. Tecadenoson, 7.5 μg/kg i.v. bolus s.d. Tecadenoson, 10 μg/kg i.v. bolus s.d. Tecadenoson, 15 μg/kg i.v. bolus s.d. Tecadenoson, 30 μg/kg i.v. bolus s.d.	32	Tecadenoson promptly prolonged AV nodal conduction at doses that did not affect sinus rate or blood pressure in patients with normal AV nodal function and may be useful for the immediate control of heart rate in atrial fibrillation or flutter and to convert paroxysmal supraventricular tachycardia to sinus rhythm	16
Supra-ventricular tachycardia	Open	Tecadenoson, 3 μg/kg i.v. bolus x 1-2 Tecadenoson, 5 μg/kg i.v. bolus x 1-2 Tecadenoson, 7.5 μg/kg i.v. bolus x 1-2 Tecadenoson, 10 μg/kg i.v. bolus x 1-2 Tecadenoson, 12.5 μg/kg i.v. bolus x 1-2 Tecadenoson, 15 μg/kg i.v. bolus x 1-2	30	Tecadenoson was well tolerated and effective in suppressing supraventricular tachycardia without causing hypotension, HV prolongation or depressing sinus or AV nodal conduction after restoring sinus rhythm in patients with supraventricular tachycardia	17
Supra-ventricular tachycardia	Open, multicenter	Tecadenoson, 9 μg/kg [mean 3-15] (n=14) Adenosine, 7 mg [mean 6-12] (n=11)	25	Tecadenoson appears to be better tolerated and less proarrythmic than adenosine in patients with supra-ventricular tachycardia	18

Results from an open-label dose-escalation study involving 30 patients with inducible, sustained supraventricular tachycardia showed the efficacy of tecadenoson (3-15 μg/kg i.v. boluses at least 2 min apart) in rapidly depressing AV nodal conduction without inducing hypotension. After one or two boluses, supraventricular tachycardias were converted to sinus rhythm in less than 1 min in 25 and 3 patients, respectively. The 2 remaining patients had only a transient slowing of supraventricular tachycardia following boluses of 5 and 10 μg/kg, respectively. The overall response was 93%. The marked increases in A-H intervals seen during supraventricular tachycardia were restored to normal or near-normal levels by tecadenoson treatment (94 ± 19 and 88 ± 22 ms at 1 and 5 min postbolus, respectively, as compared to 81± 21 and 220 ± 88 ms prior to and during supraventricular tachycardia, respectively). Tecadenoson was well tolerated with no serious adverse events or high-grade AV block reported. The agent had no significant effects on heart rate, blood pressure or H-V intervals. Results suggest that tecadenoson may be effective in controlling ventricular rate in atrial fibrillation even in patients with left ventricular dysfunction (17).

Retrospective analysis of the results of 14 patients in the above study whose supraventricular tachycardias were converted to sinus rhythm after receiving tecadenoson (3-15 μg/kg; mean dose = 9 μg/kg i.v.) as compared to 11 consecutive patients who were converted to sinus rhythm after receiving adenosine (6-12 doses, mean = 7 mg) during the same period, found that less arrhythmias were associated with tecadenoson than adenosine. Significantly fewer patients in the tecadenoson group had ventricular ectopic beats as compared to the adenosine group. In addition, the longest postarrhythmic pause in the tecadeoson group was 1.5 s as compared to 7.3 s in the adenosine group. Thus, tecadenoson may be better tolerated and less proarrhythmic than adenosine during termination of supraventricular tachycardia (18).

Tecadeonson continues to undergo phase II development as a treatment for atrial fibrillation and flutter. In addition, enrollment has recently been completed for a phase III, multicenter, randomized, double-blind, placebo-controlled study to determine the safety and efficacy of tecadeonson in converting patients with PSVT to normal sinus rhythm without causing hypotension (19).

Source

CV Therapeutics, Inc. (US).

References

1. Lum, R.T., Pfister, J.R., Schow, S.R., Wick, M.M., Nelson, M.G., Schreiner, G.F. (CV Therapeutics, Inc.). *N^6 heterocyclic substd. adenosine derivs.* EP 0920438, EP 0992510, EP 1081155, JP 2000501426, US 5789416, WO 9808855.

2. Shryock, J.C., Belardinelli, L. A*denosine and adenosine receptors in the cardiovascular system: Biochemistry, physiology, and pharmacology.* Am J Cardiol 1997, 79: 2-10.

3. Song, Y., Thedford, S., Lerman, B.B., Belardinelli, L. *Adenosine-sensitive afterdepolarizations and triggered activity in guinea pig ventricular myocytes.* Circ Res 1992, 70: 743-53.

4. Song, Y., Belardinelli, L. *Electrophysiological and functional effects of adenosine on ventricular myocytes of various mammalian species.* Am J Physiol 1996, 271: C1233-43.

5. Linden, J., Tucker, A.L., Lynch, K.R. *Molecular cloning of adenosine A_1 and A_2 receptors.* Trends Pharmacol Sci 1991, 12: 326-8.

6. Linden, J. *Cloned adenosine A_3 receptors: Pharmacological properties, species differences and receptor functions.* Trends Pharmacol Sci 1994, 15: 298-306.

7. Downey, J.M. *Ischemic preconditioning: Nature's own cardioprotective mechanism.* Trends Cardiovasc Med 1992, 2: 170-6.

8. Wainwright, C.L., Parratt, J.R. *Effects of R-PIA, a selective A_1 adenosine agonist, on haemodynamics and ischaemic arrhythmias in pigs.* Cardiovasc Res 1993, 27: 84-9.

9. Boachie-Ansah, G., Kane, K.A., Parratt, J.R. *Is adenosine an endogenous myocardial protective (antiarrhythmic) substance under conditions of ischaemia?* Cardiovasc Res 1993, 27: 77-83.

10. Strong, P., Anderson, R., Coates, J., Ellis, F., Evans, B., Gurden, M.F., Johnstone, J., Kennedy, I., Martin, D.P. *Suppression of non-esterified fatty acids and triacylglycerol in experimental animals by the adenosine analogue GR79236.* Clin Sci 1993, 84: 663-9.

11. Hendrickson, S.C., St. Louis, J.D., Lowe, J.E., Abdel-aleem, S. *Free fatty acid metabolism during myocardial ischemia and reperfusion.* Mol Cell Biochem 1997, 166: 85-94.

12. Wilbur, S.L., Marchlinski, F.E. *Adenosine as an antiarrhythmic agent.* Am J Cardiol 1997, 79: 30-7.

13. Snowdy, S., Pfister, J., Lum, R., Nelson, M., Schow, S., Wang, L., Belardinelli, L. T*he pharmacologic characterization of N^6-((S)-3-tetrahydrofuranyl)adenosine, a novel adenosine receptor agonist.* Drug Dev Res 1998, 43(1): Abst 114.

14. Snowdy, S., Liang, H.X., Blackburn, B., Lum, R., Nelson, M., Wang, L., Pfister, J., Sharma, B.P., Wolff, A., Belardinelli, L. *A comparison of an A_1 adenosine receptor agonist (CVT-510) with diltiazem for slowing of AV nodal conduction in guinea-pig.* Br J Pharmacol 1999, 126: 137-46.

15. Gao, Z., Rosete, J., Kohler, G., Huang, B.-L., Blackburn, B., Belardinelli, L. *Negative chronotropic effect of CVT-510 in anesthetized and awake rats.* Drug Dev Res 2001, 52: 424-30.

16. Lerman, B.B., Ellenbogen, K.A., Kadish, A. et al. *Electrophysiologic effects of a novel selective adenosine A_1 agonist (CVT-510) on atrioventricular nodal conduction in humans.* J Cardiovasc Pharmacol Ther 2001, 6: 237-45.

17. Prystowsky, E., Niazi, I., Curtis, A.B. et al. *CVT-510, a novel selective A_1-adenosine receptor agonist, terminates supraventricular tachycardia.* Circulation 2000, 102(18, Suppl.): Abst 3247.

18. Niazi, I., Bahnson, T.D., Lanzerotti, C., McPike, J., Kiemen, J., Kappel, D., Belardinelli, L., Cheng, J., Shreeniwas, R., Wolff, A.A. *Termination of supraventricular tachycardia with CVT-510, a selective A_1 adenosine receptor agonist, is associated with fewer arrhythmias than adenosine.* Circulation 2001, 104(17, Suppl. 2): Abst 2317.

19. *Enrollment complete in tecadenoson phase III trial.* DailyDrugNews.com (Daily Essentials) July 31, 2002.