Adenosine-Induced Ventricular Arrhythmias in Patients with Supraventricular Tachycardias

Cagatay Ertan, M.D., İlyas Atar, M.D., Oyku Gulmez, M.D., Asli Atar, M.D., Aliseydi Ozgul, M.D., Alp Aydinalp, M.D., Haldun Müderrisoğlu, M.D., and Bülent Özin, M.D.

From the Başkent University, School of Medicine, Department of Cardiology, Ankara, Turkey

Background: Adenosine is widely used for the diagnosis and the termination of supraventricular arrhythmias. There are many case reports and few series about the proarrhythmic potential of adenosine. We sought to evaluate the proarrhythmic potential of adenosine used to terminate the supraventricular arrhythmias.

Methods: The records of all patients that received adenosine for the termination of supraventricular tachycardia were reviewed retrospectively and those with a continuous electrocardiographic (ECG) recording during adenosine administration were included to the study.

Results: Our search identified 52 supraventricular episodes of 46 patients with a continuous ECG recording during adenosine administration. Following adenosine administration, premature ventricular contraction (PVC) or ventricular tachycardia (VT) developed in 22 (47.8%) patients and in 26 (50%) tachycardia episodes. No patient had a sustained VT. Nonsustained VT developed in eight (17.4%) patients. All VT episodes were polymorphic, short, and self-terminating. When the basal and demographic properties of patients with PVC or VT and those without PVT or VT were compared, there was no significant difference.

Conclusions: Adenosine is a quite safe and effective drug for the termination of narrow QRS complex tachycardia but it often induces nonsustained VT or PVC that are clinically insignificant in the absence of other accompanying heart disease.

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adenosine; proarrhythmia; supraventricular arrhythmia

Adenosine is an endogenous purine nucleoside that has become very useful for the diagnosis and treatment of supraventricular arrhythmias. Adenosine has a very short plasma half-life that causes transient atrioventricular (AV) nodal conduction block. For these properties, adenosine is currently used as first-line agent for the differential diagnosis and therapy of both narrow and wide, complex tachycardias.¹

Previously some case reports, and a retrospective study reported proarrhythmias after adenosine administration. These arrhythmias include premature ventricular complex (PVC), monomorphic sustained and nonsustained ventricular tachycardia (VT), torsade de pointes (TdP), premature

atrial complex, atrial fibrillation, and prolonged AV block.^{2–12}

Several clinical trials, published during the past 20 years, have demonstrated the efficacy of adenosine.^{13–18} Nevertheless, a substantial and alarming number of case reports exist signaling untoward and dangerous effects of adenosine, including marked increase in mean ventricular rate,^{19,20} prolonged AV block,^{21–23} atrial fibrillation,^{11,24,25} nonsustained VT,^{5,26,27} TdP,^{7,8,11} and ventricular fibrillation (VF).^{3,9,10} However, the prevalence and characteristics of adenosine-induced proarrhythmia are largely unknown.

Thus, we retrospectively studied all cases of adenosine use for tachycardia management in our

Address for reprints: İlyas Atar, M.D., Başkent Üniversitesi Hastanesi, Kardiyoloji A.B.D., 1. cad. 10. sok. Bahçelievler 06490, Ankara, Turkey. Fax: 0090312 223 73 33; E-mail: ilyasatar@gmail.com

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center over a period of 9 years to assess the proarrhythmic potential of adenosine.

METHODS

Patients

The records of all patients, who received adenosine at Baskent University Ankara Hospital between August 1998 and February 2005 were retrospectively studied. Using computerized hospital data, the files of patients who received adenosine were reviewed. This yielded 205 patients that received adenosine for any reason. Ninety-nine of these patients received adenosine for the treatment of supraventricular tachycardia. Among these patients, those with an ECG recording during adenosine administration were identified. Continuous ECG recording was defined as a recording beginning at least 5 seconds before adenosine administration and continuing at least 30 seconds following conversion or adenosine administration. If continuous ECG recordings during adenosine treatment were not available, the patient was excluded. Fifty-three patients were excluded since an ECG recording during adenosine administration was not available. By means of this review, 52 tachycardia episodes of 46 patients were identified and these 46 patients comprised the study group.

Data Collection

Demographic properties, classification of tachycardia, details of electrophysiologic study if performed, concomitant diseases, heart rate, echocardiographic findings, adenosine dose, and response to treatment were recorded. Classification into tachycardia types was based on electrophysiologic study with or without radiofrequency ablation if performed. If an electrophysiologic study was not performed, and the tachycardia could not be identified by the surface ECG before and after adenosine treatment, the tachycardia was simply classified as supraventricular tachycardia.

In all patients, adenosine was administered as a bolus from a peripheral venous access. None of the patients were receiving any medications known to lengthen QT interval. No patients had preexcitation on surface ECG after converting to sinus rhythm or no accessory pathway was disclosed in patients to whom an electrophysiologic study was performed. QT intervals during tachycardia and after the adenosine treatment were measured on a

standard electrocardiogram by averaging three consecutive beats in leads II and V₄ and corrected for heart rate with Bazett formula.

All ventricular arrhythmias were recorded after adenosine administration. When analyzing adenosine-induced ventricular arrhythmias, VT was defined as three or more consecutive beats of ventricular origin. Ventricular tachycardias with either morphology were classified as monomorphic VT and those with ectopies of both morphologies were classified as polymorphic VT.

Statistical Analysis

The statistical package SPSS (Statistical Package for the Social Sciences, version 9.0, SSPS Inc, Chicago, IL, USA) was used for statistical analyses. Continuous variables are expressed as means $\pm$ SD. Continuous variables were compared using the Mann-Whitney *U* test. For categorical variables, the chi-square test was used. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Of 52 tachycardia episodes in 46 patients, 28 (53.8%) episodes occurred in 23 (50%) women. Forty-one patients had 1, 4 patients had 2, and 1 patient had 3 tachycardia episodes for which adenosine was administered and continuous ECG recordings were taken. Patients had an average age of 58 ± 17 years (range 16–85 years). The most common concomitant disease was hypertension followed in order by coronary artery disease and diabetes mellitus. Demographic properties, concomitant diseases, and drug use in the study group are summarized in Table 1.

Table 1. Baseline Characteristics of Patients

Characteristics	N = 46
Age, years	58 $\pm$ 17
Female, no (%)	23 (50%)
Hypertension	20 (43.5%)
Diabetes mellitus	4 (8.7%)
Coronary artery disease	9 (19.6%)
Smoking	8 (17.4%)
Drug use	
Calcium channel blocker	10 (21.7%)
ACE inhibitor/ARB	14 (30.4%)
Beta-blockers	19 (41.3%)
Mean tachycardia rate, bpm	174 $\pm$ 20
Mean adenosine dose, mg	11.0 $\pm$ 4.6

Table 2. Characteristics of Patients with and without Ventricular Arrhythmias

Characteristics	Patient without Ventricular Arrhythmia (N = 24)	Patient with Ventricular Arrhythmia (N = 22)	P Value
Age, mean	60 ± 18	56 ± 16	0.335
Female gender, n (%)	11 (45%)	12 (54%)	0.768
Hypertension	10 (42%)	10 (45%)	1.0
Diabetes mellitus	2 (8%)	2 (9%)	1.0
Coronary artery disease	6 (25%)	3 (13%)	0.464
Smoking	6 (25%)	2 (9%)	0.247
Drug use			
Calcium channel blocker	5 (21%)	5 (22%)	1.0
ACE inhibitor/ARB	5 (21%)	9 (41%)	0.202
Beta-blockers	9 (37%)	10 (45%)	0.756
Mean tachycardia rate, bpm	173 ± 18	175 ± 22	0.748
Mean adenosine dose	11.3 ± 4.6	10.6 ± 4.6	0.519
QTc duration, msn	413 ± 41	430 ± 43	0.231

Patients presented with an average tachycardia rate of 174 ± 20 beats/min (range between 133 and 214 beats/min). Average adenosine dose administered was 11.0 ± 4.6 mg (range between 6 and 24 mg). Electrophysiologic study was performed in 22 of patients and 17 of these patients were diagnosed as atrioventricular nodal reentrant tachycardia (AVNRT). Adenosine was administered once in 46 and twice in 10 episodes. Of those 10 patients who received adenosine twice, 7 responded to the second dose, remaining 3 (3.5%) patients did not respond to the second adenosine administration. In those who did not respond to the first dose of adenosine administered, no ventricular arrhythmia was noted after the first dose of adenosine.

Following adenosine administration, PVC or VT developed in 22 (47.8%) patients and in 26 (50%) tachycardia episodes. There were 18 episodes of PVC and 8 episodes of NSVT. Of these PVCs, 9 were monomorphic and 17 were polymorphic. Patients had a mean of 5.2 ± 3.7 PVCs (range between 1 and 14 beats). No patient had a sustained VT. Nonsustained VT developed in eight (17.4%) patients. All VT episodes were polymorphic, short, and self-terminating (mean duration 5.6 ± 3.7 beats, range 3–14 beats) with an average rate of 198 ± 46 beats/min (range between 136 and 272 beats/min). Of these VT episodes, 2 (22%) had both right and left bundle branch block morphology, 6 (67%) had right bundle branch block (RBBB) morphology, and 1 (11%) had left bundle branch block (LBBB) morphology. When PVCs were evaluated, we observed that in 9 (50%) episodes, PVCs were monomorphic while the re-

maining 9 (50%) episodes were polymorphic. The 9 polymorphic PVCs consisted of 5 (56%) with a both RBBB and LBBB morphology, 2 (22%) with a RBBB morphology, and 2 (22%) with a LBBB morphology while 9 episodes of monomorphic PVCs consisted of 6 (67%) RBBB morphology and 3 (33%) LBBB morphology. All PVC and VT episodes were post conversion and only one was pause dependent (3120 ms following conversion). When the pause-dependent VT was excluded, the mean time to the onset of PVC-VT following conversion was 791.9 ± 247.3 ms and following adenosine administration was 10.2 ± 3.1 seconds. Demographic characteristics, concomitant systemic diseases, drug usage, mean tachycardia rate, mean adenosine dose, and basal QTc distance were not statistically different in patients with and without ventricular arrhythmias after adenosine administration (Table 2). Four patients received adenosine twice, and one patient received three times. Two of these patients had no ventricular arrhythmias in all episodes and three of them had ventricular arrhythmias at all episodes.

DISCUSSION

Many proarrhythmic effects of adenosine have been described including PVC, monomorphic and polymorphic VT, induction of atrial fibrillation, and prolonged AV block. Adenosine has some direct and indirect effects on atrial, sinoatrial, and AV nodal cells. In the atrial, sinoatrial, and atrioventricular nodal cells, adenosine activates outward potassium current that shortens the atrial action potentials and reduces the effective refractory

periods thus predisposing to the induction of atrial fibrillation.²⁸ In the ventricular myocytes, adenosine blocks the effect of catecholamines that stimulate an inward calcium current through cAMP.²⁹ By doing so, adenosine suppresses most ventricular arrhythmias but adenosine administration is followed by a sympathetic nerve traffic increase and increased catecholamine discharge that may be the cause of proarrhythmic effect.³⁰ Another possible explanation of ventricular proarrhythmia of adenosine may be its effect on purinergic sensitive ventricular neurons.¹⁶

There are many case reports and rare series of adenosine-induced proarrhythmia. Adenosine-induced VT or premature ventricular contractions are not rare but they rarely cause serious adverse outcomes. In cases of life-threatening adenosine-induced VT/VF, the underlying condition is usually acquired or congenital long QT syndrome.² In this situation, low heart rate following adenosine administration may cause TdP. Another clinical situation, where adenosine administration may be catastrophic is the presence of an accessory pathway that is capable of fast antegrade conduction. Adenosine shortens the effective refractory period of the accessory pathway leading to dangerously high ventricular rates in case a paroxysmal atrial fibrillation occurs. Adenosine-induced PVC/VT episodes may be observed in the absence of long QT, but these episodes are short and self-terminating due to the short half-life of adenosine. In this study, we did not observe any clinically significant ventricular arrhythmia in a patient group all of which had normal QT durations and this supports the latter hypothesis.

Adenosine-induced ventricular arrhythmias have been reported to be often but generally clinically insignificant.^{2,31} In one of these series, VT or PVC has been reported in 68% of patients receiving adenosine² nearly all of which were clinically insignificant. In another study, the prevalence of nonsustained VT was reported to be 5%, all of which subsided spontaneously.³¹ In this study, we observed PVC/VT in 47% of patients and nonsustained VT in 17% of patients. No patient required any further intervention due to proarrhythmia. These findings are similar to the previous reports on ventricular proarrhythmia induced by adenosine. We did not observe any cases of atrial fibrillation following adenosine administration. Atrial fibrillation following adenosine administration is reported to be 1% and 6%

in the preceding case series.^{2,31} In most cases, atrial fibrillation developed in patients with atrial flutter.² When the number of patients and the lack of atrial flutter in this series are considered, the absence of atrial fibrillation as proarrhythmia makes sense.

Study Limitations

The main limitation of this study lies in the retrospective nature of it. Because of this, there were many patients without continuous ECG recording during adenosine administration and who, therefore, could not be included to the study. Another limitation is the limited number of patients with an electrophysiologic study to confirm the nature of tachycardia.

CONCLUSIONS

Adenosine is a quite safe and effective drug for the termination of narrow QRS complex tachycardia but it often induces nonsustained VT or PVC that are clinically insignificant in the absence of other accompanying heart disease.

REFERENCES

1. Blomström-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC Guidelines for the management of patients with supraventricular arrhythmias. *Circulation* 2003;108:1871–1909.
2. Tan HL, Speckhorst HHM, Peters RJG, Wilde AAM. Adenosine induced ventricular arrhythmias in the emergency room. *Pacing Clin Electrophysiol* 2001;24:450–455.
3. Gupta AK, Shah PC, Maneshwari A, et al. Adenosine induced ventricular fibrillation in Wolff-Parkinson-White Syndrome. *Pacing Clin Electrophysiol* 2002;25:477–480.
4. Misra D, Tosh AW, Schweitzer P. Adenosine induced monomorphic ventricular tachycardia. *Pacing Clin Electrophysiol* 2000;23:1044–1046.
5. Romer M, Candinas R. Adenosine induced non-sustained polymorphic ventricular tachycardia. *Eur Heart J* 1994;15:281–282.
6. Smith JR, Goldberger JJ, Kadish AH. Adenosine induced polymorphic ventricular tachycardia in adults without structural heart disease. *PACE* 1997;20:743–745.
7. Harrington GR, Froelich EG. Adenosine induced torsades des pointes. *Chest* 1993;103:1299–1301.
8. Wesley RC, Turnquest P. Torsades de pointe after intravenous adenosine in the presence of prolonged QT syndrome. *Am Heart J* 1992;123:794–796.
9. Parham WA, Mehdirad AA, Biermann KM, et al. Case report: Adenosine induced ventricular fibrillation in a patient with stable ventricular tachycardia. *J Interv Card Electrophysiol* 2001;5:71–74.
10. Celiker A, Tokel K, Cil E, et al. Adenosine induced torsades de pointes in a child with congenital long QT syndrome. *PACE* 1994;17:1814–1817.

11. Kaplan IV, Kaplan AV, Fisher JD. Adenosine induced atrial fibrillation precipitating polymorphic ventricular tachycardia. *PACE* 2000;23:140-141.
12. Faulds D, Chrisp P, Buckley MM-T. Adenosine. An evaluation of its use in cardiac diagnostic procedures, and in the treatment of paroxysmal supraventricular tachycardia. *Drugs* 1991;41:596-624.
13. Belhassen B, Pelleg A. Electrophysiologic effects of adenosine triphosphate and adenosine in the mammalian heart: Clinical and experimental aspects. *J Am Coll Cardiol* 1984;4:414-424.
14. Belhassen B, Pelleg A. Acute management of paroxysmal supraventricular tachycardia: Verapamil, adenosine triphosphate or adenosine? *Am J Cardiol* 1984;54:225-227.
15. Belhassen B, Viskin S. What is the drug of choice for the acute termination of paroxysmal supraventricular tachycardia: Verapamil, adenosine triphosphate or adenosine? *Pacing Clin Electrophysiol* 1993;16:1735-1741.
16. DiMarco JP, Miles W, Akhtar M, et al. Adenosine for paroxysmal supraventricular tachycardia: Dose ranging and comparison with verapamil: Assessment in placebo-controlled multi center trials. *Ann Intern Med* 1990;113:104-110.
17. Rankin AC, Oldroyd KG, Chong E, et al. Value and limitations of adenosine in the diagnosis and the treatment of narrow and broad complex tachycardias. *Br Heart J* 1989;62:195-203.
18. Rankin AC, Brooks R, Ruskin JN, et al. Adenosine and the treatment of supraventricular tachycardia. *Am J Med* 1992;92:655-664.
19. Brodsky MA, Hwang C, Hunter D, et al. Life threatening alterations in heart rate after the use of adenosine in atrial flutter. *Am Heart J* 1995;130:564-571.
20. Brodsky MA, Allen BJ, Grimes JA, et al. Enhanced atrioventricular conduction during atrial flutter after intravenous adenosine. *N Engl J Med* 1994;27:288-289.
21. Webster DP, Daar AA. Prolonged bradycardia and seizures following intravenous adenosine for supraventricular tachycardia. *Am J Emerg Med* 1993;192-194.
22. Reed R, Falk JL, O'Brien J. Untoward reaction to adenosine therapy for supraventricular tachycardia. *Am J Emerg Med* 1991;6:566-570.
23. Cowell RPW, Paul VE, Ilsley CDJ. Haemodynamic deterioration after treatment with adenosine. *Br Heart J* 1994;71:569-571.
24. Jaeggi E, Chiu C, Hamilton R, et al. Adenosine-induced atrial pro-arrhythmia in children. *Can J Cardiol* 1999;2:169-172.
25. Exner DV, Muzyka T, Gillis A. Proarrhythmia in patients with the Wolff-Parkinson-White syndrome after standard doses of intravenous adenosine. *Ann Intern Med* 1995;122:351-352.
26. Tachakra SS, Robinson S. Adenosine and cardiac arrhythmias. *Br Med J* 1992;305:422.
27. Hingorani AD, Foley TH. Non-sustained broad complex tachycardia following intravenous adenosine. *J Accident Emerg Med* 1995;3:208-209.
28. Belardinelli L, Isenberg G. Isolated atrial myocytes: Adenosine and acetylcholine increase potassium conductance. *Am J Physiol* 1983;244:H734-H737.
29. Isenberg G, Belardinelli L. Ionic basis for the antagonism between adenosine and the isoproterenol on isolated mammalian ventricular myocytes. *Circ Res* 1984;55:309-325.
30. Biaggioni I, Killian TJ, Mosqueda-Garcia R, et al. Adenosine increases sympathetic nerve traffic in humans. *Circulation* 1991;83:1668-1675.
31. Camaiti A, Pieralli F, Olivotto I, et al. Prospective evaluation of adenosine-induced proarrhythmia in the emergency room. *Eur J Emerg Med* 2001;8:99-105.