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Diagnostic and Therapeutic Use of Adenosine in Patients With Supraventricular Tachyarrhythmias

JOHN P. DiMARCO, MD, PhD, FACC,* T. DUNCAN SELLERS, MD, FACC,‡
BRUCE B. LERMAN, MD,* MARK L. GREENBERG, MD,* ROBERT M. BERNE, MD,†
LUIZ BELARDINELLI, MD*

Charlottesville, Virginia and Danville, Pennsylvania

Adenosine has been shown to affect both sinus node automaticity and atrioventricular (AV) nodal conduction. The effects of increasing doses of intravenous adenosine were assessed in 46 patients with supraventricular tachyarrhythmias. Adenosine reliably terminated episodes of supraventricular tachycardia in all 16 patients with AV reciprocating tachycardia, in 13 of 13 patients with AV nodal reentrant tachycardia and in 1 of 2 patients with junctional tachycardia with long RP intervals. Adenosine produced transient high grade AV block without any effect on atrial activity in six patients with intraatrial reentrant tachycardia, four patients with atrial flutter, three patients with atrial fibrillation and in single patients with either sinus node reentry or an automatic atrial tachycardia. The dose of adenosine required to terminate episodes of supraventricular tachycardia was variable (range 2 to 23 mg). Side effects were minor and of short duration.

These results demonstrate that adenosine is useful for the acute therapy of supraventricular tachycardia whenever reentry through the AV node is involved. When arrhythmia termination is not affected, atrial activity may be more readily analyzed during adenosine-induced transient AV block.

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Since the report by Drury and Szent-Györgyi (1) in 1929, adenosine and several adenine nucleotides have been known to affect the electrophysiologic properties of cardiac tissue. These effects include depression of sinus node automaticity and atrioventricular (AV) nodal conduction, shortening and hyperpolarization of the atrial action potential, decreased automaticity in Purkinje fibers and antagonism of the effects of isoproterenol on the action potential of ventricular myocytes. These actions of adenosine are thought to be mediated directly by the effect of the nucleoside on potassium and calcium conductance as well as indirectly by antagonism of the electrophysiologic actions of intracellular cyclic adenosine-3′5′-monophosphate (2–6). Recently, we reported (7) that adenosine depressed sinus node automaticity and AV nodal conduction after intravenous administration in humans. Because adenosine is cleared from the circulation by cellular uptake and metabolism within seconds after intravenous injection (8), we postulated that its ability to transiently depress AV nodal conduction might enable it to be used for the rapid termination or diagnosis, or both, of supraventricular tachyarrhythmias. This might be of benefit in several situations. The very short duration of action of adenosine is of potential benefit in the electrophysiology laboratory because the drug can be administered repetitively without persistent effects that might influence the subsequent course of the study. In the acute clinical setting, the rapid clearance of adenosine from plasma permits the nucleoside to be administered without concern for long-lasting or cumulative adverse reactions.

In an earlier report (7), we described the electrophysiologic effects of adenosine in patients undergoing electrophysiologic studies, including some preliminary observations in six patients with supraventricular tachycardia. Our current study describes our observations on the effects of intravenous adenosine in 46 patients with supraventricular arrhythmias studied to date. These data allow a more com-

From the Departments of *Medicine and †Physiology, University of Virginia School of Medicine, Charlottesville, Virginia and the ‡Clinical Electrophysiology Laboratory, Geisinger Medical Center, Danville, Pennsylvania. This project was supported by Grant HL-10384 from the National Institutes of Health, Bethesda, Maryland and Grant-in-aid 81-911 from the American Heart Association, Virginia Affiliate, Richmond, Virginia. Dr. Belardinelli is the recipient of Research Career Development Award 1 K04 HL00969-01 from the National Institutes of Health, Bethesda, Maryland. Dr. Sellers is the recipient of Fellowship Award 3-31757 from the American Heart Association, Virginia Affiliate, Richmond, Virginia. Manuscript received November 6, 1984; revised manuscript received March 4, 1985, accepted March 15, 1985.

Address for reprints: John P. DiMarco, MD, Box 158, Department of Medicine, University of Virginia, Charlottesville, Virginia 22908.

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plete characterization of the dose-response relation of adenosine, its site of action, its potential for toxicity and the spectrum of responses when it is administered to patients with supraventricular tachyarrhythmias.

Methods

Study patients. The study group included 46 patients (26 male and 20 female) ranging in age from 10 to 85 years. Pertinent clinical characteristics are listed in Table 1. Patients were studied while undergoing electrophysiologic study (35 patients), during a spontaneous episode of clinical tachycardia in the emergency room or their hospital room (9 patients) or in both settings on separate occasions (2 patients).

Electrophysiologic studies. Electrophysiologic studies were performed with the patient in the fasting, nonsedated state after informed consent had been obtained. Four 6F quadripolar electrode catheters (USCI) with a 0.5 or 1.0 cm interelectrode distance were introduced by way of the femoral, antecubital, subclavian or internal jugular vein and advanced to the heart under fluoroscopic guidance. The catheters were positioned in the high right atrium, across the AV valve in a position that permitted reliable recording of the His bundle potential, and in the right ventricular apex. Left atrial activity was recorded with an electrode catheter that was placed either in the coronary sinus or in the left atrium by way of a patent foramen ovale. Intracardiac electrograms were filtered at less than 30 and greater than 500 Hz and were displayed simultaneously with scalar electrocardiographic leads I, II and V_1 on a multichannel oscilloscope (Electronics for Medicine, VR-16). Signals were stored on frequency-modulated magnetic tape (Honeywell model 101) and recordings reproduced for analysis on an ink-jet recorder (Mingograf-16, Siemens Medical Products). Programmed cardiac stimulation was performed using a programmable constant current stimulator (Medtronic 5325 or Bloom DTU-101) that delivered rectangular pulses 2 ms in duration at four times diastolic threshold.

The protocol for atrial and ventricular stimulation has been previously described (9). Arrhythmia mechanisms were determined on the basis of local electrogram activation patterns and responses to stimulation according to standard criteria (10).

Systemic blood pressure was continuously monitored throughout the study using an intraarterial cannula placed in a radial or femoral artery and connected to a Statham P23-ID pressure transducer (Gould Medical Products).

Patients studied in other settings. Eleven patients with supraventricular arrhythmias who were seen in the emergency room as outpatients or in the hospital were invited to participate in the trial. In each case, a 12 lead electrocardiogram and a medication history were obtained. Carotid sinus massage was performed before adenosine administration in all patients, but this did not result in arrhythmia termination or increased AV block. Arrhythmia mechanisms were tentatively classified by surface electrocardiographic criteria, by data obtained at a prior or subsequent electrophysiologic study or by analysis of atrial activity in tachycardia during adenosine-induced AV block (10). Adenosine was then administered intravenously.

Adenosine administration. Crystalline adenosine (Sigma Chemical Co.) was dissolved in normal saline solution in a concentration of 5 or 10 mg/ml. The solution was prepared under sterile conditions. Adenosine concentrations in the injectate were confirmed by high pressure liquid chromatography (11).

In all patients, adenosine was injected rapidly into a peripheral intravenous catheter and flushed in with 10 ml of saline solution. Pilot experiments had indicated that the speed and the site (central versus peripheral) of injection markedly influenced individual responsiveness to a given dose of adenosine. This finding is consistent with the fact that adenosine is cleared from the circulation by uptake and metabolism by cellular elements of blood and vascular endothelium with a half-time of less than 10 seconds (8). The initial injection used was 37.5 μg/kg. If no effect was observed within 60 seconds, a second injection of 75 μg/kg was administered. This process of increasing the dose with equal 37.5 μg/kg increments (37.5, 75, 112.5, and so on) was continued until either tachycardia termination or AV block was observed. In one patient, there was no electrophysiologic effect after injection of adenosine at any dose up to 450 μg/kg, and higher doses were not administered. This patient had been receiving theophylline for chronic obstructive pulmonary disease and her theophylline serum concentration was 19.4 μg/ml (1×10^{-4} M). This concentration of theophylline will block the electrophysiologic effects of adenosine in the isolated heart (12). In each patient studied in the electrophysiology laboratory, adenosine was administered during at least 2 (range 2 to 15) episodes of tachycardia. Patients studied outside the electrophysiologic laboratory received adenosine only once if arrhythmia termination occurred. In selected patients, adenosine was also administered during either sinus rhythm or atrial or ventricular pacing and its effects on AV conduction were also assessed.

All procedures in this study were approved by and conformed to the guidelines of the Human Investigations Committee of the University of Virginia.

Results

AV reciprocating tachycardia. Sixteen patients had an accessory AV pathway with orthodromic reciprocating tachycardia. Of these 16 patients, 8 (Cases 39 to 46) demonstrated preexcitation either during sinus rhythm or with atrial stimulation. The remaining eight (Cases 24 to 31) had a concealed bypass tract that demonstrated only retrograde

Table 1. Patient Characteristics

Case	Age (yr) & Sex	Arrhythmia Mechanism	Atrial CL	Effect of Adenosine	Dose (μg/kg)	Dose (mg)	Time (seconds) to Effect	Adverse Reaction	Other Therapy
1	55M	AAT	420	AV block	37.5	3.3	6		Dig, Ver
2	55F	AF	—	AV block	225	20.6	15	Flush	Dig
3	55M	AF	—	AV block	112.5	14.6	10		Dig
4	66F	AF	—	AV block	75	4.3	15		Dig
5	51M	AFl	190	AV block	187.5	15.6	21		
6	73F	AFl	230	AV block	112.5	8.7	26	Dyspnea	Dig, Quin
7	77M	AFl	260	AV block	75	5.0	15		Dig, Quin
8	84M	AFl	200	AV block	75	6.2	25		
9	72F	JTLRP	300	None	450	19.0	—		Theophylline
10	10F	JTLRP	335	Termination	150	4.2	17		
11	69M	AVNRT	330	Termination	187.5	11.5	26	Dyspnea	
12	73M	AVNRT	360	Termination	75	5.0	12	Flush	
13	82M	AVNRT	360	Termination	75	6.0	23		
14	42F	AVNRT	380	Termination	37.5	2.5	22	Flush	
15	68M	AVNRT	450	Termination	187.5	13.1	29		
16	38F	AVNRT	270	Termination	75	3.3	12		
17	61M	AVNRT	445	Termination	75	8.2	17		
18	70F	AVNRT	400	Termination	37.5	3.4	24		
19	56F	AVNRT	320	Termination	75 or 112.5	4.7 or 7	15	Dyspnea	
20	51F	AVNRT	400	Termination	75	5	24	Flush, dyspnea	
21	59M	AVNRT	400	Termination	37.5	3.2	20		
22	82F	AVNRT	370	Termination	37.5	4.9	18		
23	60M	AVNRT	500	Termination	37.5	4.4	9		
24	25F	AVRT-CBT	335	Termination	150	12.8	15	Flush	
25	72M	AVRT-CBT	350	Termination	75	3.1	33		Dig
26	85F	AVRT-CBT	500	Termination	75	4.4	21		Dig
27	70F	AVRT-CBT	420	Termination	75	5	22		Dig, Ver, Prop
28	59M	AVRT-CBT	350	Termination	287.5	23	25		
29	67F	AVRT-CBT	350	Termination	37.5 or 75	2.8 or 5.6	23	Dyspnea	
30	59M	AVRT-CBT	340	Termination	75 or 112.5	5.8 or 8.7	19		
31	55M	AVRT-CBT	310	Termination	75	6.4	25	Flush	Dig, Amio
32	75M	IART	305	AV block	112.5	7.5	18		
33	41M	IART	340	AV block	37.5 or 75	3.3 or 6.6	14		
34	64M	IART	310	AV block	225	25	24		Dig
35	31M	IART	260	AV block	187.5	8.5	30		
36	70F	IART	380	AV block	112.5	7.5	23	Dyspnea	
37	47M	IART	310	AV block	112.5	7.2	18		
38	55F	SNRT	400	AV block	37.5	3.4	24	Flush	
39	34M	AVRT-WPW	380	Termination	37.5 or 75	3.5 or 7	21		
40	16M	AVRT-WPW	470	Termination	37.5	2.5	24	Dyspnea	
41	31F	AVRT-WPW	370	Termination	75	15.9	20	Dyspnea	
42	48M	AVRT-WPW	260	Termination	75	7.2	21		
43	61M	AVRT-WPW	360	Termination	112.5 or 150	7.9 or 10.5	20		
44	17F	AVRT-WPW	340	Termination	37.5	2	14		Quin
45	34F	AVRT-WPW	280	Termination	112.5 or 150	5.1 or 6.8	21	Dyspnea	Ver, Diso
46	38F	AVRT-WPW	410	Termination	75	4.8	22		

AAT = automatic atrial tachycardia; AF = atrial fibrillation; AFl = atrial flutter; Amio = amiodarone; AV = atrioventricular; AVNRT = AV nodal reentrant tachycardia; AVRT-CBT = AV reciprocating tachycardia with concealed bypass tract; CL = cycle length; Dig = digoxin; Diso = disopyramide; F = female; IART = intraatrial reentrant tachycardia; JTLRP = junctional tachycardia with a long RP interval; M = male; Prop = propranolol; Quin = quinidine; SNRT = sinus node reentrant tachycardia; Ver = verapamil; WPW = Wolff-Parkinson-White syndrome.

ventriculoatrial (VA) conduction. The tachycardia cycle lengths during supraventricular tachycardia ranged from 260 to 500 ms (358 ± 33, mean ± SD). Adenosine at a dose of 91 ± 52 μg/kg terminated every episode of supraventricular tachycardia. A characteristic pattern of response was observed in each patient (Fig. 1). The tachycardia cycle length remained constant immediately after injection of adenosine. Ten to 30 seconds after injection, there was a slight lengthening of the tachycardia cycle length and a slight increase in the arterial blood pressure. The tachycardia would then terminate and the arterial pressure would return to normal with resumption of sinus rhythm. The actual doses

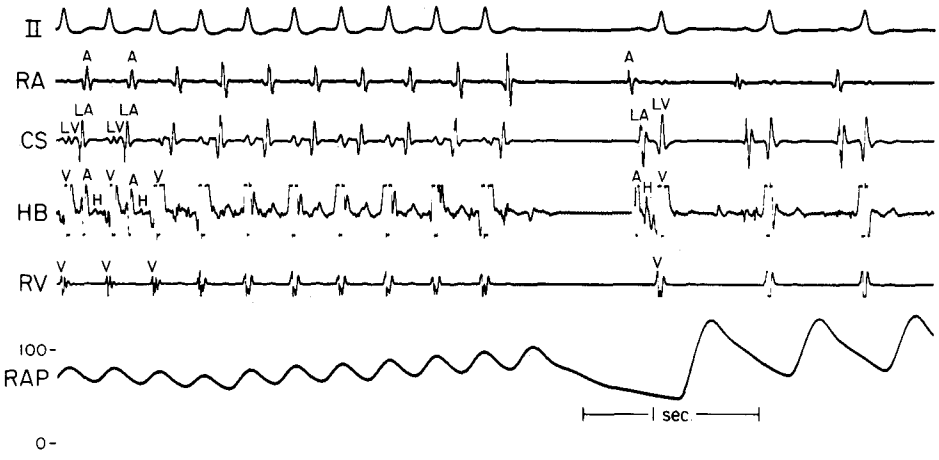

Figure 1. Case 42. Termination of AV reciprocating tachycardia with intravenous adenosine. The recordings were obtained during electrophysiologic study in a patient who had a left-sided accessory pathway. The tracings begin 18 seconds after adenosine injection and represent, from **top to bottom**, surface electrocardiographic lead II, intracardiac recordings from the right atrium (RA), coronary sinus (CS), bundle of His (HB) and right ventricle (RV) and a radial artery pressure (RAP) recording. The tachycardia terminates with block in the AV node 22 seconds after adenosine injection. Note the improvement in arterial pressure associated with arrhythmia termination. LA = left atrium; LV = left ventricle.

required for termination of the supraventricular tachycardia ranged from 2 to 23 mg (6 ± 4). Tachycardia termination occurred 21.5 ± 3 seconds after injection of adenosine. In all cases the reentrant circuit was broken by block during anterograde conduction through the AV node.

We also observed that adenosine could be used to test for the presence of preexcitation in patients with atypical manifestations of preexcitation or with only intermittent preexcitation on the surface electrocardiogram. In such patients, atrial pacing was continued during adenosine administration to eliminate the negative chronotropic effects of adenosine on the sinus node. After adenosine injection, preexcitation became more readily apparent as the contribution to ventricular activation from conduction over the AV node and His-Purkinje system was eliminated. No change in the interval between the stimulus and the onset of the delta wave during atrial pacing or in the AV interval during ventricular pacing was noted in the patients in this series with an accessory pathway.

AV nodal reentrant tachycardia. Thirteen patients (Cases 11 to 23) had AV nodal reentrant tachycardia involving anterograde conduction over a slow pathway and retrograde conduction over a fast pathway. As in the patients with AV reciprocating tachycardia, adenosine at a dose of 80 ± 47 μg/kg (5.8 ± 2.9 mg) uniformly terminated every episode of tachycardia. The time between injection and termination was also similar (19 ± 6 seconds) in both groups of patients. Intracardiac recordings showed that the block that terminated the arrhythmia could occur either during anterograde slow (5 patients), retrograde fast (2 patients) or either slow or fast (2 patients) pathway conduction (Fig. 2).

Junctional tachycardia with long RP intervals. Two patients (Cases 9 and 10) with junctional tachycardia with long RP intervals were studied. In one patient, two separate

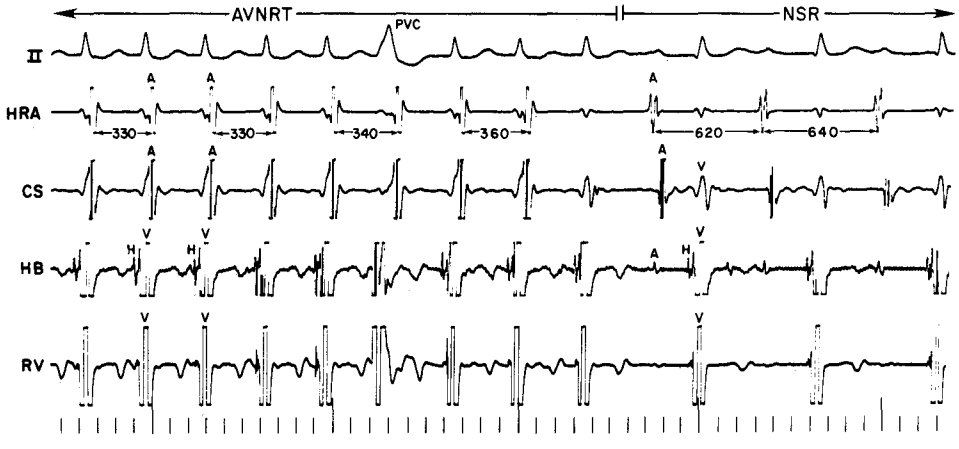

Figure 2. Case 9. Effect of adenosine on AV nodal reentrant tachycardia (AVNRT). The tracings begin 11 seconds after injection of adenosine (75 μg/kg). The lack of atrial activation after the last ventricular beat of the tachycardia indicates that the tachycardia is terminated by block during retrograde conduction. Note the prompt resumption of sinus rhythm after the tachycardia was broken. AV nodal reentrant tachycardia was observed to terminate during either anterograde or retrograde conduction in this series. HRA = high right atrium; NSR = normal sinus rhythm; PVC = premature ventricular complex; other abbreviations as in Figure 1. Time lines are at 100 ms intervals.

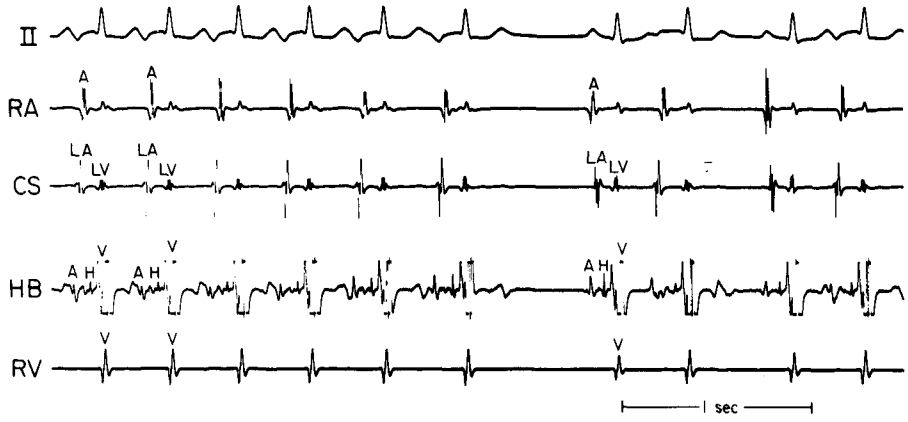

Figure 3. Case 10. Effect of adenosine on junctional tachycardia with a long RP interval. The tracings were obtained during electrophysiologic study and are labeled as in Figures 1 and 2. They begin 14 seconds after adenosine injection. The tachycardia is seen to terminate with block during retrograde conduction. Note that the second and fourth beats after tachycardia termination are echo beats. In this patient with an incessant tachycardia, the tachycardia resumed within seconds after these tracings. This was not observed in patients without incessant arrhythmias.

episodes of tachycardia were terminated with adenosine (Fig. 3). On both occasions, block occurred in the retrograde limb of the tachycardia circuit. In the other patient (Case 9), adenosine, up to a dose of 450 μg/kg, produced no effect on the tachycardia. This patient had been receiving a sustained release theophylline preparation and had a theophylline plasma concentration of 19.4 μg/ml (1×10^{-4} *M*) at the time of study.

Intraatrial reentrant tachycardia. Six patients (Cases 32 to 37) in this series demonstrated supraventricular tachycardia due to intraatrial reentry. Atrial cycle lengths during tachycardia in the absence of antiarrhythmic drugs ranged from 250 to 380 seconds (319 ± 36). Adenosine administration did not terminate any of these arrhythmias and did not affect atrial cycle length. In each case, however, second degree AV block within the AV node could be induced by adenosine administration at a mean dose of 127 ± 65 μg/kg (9.4 ± 7 mg). Second degree AV block occurred 23 ± 10 seconds after injection. In several patients whose P wave configuration was indistinct on the surface electrocardiogram, adenosine-induced AV block allowed clear visualization of atrial activity as well as differentiation between the P wave during tachycardia and that during normal sinus rhythm.

Other arrhythmias. One patient (Case 38) with sinus node reentrant tachycardia was studied. In this patient, adenosine at a dose of 37.5 μg/kg (3.4 mg) produced 2:1 AV block (Fig. 4). The next higher dose of 75 μg/kg produced a higher grade block. The atrial activation sequence and cycle length did not change. Increased doses could not be given to this patient because dyspnea occurred with administration of the larger dose.

High grade AV block without alteration of the pattern of atrial activity was also produced by adenosine injection in four patients with atrial flutter (Cases 5 to 8), in one patient with automatic atrial tachycardia (Case 1) and in three patients with atrial fibrillation (Cases 2 to 4). No effect on atrial activity was observed in these eight patients. As shown in Figure 5, the higher grade AV block seen transiently after adenosine injection frequently facilitated analysis of the mechanism of the arrhythmia from the surface electrocardiogram.

Adverse effects. Nine (20%) of 46 patients reported transient dyspnea at the time when their arrhythmia was broken by adenosine. Seven (15%) also reported flushing. All of these symptoms were described as minor and lasted only a few seconds. In two patients who received adenosine during supraventricular tachycardia at doses of the nucleoside higher than those required to produce either tachycardia termination or AV block, atrial flutter or fibrillation was observed. In both of these patients, the new arrhythmia lasted less than 1 minute. None of the 11 patients studied

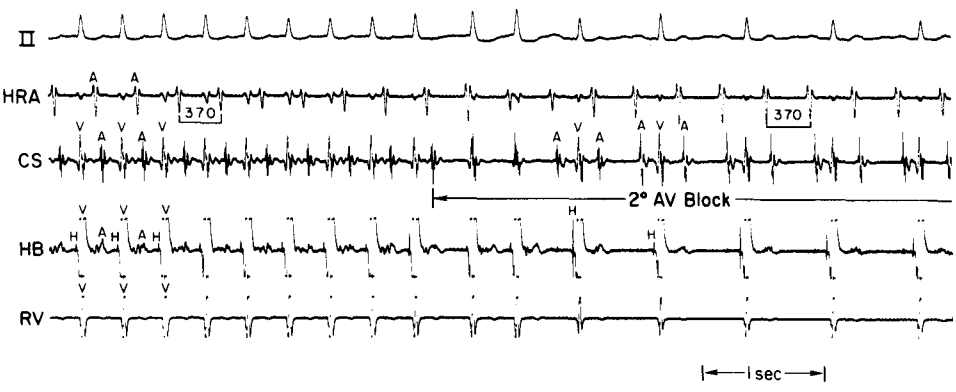

Figure 4. Case 38. Effect of adenosine on sinus node reentrant tachycardia. The tracings are labeled as in Figures 1 and 2. Adenosine (37.5 μg/kg) injected 17 seconds before the start of the tracing produces transient second degree AV nodal block. In this case, atrial activation and P wave configuration were identical to those observed during sinus rhythm.

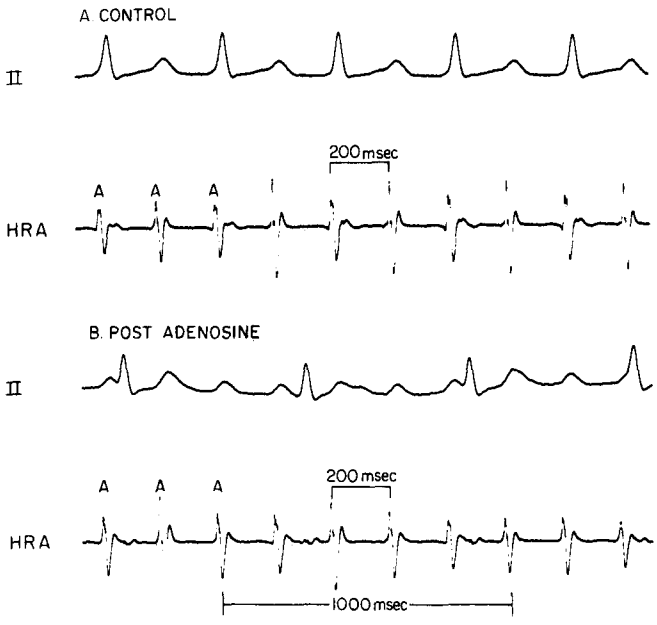

Figure 5. Case 8. Effect of adenosine on atrial flutter. The clinical diagnosis made in the emergency room was AV nodal reentrant tachycardia because atrial activity could not be defined on the initial electrocardiogram. The patient received adenosine and the correct diagnosis of atrial flutter was then made. The tracings shown here were obtained during a second adenosine trial after a pacing catheter had been positioned in the high right atrium (HRA) in an attempt to terminate the arrhythmia with rapid atrial pacing. Abbreviations as in Figure 1.

during a spontaneous clinical episode of arrhythmia developed a second atrial tachyarrhythmia after adenosine.

Three patients with recurrent supraventricular tachycardia also had clinically manifested sinus node dysfunction. When their previously inserted ventricular demand pacemaker was inhibited or reprogrammed to the slowest possible rate, periods of 2 to 5 seconds of sinus arrest were observed after termination of the supraventricular tachycardia episode by adenosine. These pauses were similar to those observed in the same patients after atrial pacing during measurement of the sinus node recovery time or after supraventricular tachycardia termination with atrial burst pacing. In all the other patients, sinus rhythm resumed promptly after termination of supraventricular tachycardia.

Drug interactions. Patients who received adenosine at the time of electrophysiologic study had their previous antiarrhythmic therapy terminated. However, patients studied during clinical episodes of arrhythmia were frequently taking antiarrhythmic drugs, and some patients received an antiarrhythmic drug during the course of electrophysiologic study and then received a subsequent adenosine trial if supraventricular tachycardia could be reinitiated. In the entire series, 11 patients had received therapeutic doses of digoxin, 3 of verapamil, 1 of propranolol, 3 of quinidine, 1 of disopyramide and 1 of amiodarone before at least one administration of adenosine. No adverse interactions were noted. Only six patients received adenosine at their electrophysiologic study both before and after administration of a second drug. Although we did not observe any change in the dosage of adenosine required for effect in these patients, this number is too small to exclude any possibility of synergistic or antagonistic drug interactions. Four patients received atropine (0.02 or 0.03 mg/kg) before at least one adenosine trial. Atropine did not affect the response to adenosine. One patient (Case 9), as described previously, was receiving sustained release theophylline. She had no electrophysiologic response after doses of adenosine up to and including 450 μg/kg.

Discussion

Therapeutic efficacy. Our data indicate that in humans, adenosine administration provides a rapid and effective method for terminating individual episodes of supraventricular tachycardia whenever intact AV nodal conduction is a required part of the reentrant circuit. Tachycardia termination was produced during the first pass of the injected adenosine bolus through the heart. The duration of the adenosine effect was brief and neither unanticipated sinus node depression nor arterial hypotension was observed after termination of the tachycardia. Patients in this series whose arrhythmias did not require intact AV nodal conduction for their continuation manifested only increased AV block in response to adenosine.

Dosage requirements. In this study we determined the minimal effective dose for each patient. There was a 7-fold range of effective doses when calculated on the basis of milligrams of adenosine per kilogram body weight and a 10-fold range when only the number of milligrams required was considered. Several factors may account for these observations. Because adenosine begins to be cleared from the circulation immediately after injection and plasma clearance is complete in less than a minute, the speed of injection, the circulation time from the site of injection to the heart and the central volume in which the bolus mixes will all affect the concentration of adenosine that reaches the cardiac adenosine receptor. The effects of each of these variables on the concentration of adenosine that reached the heart in each patient could not be determined. We did not attempt to measure adenosine concentrations in plasma because this rapid clearance of adenosine from plasma would continue during withdrawal of the sample unless an adenosine uptake inhibitor had previously been administered. Although the electrophysiologic action of adenosine is not dependent on muscarinic or adrenergic receptors, another factor that might account for the wide range of effective doses is the level of adrenergic or vagal tone that might noncompetitively antagonize or enhance the effects of adenosine. For these reasons, wide interindividual dosage requirements were not

unexpected and this variability of response makes prediction of a uniform optimal dose for all patients difficult. However, in patients who received the drug more than once, the dose required for arrhythmia termination was relatively constant for each patient at any point in time.

The need to individualize dosage for each patient is an important factor that must be considered before adenosine is widely used clinically. Overdosage might lead to prolonged asystole, hypotension or other tachyarrhythmias. Even though the direct effects of adenosine are quite brief, their duration seems to be proportional to the dose in each patient and these side effects could be serious in certain patients. However, when we used gradually increasing doses and administered only the minimal effective dose for each patient, no serious cardiac side effects were observed in well over 100 trials in the 46 patients reported here. In clinical practice, the rapid uptake and metabolism of adenosine would permit the physician to individualize the dose for each patient by simply starting with a relatively low dose of approximately 30 to 40 μg/kg for peripheral injection and then increasing the dose at 1 minute intervals until the desired effect was produced. Lower doses should be used for central administration due to the decreased circulation time before the bolus reaches the heart. We estimate that almost all episodes of supraventricular tachycardia could be effectively managed in this fashion within 5 minutes of the first adenosine injection.

Although the rapid uptake and metabolism of adenosine allow easy dose titration, they also limit the potential usefulness of the drug. All trials reported in this study involved intravenous administration of a single bolus. It is unlikely that either an oral or intramuscular route of administration would prove effective. In addition, the brief duration of action of adenosine makes it unlikely that the compound itself would be useful for chronic prophylaxis or for the control of ventricular rates in rhythms originating above the AV node. The development of longer-acting adenosine analogs might permit chronic therapy, but unless an analog specific for the AV nodal adenosine receptor is developed, the chronic adenosine-like activity of the analog in the many organs in which adenosine plays an important physiologic role would have to be considered.

Comparison with other agents. The use of intravenous verapamil and other calcium antagonists for the acute therapy of supraventricular tachycardia has largely replaced the use of digitalis, propranolol, edrophonium, vasoconstrictor agents and cardioversion (13). Verapamil has a high success rate and is usually well tolerated. However, verapamil may produce systemic hypotension and depress ventricular contractility. Should these side effects occur, they may persist for minutes or hours until the drug is cleared from the circulation.

Our series is not the first to use a purinergic compound for treating atrial arrhythmias. An injectable preparation of adenosine triphosphate (ATP) is available in some European countries and is under investigation in the United States for the therapy of supraventricular tachycardia (Striadyne, Laboratories Auclair; ATP-Ormonoterapia, Richter). It was originally postulated that ATP terminated supraventricular tachycardia by delivering a "high energy shock" to the heart (14). Recent studies in our laboratory (15) have demonstrated that the significant components of the actions of ATP are produced in most species, including humans, after its conversion to adenosine. The studies describing the efficacy of intravenous ATP for terminating supraventricular tachycardia have all employed relatively fixed doses of the drug (6,16–20). In contrast, we used gradually increasing doses of adenosine to achieve maximal efficacy with minimal toxicity and observed that a wide range of doses was required. In this study, all arrhythmia episodes that required intact AV nodal conduction with one exception were terminated with only minor side effects. We anticipate that a similar protocol for dosage adjustment that employed ATP rather than adenosine would produce the same results. Even with these reservations, the use of ATP has compared quite favorably with the use of digoxin or verapamil for treating supraventricular tachycardia (19).

Contraindications. The advantage of the very short duration of action of adenosine should not be considered applicable to patients who were receiving an agent (for example, dipyridamole) that markedly affects adenosine metabolism. At present we cannot give dosage guidance for use in such patients.

Our data suggest that there would be few other contraindications to the use of adenosine in patients with supraventricular tachycardia. Long sinus node pauses were observed in patients with previously documented sinus node dysfunction, but these were also noted when other modes of arrhythmia termination were employed. Atrial flutter or fibrillation was only noted when doses higher than necessary for supraventricular tachycardia termination or AV block were used. Nevertheless, caution should be exercised when adenosine is used in patients capable of rapid AV conduction. The only common adverse reactions, dyspnea and flushing, which were reported by one-third of the patients, were very mild and lasted only a few seconds. These side effects are presumably due to the direct actions of adenosine as a weak bronchoconstrictor (21) and cutaneous vasodilator (22).

Diagnostic uses. In addition to its potential use for treating individual episodes of supraventricular tachycardia that involve the AV node, adenosine administration may facilitate the diagnosis in patients with other mechanisms of arrhythmia. On the basis of in vitro data (2), we postulate that arrhythmias due to some types of triggered automaticity should also respond, although no patient with such an arrhythmia was available for inclusion in this series. In patients with a supraventricular arrhythmia that does not re-

quire AV nodal conduction, adenosine will not produce arrhythmia termination, but the high grade AV nodal block that it causes will allow a clear demonstration of atrial activity. This may prove useful as a diagnostic maneuver in some patients with intraatrial reentry, atrial flutter or fibrillation and those with multiple accessory pathways.

Although we were able to assess the effects of adenosine in only single patients with sinus node reentrant tachycardia, junctional tachycardia with a long RP interval or automatic atrial tachycardia, the results obtained may offer insights into the mechanisms of these arrhythmias. Adenosine has marked effects on sinus node automaticity at the same concentrations in humans which affect AV nodal conduction (9). In our patient with sinus node reentrant tachycardia, adenosine did not affect atrial activity but did produce AV block. This finding suggests that the conduction abnormality responsible for sinus node reentry either is within the node itself but has a different response from sinus node automaticity to adenosine, or that the arrhythmia in this patient arose at the sinoatrial junction.

The results in the patient with junctional reciprocating tachycardia with a long RP interval are of interest. This arrhythmia has been postulated to involve anterograde conduction over the AV node and retrograde conduction over an accessory AV node, a slow dual AV nodal pathway or, as recently demonstrated, a septal accessory pathway with decremental conduction (23–26). Adenosine interrupted the tachycardia in our patient during retrograde conduction. This would suggest that accessory pathways with decremental conduction, unlike those in our other patients, are sensitive to adenosine. The recent report by Perrot et al. (27) that some accessory pathways with long anterograde refractory periods are sensitive to adenosine triphosphate supports this hypothesis.

Atrial activity in our patient with automatic atrial tachycardia was also unaffected by adenosine administration. This patient had cardiac metastases from a mediastinal carcinoma. We postulated that his arrhythmia was caused by local invasion of the atrium and our results suggest that increased automaticity in this setting is not sensitive to adenosine.

Conclusions. It has only been recently recognized that adenosine may have an important role as an endogenous local regulator of cardiac electrophysiology. The data presented here indicate that an appreciation of the electrophysiologic properties of adenosine may permit more effective diagnostic evaluation and therapy of patients with supraventricular arrhythmias. Adenosine has a predictable onset of action, is highly effective in arrhythmias that require AV nodal conduction and has only minor toxicity. The use of adenosine in the acute treatment of supraventricular tachycardia represents an effective alternative to the present modes of therapy.

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References

1. Drury AN, Szent-Györgyi A. The physiological action of adenine compounds with especial reference to their action on the mammalian heart. J Physiol (Lond) 1929;68:214–37.
2. Belardinelli L, Isenberg G. Actions of adenosine and isoproterenol on isolated mammalian ventricular myocytes. Circ Res 1983;53:287–97.
3. Belardinelli L, Isenberg G. Isolated atrial myocytes: adenosine and acetylcholine increase potassium conductance. Am J Physiol 1983;234:H734–7.
4. Rosen MR, Danilo P Jr, Weiss RM. Actions of adenosine on normal and abnormal impulse initiation in canine ventricle. Am J Physiol 1983;244:H715–21.
5. Rardon DP, Bailey JC. Adenosine attenuation of the electrophysiologic effects of isoproterenol on canine cardiac Purkinje fibers. J Pharmacol Exp Ther 1984;228:792–8.
6. Belhassen B, Pellig A. Electrophysiologic effects of adenosine triphosphate on the mammalian heart: clinical and experimental aspects. J Am Coll Cardiol 1984;4:414–24.
7. DiMarco JP, Sellers TD, Berne RM, West GA, Belardinelli L. Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. Circulation 1983;68:1254–63.
8. Ontyd J, Schrader J. Measurement of adenosine, inosine and hypoxanthine in human plasma. J Chromatogr 1984;307:404–9.
9. DiMarco JP, Harthorne JW, Garan H, Ruskin JN. Intracardiac electrophysiology in patients with recurrent syncope. Ann Intern Med 1981;95:542–8.
10. Josephson ME, Seides SF. Supraventricular tachycardia. In: Clinical Cardiac Electrophysiology: Techniques and Interpretations. Philadelphia: Lea & Febiger, 1979:147–90.
11. Hartwick RA, Assenza SP, Brown PR. Identification and quantification of nucleosides, bases and other UV-absorbing compounds in serum using reversed-phased high performance liquid chromatography. I. Chromatographic methodology. J Chromatogr 1979;86:647–58.
12. Berlardinelli L, Fenton RA, West A, Linden J, Althaus JS, Berne RM. Extracellular action of adenosine and the antagonism by aminophylline on the atrioventricular conduction of isolated perfused guinea pig and rat hearts. Circ Res 1979;51:569–79.
13. Gettes LS, Foster JR, Simpson RJ Jr. Clinical use of antiarrhythmic drugs. In: Rosen MR, Hoffman BF, eds. Cardiac Therapy. Boston: Martinus Nijhoff, 1983:235–98.
14. Green HN. Biochemical factors in the aetiology of "shock." Br Med Bull 1945;3:102–5.
15. Belardinelli L, Shyrock J, West GA, DiMarco JP, Berne RM. Effects of adenosine and adenine nucleotides on the atrioventricular node of isolated guinea pig hearts. Circulation 1984;70:1083–91.
16. Somlo E. Adenosine triphosphate in paroxysmal tachycardia (letter). Lancet 1955;1:1125.
17. Komor K, Garas Z. Adenosine triphosphate in paroxysmal tachycardia (letter). Lancet 1955;2:93–4.
18. Coumel P, Motte G, Gourgon R, Fabiato A, Scama A, Bouvrain Y. Les tachycardies supra-ventricularies par rhythme reciproque en dehors in syndrome de Wolff-Parkinson-White. Arch Mal Couer 1970;63:35–73.
19. Greco R, Musto B, Arienzo V, Alborino A, Garofala S, Marsico F. Treatment of paroxysmal supraventricular tachycardia in infancy with digitalis, adenosine-5′-triphosphate, and verapamil: a comparative study. Circulation 1982;66:504–8.
20. Belhassen B, Pelleg A, Shoshani D, Geva B, Laniado S. Electro-

physiologic effects of adenosine-5′-triphosphate on atrioventricular reentrant tachycardia. Circulation 1983;68:827–33.

21. Cushley MG, Tattersfield AE, Holgate ST. Inhaled adenosine and guanosine on airway resistance in normal and asthmatic subjects. Br J Clin Pharmacol 1985;15:161–5.

22. Berne RM, Winn HR, Knabb RM, Ely SW, Rubio R. Blood flow regulation by adenosine in heart brain and skeletal muscle. In: Berne RM, Rall TW, Rubio R, eds. Regulatory Function of Adenosine. Boston: Martinus Nijhoff, 1983:293.

23. Wolff GS, Sung RJ, Pickoff A, et al. The fast:slow form of atrioventricular nodal reentrant tachycardia in children. Am J Cardiol 1979;43:1181–8.

24. Epstein ML, Stone FM, Benditt DG. Incessant atrial tachycardia in childhood: association with rate-dependent conduction in an accessory pathway. Am J Cardiol 1979;44:498–504.

25. Guarnieri T, Sealy WC, Kasell JH, German LD, Gallagher JJ. The nonpharmacologic management of the permanent form of junctional reciprocating tachycardia. Circulation 1984;69:269–77.

26. Critelli G, Gallagher JJ, Monda V, Coltori F, Scherillo M, Rossi L. Anatomic and electrophysiologic substrate of the permanent form of junctional reciprocating tachycardia. J Am Coll Cardiol 1984;4:601–10.

27. Perrot B, Clozel JP, Faivre G. Effect of adenosine triphosphate on the accessory pathways. Eur Heart J 1984;5:382–93.