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Intravenous adenosine in the treatment of supraventricular tachycardia: a dose-ranging study and interaction with dipyridamole

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Increasing doses of adenosine were given by rapid intravenous bolus to seven patients with spontaneous supraventricular tachycardia. Adenosine restored sinus rhythm in 10 of 14 episodes of narrow complex tachycardia. In those patients in whom adenosine produced only transient ventricular slowing the underlying rhythm was atrial flutter. Transient dyspnoea occurred in all patients. In two patients taking dipyridamole the mean dose of adenosine which produced an electrophysiologic effect (restoration of sinus rhythm or ventricular slowing to under 100 beats min^{-1}) was 1.0 ± 0.52 mg, whereas in other patients the mean dose was 8.8 ± 2.6 mg, suggesting potentiation of the action of adenosine by dipyridamole.

Keywords adenosine dipyridamole supraventricular tachycardia interaction

Introduction

The cardiac effects of adenosine were first described by Drury & Szent-Gyorgyi (1929), including effects on the sinoatrial and atrioventricular nodes. They found adenosine to terminate induced artrial fibrillation in animal hearts, but in a clinical context of long-standing atrial fibrillation adenosine was found to produce only transient slowing of the ventricular rate (Honey *et al.*, 1930; Jezer *et al.*, 1933). The cardiac electrophysiologic effects of adenosine were then largely ignored by clinicians until Di Marco *et al.* (1983b) showed intravenous adenosine to be an effective treatment of supraventricular tachycardia induced in the electrophysiology laboratory. Only one study has been published on the use of intravenous adenosine when the arrhythmia arises spontaneously (Munoz *et al.*, 1984) and these investigators did not examine the dose-relationship of the therapeutic effect.

We report the findings of a dose-ranging study of intravenous adenosine in the treatment of spontaneously occurring supraventricular tachycardia.

Part of these data was presented in abstract form to the British Cardiac Society, April 1985.

Methods

Fourteen episodes of spontaneous supraventricular tachycardia arising in seven patients (five male) aged 22–73 years were studied. Supraventricular tachycardia was defined as a regular, narrow complex (< 0.12 s) tachycardia usually of 150 beats min^{-1} or faster.

Two patients had recently had coronary artery surgery (both were taking oral dipyridamole therapy), one had ischaemic heart disease, one had recently had peripheral arterial surgery, two had aortic stenosis and one had an apparently normal heart apart from paroxysmal tachycardia (see Table 1). One patient was taking amiodarone and metoprolol and another was on digoxin

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Table 1 Patient characteristics and results following intravenous adenosine in the treatment of their arrhythmia

Patient	*Age/Sex (years)*	*Other conditions*	*Cardiac drugs*	*Adenosine effect*
1	70 M	Post-peripheral artery surgery	—	Transient slowing
2	73 M	Aortic valve disease	Amiodarone, metoprolol	Transient slowing
3	63 M	Post-coronary surgery	Dipyridamole	Transient bradycardia
4	72 M	Aortic valve disease	—	Sinus rhythm (3)
5	22 F	—	—	Sinus rhythm (5)
6	57 F	Post-coronary surgery	Dipyridamole	Sinus rhythm (2)
7	62 M	Ischaemic heart disease	Digoxin	Transient slowing

treatment; in neither of these subjects did adenosine restore sinus rhythm. Written informed consent was obtained from all patients according to a protocol approved by the local hospital ethics committee.

The preparation of adenosine used was a sterile solution of adenosine (Sigma) dissolved in 0.9% sodium chloride with 0.1% sodium metabisulphite. This was prepared for us by the Pharmacy Department, University Hospital of Wales. The maximum concentration of adenosine which did not partially crystallise out during cooling after autoclaving was 5 mg ml^{-1}, and this preparation was used.

Adenosine was administered as successive rapid boluses via an indwelling cannula in an antecubital vein, the initial dose being 40 $\mu g\ kg^{-1}$, increasing as necessary in steps of 40 $\mu g\ kg^{-1}$ to a possible maximum dose of 200 $\mu g\ kg^{-1}$. In one patient taking dipyridamole the initial dose of adenosine used was 10 $\mu g\ kg^{-1}$. The study was discontinued at a lower dose if sinus rhythm was restored or if adenosine produced transient slowing of the ventricular rate to less than 100 beats min^{-1}.

Comparison of doses used in treating episodes in patients taking dipyridamole and those not taking that drug were made using the unpaired Student's *t*-test. Statistical significance was assumed if $P < 0.05$.

Results

Intravenous adenosine restored sinus rhythm (Figure 1) in 10 episodes of tachycardia in three patients, the restoration of sinus rhythm occurring about 20 s after the bolus injection of adenosine and approximately coinciding with the adenosine-induced stimulation of respiration which we have described elsewhere (Watt & Routledge, 1985). In one of the patients taking dipyridamole, adenosine in a dose of only 10 $\mu g\ kg^{-1}$ (given because of profound bradycardia induced by adenosine in the other patient taking dipyridamole) was successful in restoring sinus rhythm on two occasions, whereas the lowest effective dose in patients not taking dipyridamole was 80 $\mu g\ kg^{-1}$.

In four episodes in four patients adenosine did not restore sinus rhythm but produced transient slowing of the ventricular rate lasting for a few seconds. In one of these patients who was taking dipyridamole ventricular standstill lasting several seconds occurred, followed (without medical intervention) by a gradually increasing ventricular rate over a period of about 30 s until the pre-existing rate of 150 beats min^{-1} was restored. In all four of these patients atrial flutter was seen to be the underlying rhythm, either during the adenosine-induced slowing or when given verapamil to control ventricular rate.

The mean absolute dose of adenosine exerting an electrophysiologic effect (restoration of sinus rhythm or ventricular slowing to under 100 beats min^{-1}) was 8.8 ± 2.6 mg in patients not taking dipyridamole but was 1.0 ± 0.6 mg in patients taking dipyridamole ($P < 0.001$).

Adverse effects, apart from the severe but self-limiting bradycardia produced in one patient taking dipyridamole, consisted of transient breathlessness and facial flushing.

Discussion

The results of this study confirm that intravenous adenosine can restore sinus rhythm in some patients with spontaneous regular narrow-complex tachycardia. This agrees with the results of DiMarco *et al.* (1983b) in the treatment of electrically induced supraventricular tachycardia and those of the smaller study by Munoz *et al.* (1984) in the treatment of spontaneous episodes of arrhythmia. The systematic increase in doses used in our study contrast with the random use of varying doses by Munoz *et al.* (1984).

It may be suggested that the electrophysio-

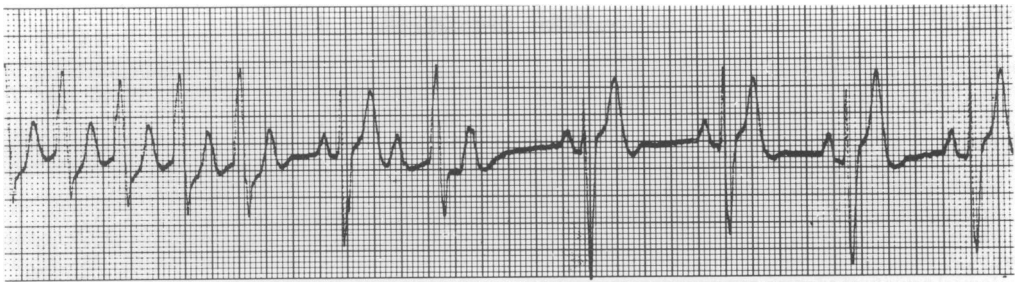

Figure 1 Termination of supraventricular tachycardia and restoration of sinus rhythm following intravenous adenosine.

logical effects seen here could be due simply to a rapidly injected bolus of physiological salt solution. We have shown in normal individuals that injection of an appropriate placebo solution causes no changes in heart rate, whereas adenosine produces a transient but significant bradycardia (unpublished observations) attributable to effects on the sinoatrial and atrioventricular nodes (Di Marco *et al.*, 1983b). The onset of electrophysiological effect also occurred at almost the same time as the respiratory stimulation which adenosine, but not placebo, produces (Watt & Routledge, 1985).

Our results allow provisional recommendations to be made regarding dosage of adenosine which would be appropriate in further studies using the nucleoside in the treatment of supraventricular tachycardia. The mean effective dose was 8.8 ± 2.6 mg in patients not receiving dipyridamole, with the lowest dose producing electrophysiological effect being 5.6 mg and the highest 12 mg. Thus we would suggest an initial dose of 10 mg, this being a volume of 2 ml of the sterile solution which we use (followed if necessary by doses of 15 mg and 20 mg). In patients who are already taking dipyridamole care should be exercised and we would suggest that the initial dose should not exceed 1 mg if alarming bradyarrhythmias are to be avoided.

The half-life of adenosine *in vivo* is probably less than 10 s (Klabunde, 1983) due to rapid uptake and degradation of adenosine by red blood cells and many other cell types. Dipyridamole is a competitive inhibitor of this transport process (Klabunde, 1983). Therefore in the presence of dipyridamole the concentration of adenosine, for any given dose administered, is likely to be increased in the interstitial space and hence at the cell surface where adenosine receptors are located (Londos *et al.*, 1980). This may explain the potentiation of the bradycardic action of adenosine. Alternatively the apparent effect of dipyridamole may be due to inter-individual variability or alteration in sensitivity to adenosine produced by recent surgery or anaesthesia.

A rapid intravenous bolus is essential to optimise the chance of achieving therapeutic success as slow injections produce no detectable effect in patients in sinus rhythm (A. H. Watt, unpublished observations). The results which we describe relate to injections from an antecubital vein whereas injections from a more central vein (Di Marco *et al.*, 1983a) require a lower dose. Our mean effective dose was 135 $\mu g\ kg^{-1}$ in patients not taking dipyridamole, compared to 83 $\mu g\ kg^{-1}$ in the results of Di Marco *et al.* (1983b). This difference may be due to the known rapid red cell uptake of adenosine (Klabunde, 1983) and the different times adenosine is in contact with red cells before reaching the heart when injected from peripheral and central venous sites.

We appear to have studied a slightly atypical group with supraventricular tachycardia, as four out of seven had atrial flutter. About 90% of episodes of supraventricular tachycardia are said to be due to re-entry circuits involving the atrioventricular node, a situation where adenosine would be expected to restore sinus rhythm (Di Marco *et al.*, 1983b). It would appear likely that such a mechanism was involved in our patients where sinus rhythm was restored.

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References

Di Marco, J. P., Sellers, T. D., West, A. & Belardinelli, L. (1983a). Adenosine: electrophysiologic effects in man. *J. Am. Coll. Cardiol.*, **1**, 730.

Di Marco, J. P., Sellers, T. D., Berne, R. M., West, G. A. & Belardinelli, L. (1983b). Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. *Circulation*, **68**, 1254–1263.

Drury, A. N. & Szent-Gyorgyi, A. (1929). The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. *J. Physiol.*, **68**, 213–237.

Honey, R. M., Ritchie, W. T. & Thomson, W. A. R. (1930). The action of adenosine upon the human heart. *Quart. J. Med.*, **23**, 485–489.

Jezer, A., Oppenheimer, B. S. & Schwartz, S. P. (1933). The effect of adenosine on cardiac irregularities in man. *Am. Heart J.*, **9**, 252–258.

Klabunde, R. E. (1983). Dipyridamole inhibition of adenosine metabolism in human blood. *Eur. J. Pharmac.*, **93**, 21–26.

Londos, C., Cooper, D. M. F. & Wolff, J. (1980). Subclasses of external adenosine receptors. *Proc. Nat. Acad. Sci. U.S.A.*, **77**, 2551–2554.

Munoz, A., Leenhardt, A., Sassine, A., Galley, P. & Puech, P. (1984). Therapeutic use of adenosine for terminating spontaneous paroxysmal supraventricular tachycardia. *Eur. Heart J.*, **5**, 735–738.

Watt, A. H. & Routledge, P. A. (1985). Adenosine stimulates respiration in man. *Br. J. clin. Pharmac.*, **20**, 503–506.

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