Proarrhythmic effects of adenosine: a review of the literature

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Adenosine is widely used as an antiarrhythmic agent for the investigation and management of both narrow complex and, less often, broad complex tachycardias. Over the past 10 years or so, reports of severe bradycardias and tachyarrhythmias being induced by this agent have appeared in the literature. As adenosine is increasingly used in emergency departments and indeed outside the hospital setting, a greater awareness of these potential problems is important. In this paper the evidence for such effects is summarised, and the mechanisms involved discussed.

Adenosine is considered first line therapy for the investigation and termination of supraventricular tachycardias because of its efficacy and safety. It is also being used in some areas to aid in the diagnosis of broad complex tachycardias, usually if they have not responded to lignocaine (lidocaine). A number of studies and reports, however, indicate that the drug can cause severe bradyarrhythmias and also both ventricular and supraventricular tachycardias, some of which have been life threatening. These problems with adenosine are uncommon, but they may not yet be widely known in emergency departments. This paper seeks to raise the awareness of these problems and describes the underlying mechanisms.

REPORTS OF BRADYARRHYTHMIAS

The side effects of bronchospasm and chest pain after the administration of adenosine are commonly encountered but, even if rated severe, are always transient.1 Pauses and minor bradyarrhythmias are also well known as they are frequently encountered, but occasionally these can be significant: transient sinus arrest, bifascicular block,2 and complete heart block3 have occurred, the latter in a patient who had also been treated with digoxin and verapamil. Ventricular standstill and asystole4 have also been reported, and in one prospective series asystole >4 seconds occurred in 7% of patients given adenosine.5 In one patient treated with adenosine out of hospital asystole was fatal.6

REPORTS OF TACHYARRHYTHMIAS

Ventricular ectopy and non-sustained monomorphic ventricular tachycardia (VT) are frequently seen after the administration of adenosine.7,8 and non-sustained VT has also occurred during pharmacological stress testing with adenosine.9 Episodes of non-sustained polymorphic VT have been reported, both in patients with structurally normal hearts and normal QT intervals,10-12 and in the presence of congenital17 and acquired18 prolonged QT interval. These are of little importance and require no intervention. Significant tachyarrhythmias are more rarely encountered, but can be of many different types: these will be considered in more detail.

After the administration of adenosine, sustained tachycardias de points requiring cardioversion19 or procainamide20 has occurred; one such case in a patient with a drug induced prolonged QT interval. Patients predisposed to ventricular tachyarrhythmias may have these events triggered by adenosine induced pauses or ventricular ectopy; however some of the reported cases were not pause dependent, and the mechanism for these instances of torsades is less clear. Two cases of ventricular flutter degenerating into fibrillation have been reported,21,22 one in an elderly woman who had previously been given digoxin and verapamil. Ventricular fibrillation has been seen after adenosine in a patient with stable VT,23 and also in three patients with pre-excitation atrial fibrillation.24-26 The details of a further eight cases of ventricular fibrillation remain unpublished.11 Hernandez and Ribeiro have discussed27 the mechanisms involved in the excitatory effects of adenosine on ventricular automaticity.

Dangerous increases of the ventricular rate in atrial flutter have followed the administration of adenosine, with conduction increasing from 2:1 to 1:1 after a brief period of high grade atrioventricular block.1,28-30 Three of these five reported cases required electrical cardioversion. The secondary enhancement of atrioventricular (AV) nodal conduction following initial AV block was thought to be related to sympathetic activation, which was then perpetuated by the onset of 1:1 conduction. Ventricular flutter has also occurred after adenosine in the context of ethanol intoxication.31 A similar transient rapid increase in the ventricular rate in the context of

Abbreviations: VT, ventricular tachycardia; AV, atrioventricular
normally conducted atrial fibrillation has been reported.\cite{18} This effect was similarly attributed by the author to an increase in sympathetic discharge predominating over the atrioventricular nodal blocking action of adenosine.

Garratt et al found supraventricular proarrhythmic effects in three patients:\cite{24} a rapid pre-excited atrial fibrillation which was poorly tolerated and subsequently terminated by intravenous flecainide, a pronounced acceleration of an AV re-entrant tachycardia, and a rapid pre-excited atrial tachycardia that required atrial pacing for termination. None of these arrhythmias had occurred previously, and all resulted in severe haemodynamic compromise. Atrial arrhythmias therefore can themselves be induced by adenosine, including atrial tachycardias and atrial flutter.\cite{25} In fact, the induction of atrial fibrillation by adenosine is now well recognised,\cite{26,27} and in some more cases has been associated with ventricular pre-excitation and haemodynamic collapse.\cite{28,29}

Adenosine is effective in terminating AV nodal re-entry tachycardias, but these have also been reported as having been induced by adenosine;\cite{30} indeed Curtis et al found that low dose adenosine could induce AV nodal re-entrant tachycardias in 9 of 16 patients who were known to experience this tachycardia. The effect of adenosine on the underlying dual AV node pathways in these patients was investigated, and in common with other workers,\cite{31} adenosine was shown preferentially to block the fast antegrade pathway, thus allowing a re-entry circuit to develop. A similar response to adenosine has been observed when it was erroneously given to a patient with a sinus tachycardia (personal communication), who had presented to the emergency department with a history of recurrent palpitation; on three consecutive occasions a brief period of narrow complex tachycardia (probably AV nodal re-entry tachycardia) was induced, followed by return to sinus tachycardia.

Adenosine has also been shown to provoke an AV re-entry tachycardia;\cite{32,33} in these patients a critical prolongation of antegrade AV nodal conduction was thought to have allowed retrograde activation of the atrium via an accessory pathway and thus the emergence of the reciprocating tachycardia. As already mentioned, adenosine has also been found to increase the ventricular rate substantially in an existing AV re-entry tachycardia;\cite{34} in this case it was thought to be caused by an increase in the rate of retrograde conduction through the AV node. Two further cases have been reported in which adenosine caused a similar immediate increase in the rate of a narrow complex tachycardia (see table 1).\cite{35}

### DISCUSSION

Adenosine shortens atrial action potentials, reducing the effective refractory period and thus promoting the development of atrial flutter and fibrillation. In addition, adenosine causes a reflex increase in circulating catecholamine levels and sympathetic nerve traffic by sympathetic stimulation in the carotid body chemoreceptors.\cite{36} This results in a transient sinus tachycardia and atrial or ventricular ectopy, and these ectopies may provoke the reinitiation of re-entrant arrhythmias.\cite{37} As discussed above the catecholamine release is also thought in some patients to underlie the increased conduc- tion velocity in accessory AV pathways that can be manifest as a problematic tachycardia.

The negative chronotropic action of adenosine can be particularly pronounced in the presence of sinus node dysfunction, and this has in fact been proposed as the basis for a non-invasive diagnostic test for sick sinus syndrome.\cite{38} Particular care therefore needs to be taken in such patients, who may present with a tachycardia as part of a tachy-brady syndrome: these patients are especially prone to developing prolonged pauses or asystole.\cite{39} Animal studies\cite{40} suggest that increasing age may predispose to increased functional A1 receptor sensitivity and impaired adenosine transport, and would imply that extra caution be exercised in older patients. Lower doses should be used if the drug is administered centrally.\cite{41}

There are a few significant drug interactions with adenosine that must be borne in mind. Patients taking dipyridamole (including combination preparations with aspirin) need a lower dose of adenosine as dipyridamole blocks its cellular uptake and thus inhibits its metabolism.\cite{42} Care must also be exercised with patients taking carbamazepine, which increases the action of adenosine, and can cause additional AV block. Conversely, methylxanthine compounds such as theophylline and caffeine inhibit adenosine competitively at the A1 receptor, and therefore can reduce or block its action, although there is some suggestion that long term administration of these agents may lead to up-regulation of the A1 receptors.\cite{43} These patients therefore usually but not always require higher doses of adenosine (see table 2).

### Table 1
Reported arrhythmias precipitated by adenosine

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradyarrhythmias</td>
<td>Prolonged sinus bradycardia, sinus arrest</td>
</tr>
<tr>
<td>Ventricular tacharythmias</td>
<td>Atrial fibrillation, atrial flutter, atrial tachycardia, AV and AV nodal re-entry tachycardias</td>
</tr>
</tbody>
</table>

### Table 2
Patient groups requiring particular care

<table>
<thead>
<tr>
<th>Potential for enhanced effects of adenosine</th>
<th>Elderly people (sinus node dysfunction), Hypertension, Diabetes, Long QT syndrome, Heart failure</th>
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<tbody>
<tr>
<td>Potential for reduced effect of adenosine</td>
<td>Caffeine, Theophylline, Dipyridamole, Beta blockers</td>
</tr>
<tr>
<td>Potential for induction of tacharythmias</td>
<td>History of recurrent palpitation (suggesting possibility of latent pre-excitation or dual AV node physiology)</td>
</tr>
</tbody>
</table>

- **Key points**
  - Adenosine is generally a safe and effective anti-arrhythmic agent.
  - It can cause clinically significant bradyarrhythmias and tachyarrhythmias, which may rarely be life threatening.
  - Clinically significant interactions can occur, especially with dipyridamole and theophyllines.
  - Extra caution is required with the elderly population and in patients with sinus node disease.
  - Adenosine should only be given where the expertise and facilities for managing its side effects are available.
CONCLUSION
Adenosine is widely used in hospital and, outside the UK, increasingly in the UK, to treat supraventricular tachyarrhythmias (SVT). It is thought to work by inducing atrioventricular (AV) block. Although it is effective in many cases, it is not without side effects, and the potential for proarrhythmia remains a concern. When used in patients with preexcited junctional tachycardias, adenosine can cause a paradoxical effect of AV block. The incidence of proarrhythmic events is low, but clinicians should be aware of the potential for proarrhythmia when using adenosine in these patients. The use of adenosine in SVT is widely accepted, but further research is needed to better understand its mechanism of action and to improve its safety profile.