

Antiarrhythmic drug safety/proarrhythmia: five cautionary tales

Dr Edward Keelan

Earlier articles in this esteemed journal have discussed different aspects of the management of heart rhythm problems. The attention has focused on the great technological advances that have been made in this field in recent years. However, we must realise that while appropriate investigation ensures that we can offer reassurance to some patients and the prospect of a curative ablation procedure to others, we do still have to rely on long-term drug therapy for a sizeable proportion of patients with recurrent arrhythmia. Fortunately, these days there is a large armamentarium of different agents from which we can hopefully find a drug which is effective, well tolerated and safe.

Focus on safety

This article will focus on the last of these three essential attributes – drug safety. We are all aware that any drug may have potential side-effects ranging from the benign and reversible to the serious and even life-threatening. When it comes to the treatment of heart rhythm problems, it is the latter category that causes the greatest concern. In discussing this, one must attempt to announce some basic principles.

The first principle is that all antiarrhythmic drugs have potential proarrhythmic effects; these may range from simple sinus bradycardia to fatal ventricular arrhythmias. The second is that all studies to date indicate that it is those patients with significant structural heart disease who are at greatest risk of the most serious complications. Therefore, caution is required when prescribing antiarrhythmic drugs for patients with impaired cardiac function.

It would be impossible to cover all the side effects of the available antiarrhythmic drugs in a single article. At best,

one could hope to highlight some of the potential problems. There follows five cautionary tales that illustrate the potential proarrhythmic effects of antiarrhythmic drugs. All the patients were treated successfully without coming to any harm; however, other patients with similar problems may not have been so fortunate over the years.

Case 1

A 51-year old man with a history of paroxysmal atrial fibrillation had been treated with quinidine and digoxin for over five years. During a routine nuclear stress test performed before commencing an exercise programme, a perfusion defect was noted. This raised concern about possible occult coronary disease and metoprolol 50mg bid was added to his regimen pending further investigation.

Over the next few days, the man experienced recurrent dizzy spells which became increasingly severe. He saw his local doctor who noted nothing untoward on examination or ECG. Two days later, while driving home from the shopping mall (this is a case from the US!) with his three children in the car he had a severe presyncopal spell during which he almost lost control of the car. It passed over and he continued to drive home, albeit more cautiously. During the remainder of the journey, he had two more spells of severe lightheadedness. His wife then drove him to the local hospital emergency room and ECG rhythm strips (see Figure 1) were recorded there and during his subsequent admission. In both Figures 1a and 1b, there are rhythm strips documenting conversion from atrial fibrillation to sinus rhythm with prolonged sinus pauses. This suggests atrial fibrillation with underlying sick sinus syndrome aggravated or unmasked by the addition of the beta-blocker to his drug regimen.

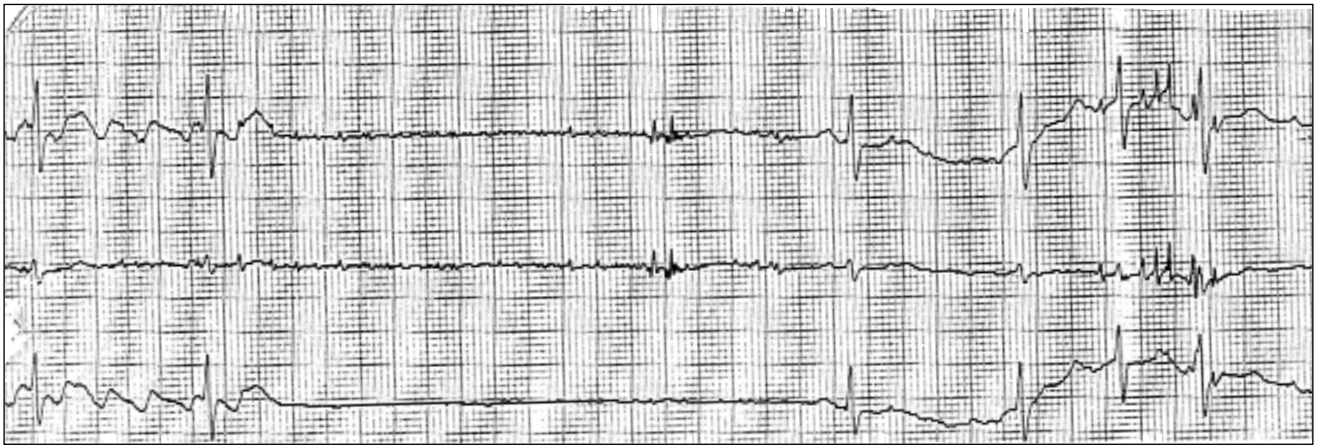


Figure 1a. ECG monitor recording showing conversion of atrial fibrillation (first two QRS complexes) to sinus rhythm to sinus rhythm with a prolonged sinus pause.

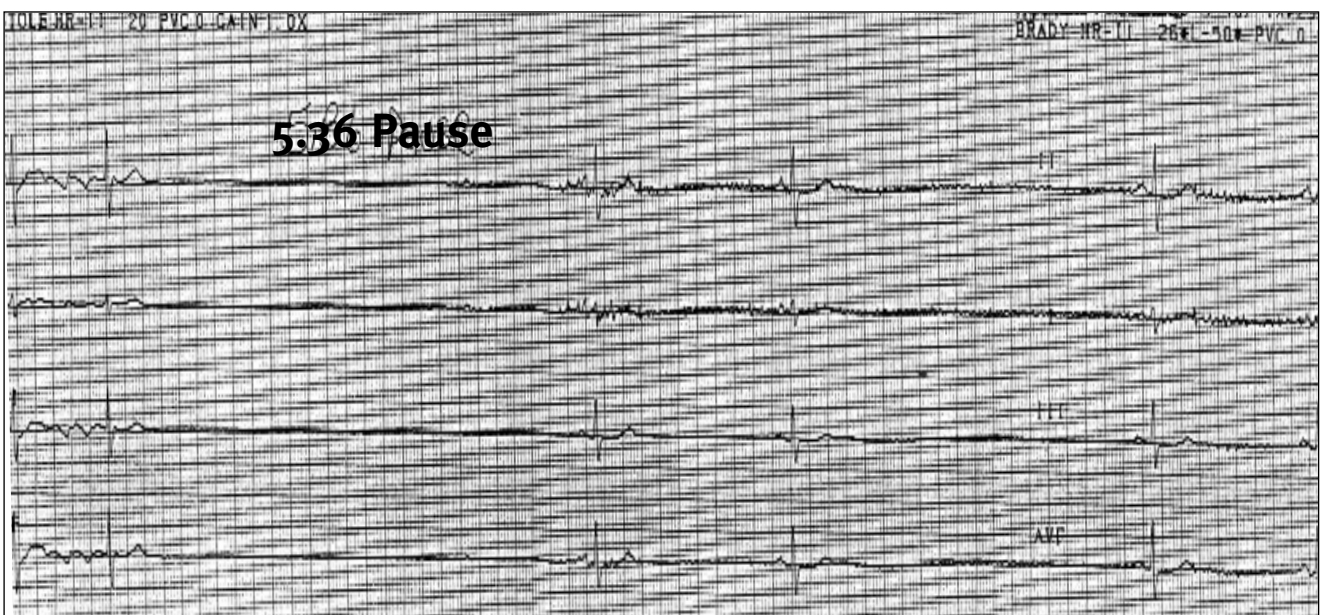


Figure 1b. Another example, this time with more prolonged sinus slowing.

It is unusual to see such a dramatic example in a relatively young patient. One must conclude that the combination of three different drugs (two in the category of rate-controlling agents and one in the antiarrhythmic drug group) was sufficient to produce this potentially fatal effect. The lessons here are that one must use combination therapy cautiously, one must consider the possible additive effect of drugs started for other indications and that follow up monitoring to exclude excessive slowing is important. Finally, although not

directly relevant here, one must always have concern about the use of class I antiarrhythmic agents in patients with suspected coronary disease.

Subsequent angiography showed normal coronary arteries and with this reassurance the patient was changed from triple therapy to flecainide (class I Ic antiarrhythmic agent) and he had a back up atrial pacemaker implanted.

Case 2

A similar presentation, this time of a patient in her mid 60s with paroxysmal atrial fibrillation which was regarded as inadequately controlled by single antiarrhythmic drug therapy. She was then started on a combination of propafenone and sotalol. When seen, she described quite clearly the irregular heart beating consistent with her documented paroxysmal atrial fibrillation. She also described episodes of light-headedness or presyncope which on closer questioning seemed to correlate with the time of conversion from irregular to regular heart beating. The rhythm strip in Figure 2

illustrates the problem.

As in case 1, on conversion from atrial fibrillation to sinus rhythm, there is a prolonged sinus pause which accounted for her symptoms. Again, combination therapy started for 'unresponsive' fibrillation produced problems of its own which may have caused more harm than the arrhythmia being treated. Here again, management consisted of simplification of her antiarrhythmic drug therapy and the implantation of an atrial pacemaker for the underlying sick sinus syndrome.

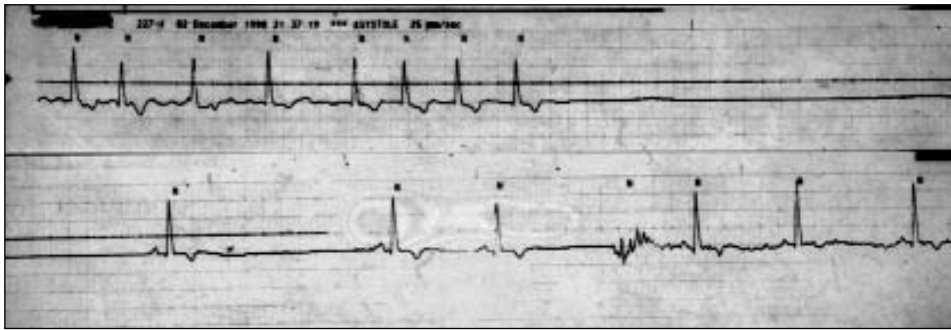


Figure 2. ECG monitor strip showing conversion of atrial fibrillation to sinus rhythm with a prolonged sinus pause.

Case 3

A stoical middle-aged farmer from the US Mid-West with recurrent atrial flutter had been tried on a number of different antiarrhythmic agents over a period of some years. None had prevented the recurrences for which he had required repeated hospital admission and cardioversion.

Having tried several agents, he was started on flecainide but it was then that his problems became much worse. His palpitations (which had been previously troublesome but bearable) became very severe. He found that any exertion led to severe dyspnoea and presyncope. He would have to stop and rest for prolonged periods. The rhythm strips from a routine Holter monitor (shown in Figure 3) give the answer to his problem. In Figure 3a, we see atrial flutter

with varying AV block giving a controlled ventricular rate of 60-90 bpm; while Figure 3b shows a broad complex tachycardia of about 160 bpm recorded during activity.

This is a proarrhythmic effect of the flecainide which acts to slow the flutter rate within the atria. This then leads to reduced AV block which causes paradoxical acceleration of the ventricular rate and the flecainide also causes broadening of the QRS complexes. For this reason, class I antiarrhythmic agents should not be prescribed for atrial flutter (or atrial fibrillation with intermittent flutter) without a concomitant AV nodal blocking agent. This patient underwent curative ablation for his atrial flutter which obviated the need for antiarrhythmic drug therapy.

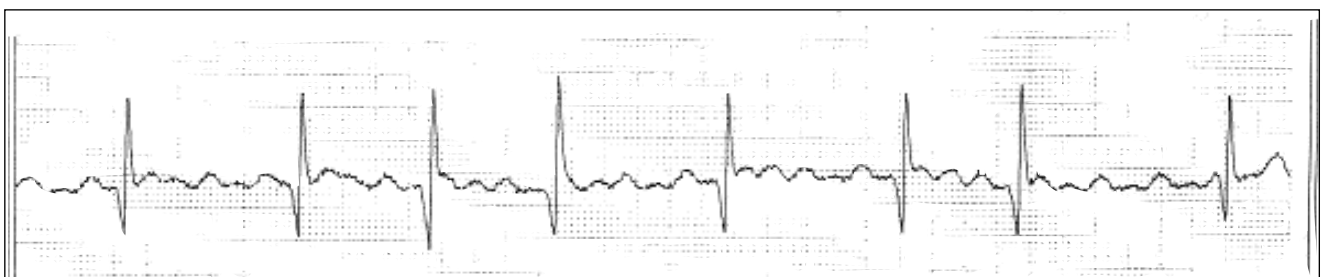


Figure 3a. A Holter monitor recording showing atrial flutter with varying AV block and controlled ventricular rate.

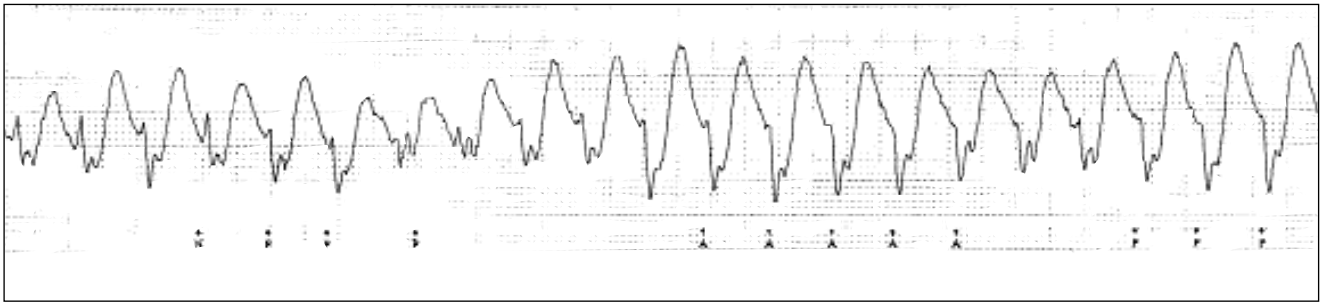


Figure 3b. Later during the monitored period, recording showing acceleration of the ventricular rate and broadening of the QRS complexes (mimicking ventricular tachycardia) produced by flecainide.

Case 4

An elderly woman with mitral valve disease and troublesome atrial fibrillation was prescribed sotalol and subsequently became very unwell with episodic nausea and lightheadedness culminating in a syncopal spell. The ECG and rhythm strips (shown in Figure 4) give the answer to her problem. She had developed marked sinus bradycardia and prolongation of the QT interval (see Figure 4a), the latter resulting in recurrent nonsustained ventricular tachycardia (see Figure 4b). These potentially fatal heart rhythm distur-

bances had resulted from the treatment of a relatively benign, if potentially troublesome, atrial arrhythmia.

Of particular note, this lady had baseline renal impairment and sotalol is excreted by the kidneys so this undoubtedly contributed to increased plasma drug levels and secondary effects. Knowledge and understanding of the pharmacokinetics of the different antiarrhythmic drugs is therefore very important for the prescribing physician. The sotalol was discontinued and she was started on verapamil.

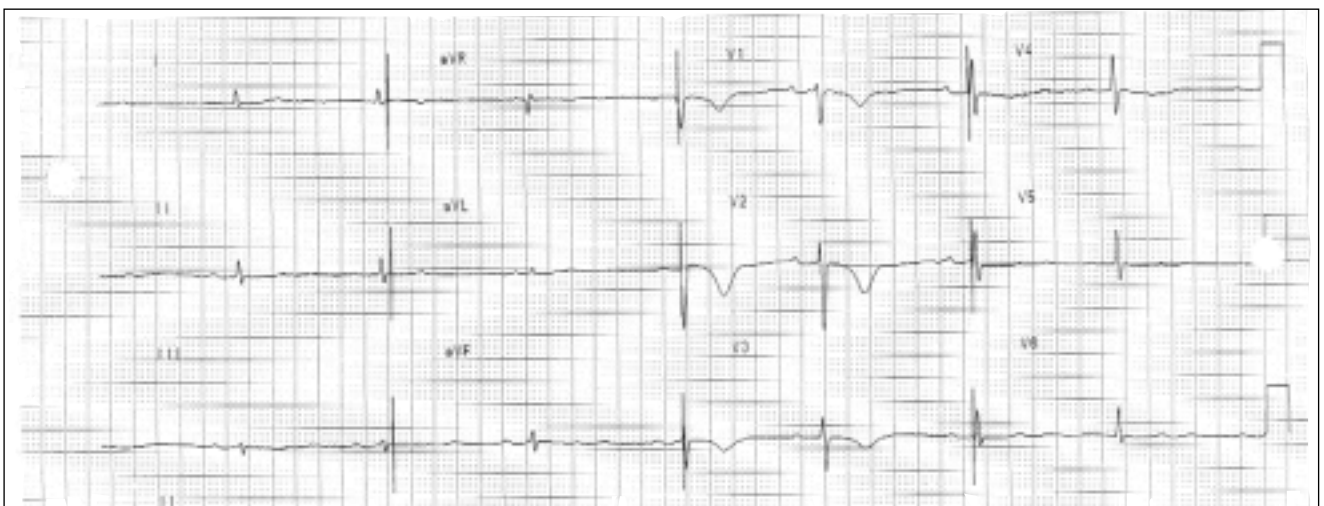


Figure 4a. 12-lead ECG showing sinus bradycardia with prolongation of the QT interval due to sotalol.



Figure 4b. ECG monitor strip recorded later showing more marked sinus bradycardia with recurrent non-sustained ventricular tachycardia.

Case 5

This case is a little different as it doesn't involve the prescription of antiarrhythmic drugs. The patient was a woman in her mid 70s prescribed atenolol and bumetanide for control of hypertension. She had experienced frequent falls for some months which she had attributed to 'tripping' or 'stumbling'.

One day she was found at home by her family, having fallen onto the couch and remained there for an indeterminate time. Her ECG on admission to hospital is shown in

Figure 5a. It shows an extremely prolonged QT interval due, in this case, to profound hypokalaemia (potassium=2.5mmol/l) caused by the unopposed loop-blocking diuretic. In Figure 5b we see short paroxysms of polymorphic ventricular tachycardia occurring as a result of the hypokalaemia. These undoubtedly caused this woman's recurrent falls and loss of consciousness. The changes were reversed by potassium supplementation and then by addition of a potassium-sparing diuretic.

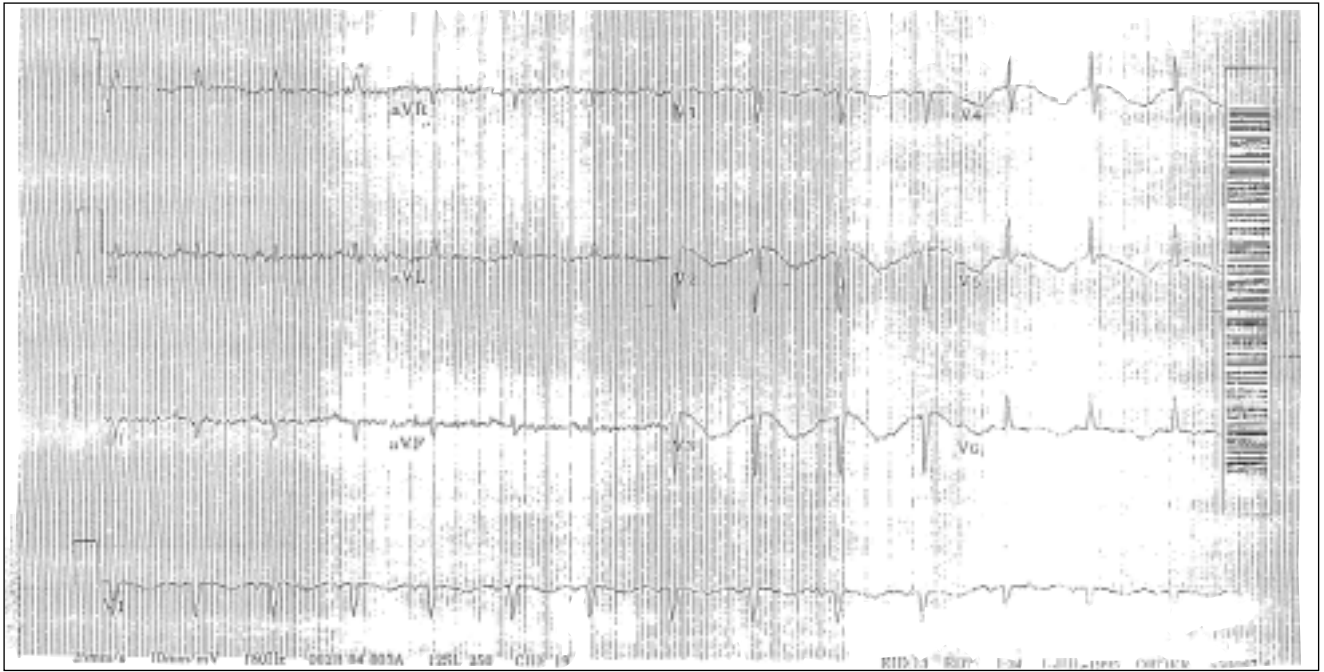


Figure 5a. 12-lead ECG showing sinus rhythm with marked QT prolongation.

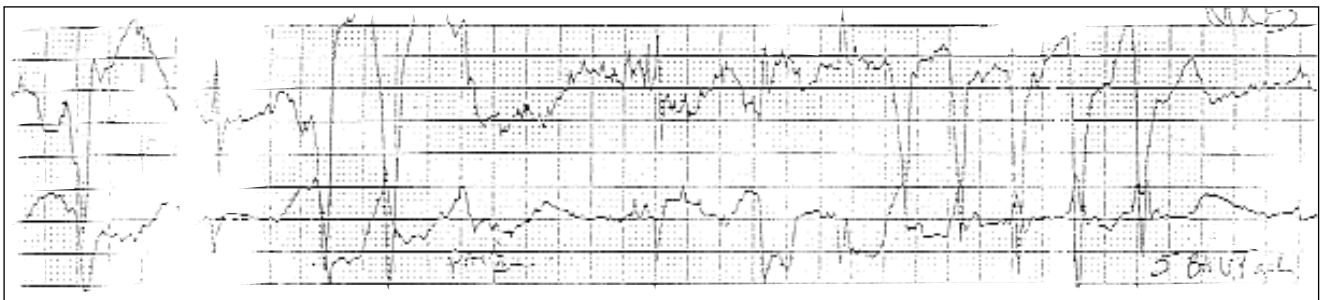


Figure 5b. ECG monitor strip showing up to five beats of nonsustained ventricular tachycardia.

Conclusions

These five cases provide examples of the potential hazards associated with the treatment of the most basic cardiac problems such as atrial fibrillation and hypertension. Of course, many thousands of patients with these and other cardiac problems are treated successfully over many years.

However, while the availability of new drugs offers new therapeutic possibilities, there are always potential hazards: witnessed most recently was the t-channel calcium channel blocker which had to be withdrawn because of drug interaction. It therefore behoves us to be aware of the potential side effects and interactions as much as the benefits of antiar-

rhythmic drugs prescribed. I have deliberately not included discussion of the more difficult cases of potentially life-threatening ventricular arrhythmias occurring in the presence of significant structural heart disease because pharmacological options in these settings are limited and therapy with drugs other than sotalol or amiodarone is almost never advised. In addition, formal electrophysiological assessment with possible defibrillator implantation may be required.

Dr Edward Keelan MB MRCPI MRCP (UK), is a consultant cardiologist at the Mater Private hospital, Dublin.