Electrophysiological assessment of amiodarone in treatment of resistant supraventricular arrhythmias*

EDWARD ROWLAND, DENNIS M KRIKLER

From the Division of Cardiovascular Disease, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London

SUMMARY Oral amiodarone has been used to treat 21 patients with various supraventricular arrhythmias; 13 had Wolff-Parkinson-White syndrome, which was complicated by atrial fibrillation and re-entry atrioventricular tachycardia in four, and re-entry tachycardia alone in the other nine. The remaining eight patients had paroxysmal atrial fibrillation or flutter without pre-excitation. All were refractory to conventional treatment and had undergone intracardiac electrophysiological study. Fifteen have been controlled with amiodarone, this treatment proving most effective in atrial fibrillation or flutter with or without pre-excitation. Amiodarone was successful in only four of the nine patients with re-entry atrioventricular tachycardia. In two patients who responded well the drug had to be discontinued because of side effects.

Despite the abundance of drugs available for the prophylaxis of supraventricular arrhythmias there are some patients in whom conventional anti-arrhythmic medications fail. While surgery is feasible in these resistant cases it is usually reserved for life-threatening arrhythmias. Amiodarone, a benzafuran derivative originally introduced as an antianginal agent, has been shown to be effective in a wide variety of supraventricular arrhythmias including those complicating pre-excitation. Subsequent reports, however, have not confirmed the original high success rates.

Though relatively little is known of its pharmacological behaviour, there is evidence that amiodarone is slowly absorbed, has a long half-life, and a persistent action. Its antiarrhythmic action appears to differ when given intravenously as opposed to orally. We investigated the action of oral amiodarone in 21 patients with supraventricular arrhythmias after electrophysiological study had been performed to define the precise nature of arrhythmia. All were evaluated during treatment by repeated 24-hour ambulatory electrocardiographic monitoring. Limited electrophysiological testing was performed during treatment in nine of the patients with the Wolff-Parkinson-White syndrome. The results were then compared with symptoms during the follow-up period (three to 25 months). The repeat electrophysiological studies provided further information on the therapeutic efficacy of amiodarone and its range of action, and clarified why it failed in some.

Methods

Twenty-one patients, all with a history of recurrent palpitation, underwent intracardiac electrophysiological testing to determine the nature of their arrhythmias. The studies were performed according to our standard procedure with modifications discussed below. Each study was performed in the fasting state after informed consent had been obtained and after all medications had been stopped for at least 72 hours.

Electrodes for stimulation and recording were positioned in the high right atrium, close to the septal cusp of the tricuspid valve, and at the apex of the right ventricle. A fourth electrode was used for atrial endocardial mapping and to allow stimulation from atrial sites other than the high right atrium. The recordings obtained were led via isolated selection boxes to the high-gain amplifiers (15 to 1200 Hz) of an ink-jet recorder and displayed at a paper speed of 100 mm/s, together with surface electrocardiograph leads I, III, V1, and V6. All information was recorded on a high-fidelity multichannel tape recorder for later retrieval. Stimulation studies were performed using a programmable

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stimulator (Devices 4971) delivering impulses of 2 ms duration at twice diastolic threshold.

The following electrophysiological measurements were made during the study.

1. Corrected sinus node recovery time after high right atrial pacing for one minute at 80, 120, and 140 stimuli a minute.13

2. Effective refractory periods of atrial and ventricular myocardium.

3. Effective refractory period and functional refractory period of the atrioventricular node in the anterograde direction and the refractory periods of any other anterogradely functioning atrioventricular pathway. The values for the atrioventricular node were determined by the introduction of premature stimuli in the high right atrium. In the presence of accessory atriocorventricular pathways (Wolff-Parkinson-White syndrome) pacing was performed as close as possible to the atrial insertion of the pathway, as determined by atrial mapping during ventricular pacing or induced orthodromic reciprocating atrioventricular tachycardia (in which the reentrant impulse uses the atrioventricular node as the anterograde limb of the circuit and the accessory pathway in the retrograde direction).

4. Continuous and incremental high right atrial pacing was performed to determine the highest atrial cycle length which would support 1:1 anterograde conduction via the atrioventricular node. In patients with accessory pathways the test was repeated from a pacing site as close to the accessory pathway as possible to determine the highest rate at which it could conduct 1:1.

5. The mechanism of reciprocating atrioventricular tachycardia was confirmed by endocardial mapping of ventricular atrial conduction during the tachycardia.

6. In those patients in whom reciprocating tachycardia could be initiated the zone over which atrial premature beats, both from the high right atrium and from an atrial site close to the accessory pathway, could initiate tachycardia was recorded (initiation zone). The cycle length of tachycardia and the conduction times of the components of the re-entry circuit were measured.

7. Atrial fibrillation was induced by rapid atrial pacing in those patients in whom this arrhythmia was the presenting rhythm disturbance and in the one patient in whom no arrhythmia had previously been documented. During atrial fibrillation the ventricular response was assessed by recording the shortest and mean RR intervals.

The electrophysiological studies defined three groups of patients. Group 1 consisted of those patients with the Wolff-Parkinson-White syndrome in whom rapidly conducted atrial fibrillation (mean ventricular rate in excess of 250 a minute) was the major rhythm disturbance (Fig. 1). In addition, these patients had orthodromic reciprocating atrioventricular tachycardia. In two patients this arrhythmia degenerated spontaneously to atrial fibrillation (Fig. 2). There was sustained atrial fibrillation in three patients while in the other the first episode of atrial fibrillation terminated spontaneously while the second was sustained. Reciprocating atrioventricular tachycardia was induced by single atrial extrastimuli in three patients: in the other neither single nor double atria extrastimuli succeeded (case 1). In none of these patients was it possible to assess the highest rate of 1:1 conduction down the accessory pathway because of the development of atrial fibrillation. In one patient (case 3) atrioventricular nodal function suggested an accessory atrio-His pathway.13

Nine patients had reciprocating atrioventricular tachycardia alone (group 2); this was associated with an accessory atrioventricular pathway (Wolff-Parkinson-White syndrome) in seven while the remainder had intranodal re-entry. Only one patient had overt Wolff-Parkinson-White syndrome, the other six having concealed accessory pathways.14

Group 3 comprised those with paroxysmal atrial fibrillation or flutter unassociated with pre-excitation. The control studies demonstrated a prolonged corrected sinus node recovery time in one patient (case 16) though there was no history

![Image](https://example.com/image.png)

Fig. 1 Case 1: electrocardiogram during sinus rhythm shows Wolff-Parkinson-White syndrome type A. Rhythm strip (lead II) shows atrial fibrillation: ventricular rate exceeds 400/min.
or other evidence suggestive of sinus atrial disease.\textsuperscript{15} One patient known to have paroxysmal atrial fibrillation and flutter developed persistent atrial flutter and was then started on amiodarone.

**Drug Regimen**

Treatment with amiodarone was begun after suitable trials of appropriate conventional antiarrhythmic drugs had failed (Table 1). The dose was 600 mg a day for the first month and 400 mg a day for the next month, with maintenance on 200 mg a day if the response was satisfactory.

**Therapeutic Assessment**

The method of assessment of therapeutic benefit varied with the nature of the arrhythmia. In group 1 (Table 2) in whom rapidly conducted atrial fibrillation complicating the Wolff-Parkinson-White syndrome was the major rhythm disturbance, limited electrophysiological testing was performed. A single quadripolar electrode was used to stimulate and record from the high right atrium and then moved to a site as close as possible to the atrial insertion of the accessory pathway. From these two positions it was possible to measure corrected sinus node recovery times, atrial effective refractory period, and the highest 1:1 rate sustained by the accessory pathway in the anterograde direction. The ability to initiate re-entry tachycardia by single or multiple atrial premature stimuli was assessed (Table 3); where a single stimulus succeeded the initiation zone was measured. Atrial fibrillation was induced in all patients and the ventricular response assessed. In all four the study was performed three months after the start of treatment.

In the second group of patients (Table 3) reassessment was performed by repeated 24-hour ambulatory electrocardiographic monitoring using Oxford Medilog recorders and a Reynolds Pathfinder analyser; six underwent limited electrophysiological investigation because they remained symptomatic: case 8 only developed recurrent arrhythmia during transient reduction to 200 mg a day.

Assessment of the third group was by ambulatory

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*Fig. 2 Case 1: intracardiac and surface electrocardiograms (paper speed 25 mm/s). HRA, high right atrial electrogram; PCS, proximal coronary sinus electrogram; HBE, His bundle electrogram; DCS, distal coronary sinus electrogram. During right ventricular pacing a critically-timed ventricular extrastimulus and a ventricular extrasystole (complexes 4 and 5) initiate re-entry atrioventricular tachycardia which leads to atrial fibrillation.*
Table 1  Patients

<table>
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WPW, Wolff-Parkinson-White syndrome; AF, atrial fibrillation; A Fl, atrial flutter; RT, re-entry tachycardia; Conc, concealed; Pr, propranolol; Po, pindolol; Pc, practolol; D, digoxin; Di, disopyramide; V, verapamil; O, oxprenolol; Q, quinidine; S, sotalol.

monitoring without repeat electrophysiological study.

Ophthalmological examination was undertaken at three months to observe the corneal microdeposits known to be a marker of treatment with this drug. Biochemical estimation of thyroid function was also performed to exclude hypothyroidism\textsuperscript{17} and hypothyroidism\textsuperscript{18} known sometimes to be a complication of treatment.

Results

The findings of the limited electrophysiological study performed in group 1 three months after starting treatment are shown in Table 3. All showed an increase in the effective refractory period of the atrium but, more importantly, atrial fibrillation was more difficult to induce than during the control study, was conducted with a mean ventricular rate below 200 a minute, and was now well tolerated. Atrial fibrillation was only produced in the patients on amiodarone by rapid atrial pacing, whereas there had been spontaneous transformation from re-entry tachycardia in two patients during the control study.\textsuperscript{19} Atrial fibrillation terminated spontaneously in three patients (Fig. 3) but only in one when not on treatment. The influence of the drug on the ability of atrial premature beats to initiate re-entry atrioventricular tachycardia was variable. In the patient (case 1) in whom neither
single nor double premature stimuli could initiate tachycardia in the first study it was possible to induce tachycardia from the atrium with single stimuli though over a narrow zone (10 ms). In two patients the zone remained similar in width but the coupling intervals were longer; in the fourth patient (case 3) the zone was abolished. The rate of sustained re-entry tachycardia was slower in all. In three patients re-entry tachycardia terminated spontaneously after a brief period (Fig. 4); this had never occurred during the control study. In two patients termination occurred in the anterograde direction while in the other it occurred in the retrograde pathway.

The results of treatment with amiodarone in group 2 are shown in Table 3. Four patients remained symptom-free on maintenance therapy, though one patient suffered a relapse of his tachycardia six weeks after his dose was decreased to 200 mg a day; he has been maintained on 400 mg a day without symptoms. Six patients had limited electrophysiological studies while on amiodarone and it was possible to initiate sustained re-entry tachycardia in all; this complemented the findings of ambulatory monitoring in the five patients who noticed no improvement. As in group 1, the tachycardia was slower and the initiation zone did not change consistently: it was wider in three and narrower in two. In the other patient two atrial extrastimuli were required to initiate tachycardia both during the control study and while on amiodarone. In one patient (case 13) in whom a
more complete electrophysiological study was performed while on amiodarone the change in rate of the tachycardia was the result of lengthening of conduction time in both the atrioventricular node and the accessory pathway. The limited study on the patient who relapsed on the maintenance dose of amiodarone (case 8) showed that it was possible to initiate re-entry tachycardia but that each episode terminated with block in the retrograde limb of the circuit (Fig. 5). The results of ambulatory monitoring performed on the patients who became asymptomatic on amiodarone showed them to be virtually free of extrasystoles, while the symptomatic group continued to have extrasystoles which often initiated tachycardia (Fig. 6). Of the patients in groups 1 and 2 who had reciprocating atrioventricular tachycardia and were studied while on amiodarone there was no consistent difference in the electrophysiological changes between those who responded and those who did not.

All but one in group 3 were asymptomatic after three months of treatment, the failure occurring in a patient with atrial flutter. In the other patients ambulatory monitoring showed that, in keeping with the clinical features, there was no sustained arrhythmia: in particular, the two patients with prolonged sinus node recovery times showed neither bradycardia nor sinus arrest. The conspicuous action of amiodarone on atrial myocardium was demonstrated in the patient in whom atrial flutter became established (Fig. 7). In the control state the atrial rate was 330 a minute with 2:1 atrioventricular conduction (Fig. 7b). After two weeks of treatment with amiodarone the atrial rate had fallen to 220 and 2:1 block persisted (Fig. 7c). Two weeks later the atrial rate was even slower at 190 a minute, still showing a 2:1 atrioventricular response (Fig. 7d). Rapid right atrial pacing induced sinus rhythm (Fig. 7e) which has been maintained on continuous treatment (Fig. 7f).

**SIDE EFFECTS**

Corneal microdeposits were seen in all patients but in none was it necessary to discontinue the drug: there were no visual symptoms. The alterations in thyroid function tests reflected the interference of amiodarone with the metabolism of thyroid hormones\(^{50, 51}\); all patients remained euthyroid.

Two patients stopped amiodarone because of other side effects, in both after several months of successful treatment. Case 6 had been free of arrhythmia for 23 months for the first time in 36 years when he developed photodermatitis\(^{52}\); when treatment was stopped, tachycardia recurred and...
the dermatitis gradually improved. In case 19 in whom paroxysmal atrial fibrillation occurred two to six times a week he had no attacks for four months while on amiodarone. He stopped treatment, however, because of persistent insomnia, restlessness, and nightmares; subsequently arrhythmias have recurred though less frequently. In other patients difficulty in sleeping, unpleasant dreams, a bitter taste in the mouth, and restlessness have been noted, but in none were the symptoms severe enough to warrant discontinuing treatment.

**Discussion**

Amiodarone was introduced for the treatment of coronary artery disease because it was shown to cause coronary vasodilatation and to reduce the heart rate and thereby decrease myocardial oxygen consumption. At the cellular level there is no apparent membrane stabilising effect when it is given orally and its antiarrhythmic action appears to result from prolongation of the duration of the action potential of myocardial cells. No effect has been seen on resting membrane potential or action potential amplitude and there is only minimal change in the maximum rate of rise of the action potential. Precisely how these effects are achieved is uncertain though non-competitive antagonism of both alpha- and beta-adrenergic activity, and attenuation of the effects of glucagon on the heart have been described. Though the clinical action of the drug in man mimics the effects of hypothyroidism and it is an iodinated compound, there is no evidence that it interferes with the cardiac effects of thyroid hormones.

Electrophysiological studies in man have disclosed that amiodarone increases the refractory periods of atrial and ventricular myocardium, prolongs conduction time in the atrium, and lengthens the refractory period of the atrioventricular node and accessory pathways. In clinical studies it has been shown to be effective against a wide variety of ventricular and supraventricular arrhythmias, particularly reciprocating atrioventricular tachycardia associated with the Wolff-Parkinson-White syndrome. Wellens et al. were able to initiate tachycardia on repeat electrophysiological testing in 10 of their 15 patients: the possibility that this was because their second study was too soon (two weeks) after the start of treatment is not applicable to our patients who were tested three months after the start of treatment. This latter study was performed 26 to 85 days after the start of treatment and re-entry tachycardia could not be initiated in any of the four patients re-tested.

The limited pharmacodynamic information suggests that amiodarone is somewhat variably absorbed resulting in low blood levels because of strong tissue-binding and long half-life of about 28 days.

In this study 21 patients were treated with the...
same reducing regimen of oral amiodarone. Restrictions on its use in Great Britain allow it to be tried only after conventional treatment has failed. Fifteen became asymptomatic during the first month of treatment and all but one could be maintained on 200 mg a day.

In group 1 various combinations of conventional antiarrhythmic drugs including disopyramide, quinidine, and procainamide had failed to control the symptoms or reduce the ventricular rate appreciably during atrial fibrillation. The atrial stabilising property of amiodarone was reflected in a greater resistance to the induction of atrial fibrillation, and in its spontaneous termination. The depressant action of the drug on antegrade conduction via the accessory pathway protected against the profound haemodynamic effects of atrial fibrillation in these patients.

Drugs that prevent re-entry atrioventricular tachycardia may do so by abolishing initiating extrasystoles or modifying circuit behaviour, as well as other less common factors. Modifications of circuit behaviour include abolishing the initiation zone as well as depressing conduction in either atrioventricular pathway so that any tachycardia is terminated promptly. In this series clinical benefit seemed more closely related to spontaneous termination of induced tachycardia than to changes in initiation zone from the atria. The method of termination was either by block in the retrograde direction, presumably the accessory pathway, or in the antegrade direction. While antegrade block may occur in either the atrioventricular node or His-Purkinje system, its occurrence in one patient when he was supine, but not when he was upright, suggested termination in the atrioventricular node.29 We have examined only one method of initiation of re-entry tachycardia, albeit the most common, and it may be that other effects on the mechanism of induction of tachycardia played a part. Paradoxical aggravation of the tendency to tachycardia sometimes seen with drugs30 did not occur in any patient.

Twenty-four-hour monitoring corroborated the clinical impression of therapeutic benefit. In those patients who failed to respond, supraventricular extrasystoles persisted, often followed by paroxysms of re-entry tachycardia, while in the asymptomatic group the absence of extrasystoles was striking.

In the patients with atrial fibrillation and flutter, the absence of arrhythmias during 24-hour electrocardiographic monitoring correlated well with clinical improvement. No patient had asystolic pauses or periods suggesting sinusatural block. While the clinical importance of any action of amiodarone on the sinus node remains unresolved31 32 none of our patients had prolonged sinus node recovery times after amiodarone.

The regimen in these patients is similar to that used by other investigators8; available evidence suggests that a steady state is achieved using a single daily dose though there is no information at present on the range of blood levels achieved. While variability in the metabolism and excretion of the drug may well explain the differences in clinical efficacy, those who failed to benefit did so at the maximum dose. The selection of patients by virtue of their failure to respond to conventional antiarrhythmic agents may partly explain our lower success rate than that of others.8

Amiodarone appears to act widely on the conducting system and myocardium and may, therefore, be particularly effective in complex arrhythmias, including some cases of paroxysmal re-entry atrioventricular tachycardia. We have found it especially effective in atrial fibrillation, and where this is associated with a rapid ventricular rate because of the Wolff-Parkinson-White syndrome amiodarone may obviate surgical treatment. The incidence of side effects remains small but because experience is still somewhat limited close observation is recommended. Further pharmacodynamic studies are required to determine the absorption and metabolism of the drug and to ensure that it is used safely and effectively in suitable patients.

References


Requests for reprints to Dr Dennis Krikler, Hammersmith Hospital, Du Cane Road, London W12 0HS.