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Amiodarone prophylaxis for tachycardias after coronary artery surgery: a randomised, double blind, placebo controlled trial

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Abstract

***Background*—Arrhythmias are a common cause of morbidity after cardiac surgery. This study assessed the efficacy of prophylactic amiodarone in reducing the incidence of atrial fibrillation or flutter and ventricular arrhythmias after coronary artery surgery.**

***Methods*—A double blind, randomised, placebo controlled trial. 60 patients received a 24 hour intravenous infusion of amiodarone (15 mg/kg started after removal of the aortic cross clamp) followed by 200 mg orally three times daily for 5 days, and 60 patients received placebo.**

***Results*—6 patients (10%) in the amiodarone group and 14 (23%) in the placebo group needed treatment for arrhythmias (95% confidence interval (95% CI) for the difference between groups was 0 to 26%, p = 0·05). The incidence of supraventricular tachycardia detected clinically and requiring treatment was lower in the amiodarone group (8% amiodarone *v* 20% placebo, 95% CI 0 to 24%, p = 0·07). The incidence detected by 24 hour Holter monitoring was similar (17% amiodarone *v* 20% placebo). Untreated arrhythmias in the amiodarone group were either clinically benign and undetected (n = 3) or the ventricular response rate was slow (n = 2). Age > 60 years was a positive risk factor for the development of supraventricular tachycardia in the amiodarone group but not in the placebo group. Fewer patients had episodes of ventricular tachycardia or fibrillation recorded on Holter monitoring in the amiodarone group (15% amiodarone *v* 33% placebo, 95% CI 3 to 33%, p = 0·02). Bradycardia (78% amiodarone *v* 48% placebo, 95% CI 14% to 46%, p < 0·005) and pauses (7% amiodarone *v* 0% placebo) occurred in more amiodarone treated patients. Bradycardia warranted discontinuation of treatment in one patient treated with amiodarone.**

***Conclusions*—The incidence of clinically significant tachycardia was reduced by amiodarone. The ventricular response rate was slowed in supraventricular tachycardia, but the induction of bradycardia may preclude the routine use of amiodarone for prophylaxis.**

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Supraventricular tachycardias are a common cause of morbidity after coronary artery surgery, with a reported incidence of 10%–40%.[1–3] Although these are usually benign arrhythmias, potential complications include sustained atrial fibrillation, embolic cerebrovascular accidents, and haemodynamic compromise. To these may be added the adverse effects of antiarrhythmic drugs and a prolonged stay in hospital.[4] Ventricular arrhythmias are less common but potentially fatal when they occur.

Several studies have investigated the efficacy of pharmacological prophylaxis in reducing the incidence of supraventricular tachycardias after cardiac surgery. A variety of β blockers has been used with variable success.[5–7] Digoxin has not always been effective and may increase the incidence of ventricular extrasystoles.[8 9] Verapamil has generally not been effective and has significant negatively inotropic effects.[10 11] Interpretation of many of these studies is hampered by study design, the exclusion of large groups of patients, small study groups, and varying methods of clinical detection of arrhythmias.

Amiodarone is a Vaughan-Williams classification class III antiarrhythmic agent that prolongs the duration of action potentials in both atrial and ventricular muscle.[12] It also has non-competitive α and β sympathetic blocking effects[13] and is a coronary vasodilator.[14] Amiodarone is effective in converting atrial fibrillation to sinus rhythm[15] and in the chronic prophylaxis of atrial fibrillation refractory to other drugs.[16] Defibrillation after cardiac surgery is easier in patients pretreated with amiodarone.[17] Intravenous amiodarone suppressed both supraventricular and ventricular arrhythmias in a study of patients after coronary artery surgery.[18]

In this randomised, double blind, placebo controlled study, we tested the hypothesis that prophylactic amiodarone would reduce the incidence of tachycardia after coronary artery surgery.

Patients and methods

Over a two year period, from March 1989 to November 1990, 120 patients undergoing coronary artery surgery at the Oxford Heart Centre were entered into the study. Exclusion criteria were a history of supraventricular or ventricular arrhythmias, atrioventricular conduction abnormalities, thyroid disease, warfarin treatment, and the need for concomitant surgery.

On a double blind basis, patients were randomly assigned to receive amiodarone or placebo. Twenty four hour intravenous infusion of amiodarone (15 mg/kg to a maximum of 1500 mg) or placebo (5% dextrose) was started after removal of the aortic cross clamp and was followed by 200 mg of amiodarone or placebo orally three times daily for five days.

On entry into the study the following data were recorded (table 1): demography; New York Heart Association anginal class; history of myocardial infarction, hypertension, and diabetes mellitus; cardiothoracic ratio; vessels significantly diseased (> 50% reduction in luminal diameter) and, left ventricular ejection fraction (by angiogram). No patient had clinical or biochemical evidence of significant renal dysfunction and lung fields were clear on all preoperative chest *x* ray films.

Standard anaesthetic and surgical techniques were used, with all operations performed by one surgeon (SW). Regular medications apart from aspirin were continued up to the morning of operation. Forty seven (78%) patients in the amiodarone group and 48 (80%) patients in the placebo group were taking , blockers before the operation. Premedication was by papaveretum (10–20 mg) and hyoscine (0·4 mg) intramuscularly one hour before operation. Anaesthetic induction, maintenance, and neuromuscular blockade were achieved with fentanyl (10–15 Ìg/kg), thiopentone (1–2 mg/kg), pancuronium bromide (0·1–0·15 mg/kg), oxygen with nitrous oxide (50%), and halothane (0·5%–1·0%). The extracorporeal circuit consisted of a roller pump, a two stage right atrial cannula for venous drainage, a cardiotomy reservoir (Sorin Biomedica), a membrane oxygenator (Cobe CML), and an arterial line filter (Pall) with arterial return to the ascending aorta. The circuit was primed with 2–2·5 l Ringer's lactate. Heparin (3 mg/kg body weight) was infused to maintain an activated clotting time of over 400 seconds during bypass. Flow rates of 2·4 l/m2/min were used, to maintain a systemic perfusion pressure of 40–60 mm Hg. Myocardial preservation was by cold cardioplegia supplemented by ice or slush topical hypothermia and a core temperature of 30°C to 32°C. At the end of bypass, anticoagulation was reversed by protamine sulphate (1 mg/kg body weight). A temporary ventricular epicardial pacing wire was left in situ in all patients. Table 2 gives details of the operation.

Continuous electrocardiographic Holter monitoring (Oxford Medilog 4000-III, Oxford Medical Limited) was started after skin closure and continued for six days. Twelve lead electrocardiograms were recorded before operation and on days 1, 3, and 5 after operation, and when any arrhythmia was clinically detected. Clinical assessment of arrhythmias was by continuous bedside electrocardiographic monitoring for the first 48 hours after operation with single lead printout of any arrhythmias, followed by four to six hourly routine nursing observations.

Clinically significant supraventricular tachycardia was defined as a sustained (over five minutes) supraventricular rhythm of > 100 beats per minute other than sinus tachycardia; this was considered to require treatment. Significant supraventricular tachycardia on Holter monitoring was defined as any episode of atrial fibrillation or flutter lasting more than one minute. On development of a supraventricular or ventricular arrhythmia judged on clinical grounds to require treatment, patients were withdrawn from the study and the blinding code broken; digoxin was then used as primary treatment of supraventricular tachycardia with the dose halved in patients already given amiodarone.

For statistical analysis, all patients were included in the intention to treat population. Pearson's χ^2 test was used for comparison of categorical variables. In all analyses a two tailed significance level of 5% was regarded as significant. The software package SAS was used for analysis.

All patients gave verbal informed consent for the study, which had local ethics committee approval.

Table 1 Preoperative data

Data	*Amiodarone (n = 60)*	*Placebo (n = 60)*
Age (yr):		
Mean (SD)	59 (7·6)	60 (9·1)
Range	35–76	36–73
Sex M:F, (n)	55:5	50:10
NYHA anginal class (n):		
II and III	35	45
IV	25	15
Diabetes mellitus (n)	5	4
Previous infarct (n)	30	34
Hypertension (n)	21	25
Cardiothoracic ratio (mean (SD))	47 (4·3)	47 (4·3)
LVEF:		
Mean (SD)	0·65 (0·12)	0·61 (0·15)
Range	0·39–0·88	0·22–0·91
Diseased vessels per patient (n)		
Left main	2	7
1	0	5
2	23	12
3	35	36

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

Results

There were no deaths in this series. The overall need for treatment of arrhythmias was six (10%) in the amiodarone group and 14 (23%) in the placebo group, the 95% confidence interval (95% CI) of the difference between groups was 0% to 26%, p = 0·05.

Clinically significant supraventricular

Table 2 Details of operation

Data	*Amiodarone*	*Placebo*
Duration (min):		
Bypass (mean (SD))	56·8 (14·7)	54·8 (13·9)
Cross-clamp (mean (SD))	34·0 (8·7)	34·0 (9·4)
Internal mammary artery graft (n)	32	37
Grafts per patient (n):		
1	0	2
2	18	15
3	32	28
4	10	15

tachycardia occurred in five (8%) amiodarone treated patients (four atrial fibrillation, one atrial flutter) and in 12 (20%) of the placebo group (10 atrial fibrillation, two atrial flutter). This difference did not achieve statistical significance (95% CI 0% to 24%, p = 0·07).

On Holter analysis, the incidence of supraventricular arrhythmias was similar between the two groups (10 (17%) amiodarone, 12 (20%) placebo). Two untreated patients in the amiodarone group also had the arrhythmia detected clinically but intervention was not required as the ventricular response rate was slow (maximum pulse rates 90 and 110 beats/min).

On Holter analysis, the maximum ventricular rates in patients with supraventricular tachycardia were slower in amiodarone treated patients (median 158 (130–217) beats/min amiodarone, 190 (140–219) beats/min placebo, median difference 31, 95% CI −4 to 45, p = 0·08).

All supraventricular tachycardias detected occurred during the first five postoperative days. The peak time of occurrence was 48–96 hours in the amiodarone group and 24–72 hours in the placebo group.

One patient in the amiodarone group (ventricular fibrillation) and two patients in the placebo group (one ventricular fibrillation, one multifocal ventricular extrasystoles) required treatment for ventricular arrhythmias; ventricular fibrillation on both occasions occurred during the first 12 hours after operation and both had new Q waves on the electrocardiogram. Fewer amiodarone treated than placebo patients had salvos of ventricular tachycardia (three or more consecutive ventricular extrasystoles) recorded on Holter (nine (15%) amiodarone, 20 (33%) placebo, 95% CI 3% to 33%, p = 0·02).

In the amiodarone group, two patients required inotropic (adrenaline) and three required chronotropic (isoprenaline) support in the first 24 hours after operation. No patients in the placebo group required inotropic or chronotropic support.

Ventricular pacing was required in 10 amiodarone treated and five placebo treated patients, all for a period of less than 24 hours immediately after operation. The overall greater need for isoprenaline or pacing in patients receiving amiodarone was not significant (95% CI 0% to 24%, p = 0·07).

Bradycardia (< 50 beats/min) occurred in more amiodarone treated patients (47 (78%) amiodarone, 29 (48%) placebo, 95% CI 14% to 46%, p < 0·005) and led to discontinuation of the infusion after seven hours in one patient. Pauses (> 1·9 s) were recorded in four amiodarone treated patients and no patients in the placebo group. None of these episodes was recurrent or required intervention. On postoperative electrocardiograms, atrioventricular block was shown in two amiodarone (one 1st degree, one Mobitz type II), and two placebo patients (both 1st degree). Three amiodarone patients had right bundle branch block and two placebo patients had left bundle branch block. New Q waves (>0·04 s duration) occurred in five (8%) amiodarone and seven (12%) placebo patients.

Table 3 Risk factors for supraventricular arrhythmia on 24 hour Holter analysis

Risk factors	*Amiodarone*	*Placebo*
Age (yr):		
<60	0/24 (0%)	6/33 (17%)
>60	10/36 (28%)	6/27 (22%)
Angina:		
On exertion	6/35 (17%)	8/45 (18%)
At rest	4/25 (16%)	4/15 (27%)
Endarterectomy:		
Yes	3/15 (20%)	2/14 (14%)
No	7/45 (16%)	10/46 (22%)
Cross clamp (min)		
<35	2/31 (6%)	9/32 (28%)
>35	8/29 (28%)	3/28 (11%)
LVEF:		
<0·65	5/26 (19%)	7/34 (21%)
>0·65	5/32 (16%)	5/25 (20%)

*p < 0·05.
LVEF, left ventricular ejection fraction.

There was an increased incidence of supraventricular tachycardia with age >60 years in the amiodarone but not in the placebo group. Anginal class, ejection fraction at entry, right coronary endarterectomy, and ischaemic time had no significant effect on the incidence of supraventricular tachycardia (table 3).

Three amiodarone treated patients had adverse events. One cerebrovascular accident, and one acute sinus node dysfunction (withdrawn from study) were not considered to be drug related; bradycardia in one patient required ending the treatment. Two patients in the amiodarone group did not complete the study, refusing to continue because of nightmares. One adverse event (rash) occurred in the placebo group.

Time to discharge from hospital was similar in the two groups (median seven (six to 15) days amiodarone, seven (six to 38) days placebo).

Discussion

Amiodarone significantly reduced the incidence of clinically significant tachycardia in this study. In the supraventricular subgroup, Holter monitoring data showed that the effect of amiodarone was due to reduction of the ventricular response rate rather than overall prevention of the arrhythmias.

Amiodarone is potentially useful for prophylaxis of arrhythmias, but has complex side effects associated with chronic use.[19] Short-term use, however, has been shown to be effective and safe in the suppression and treatment of atrial and ventricular arrhythmias after cardiac surgery.[18 20] An advantage of amiodarone is that negative inotropic effects are uncommon when given slowly,[14] although an initial intravenous bolus dose may cause significant myocardial depression in patients with an ejection fraction < 0·35.[21] Patients with low ejection fractions, those most at risk of haemodynamic compromise in the presence of supraventricular tachycardia, were not excluded from our study.

The amiodarone dose used was empirical. As oral amiodarone does not reach its maximal antiarrhythmic effect for seven to 20

days,[22] an intravenous infusion was given over the first 24 hours. Onset of the antiarrhythmic effect of intravenous amiodarone is probably rapid, as it converts atrial fibrillation to sinus rhythm in almost 50% of patients within 30 minutes.[23] Plasma concentrations of amiodarone or its metabolite desmethylamiodarone were not measured in our study as they correlate poorly with clinical effects.[24]

The reduction in the ventricular response rate in the presence of supraventricular tachycardia may be explained by prolongation of the refractory period of the atrioventricular node.[25] Amiodarone also has calcium slow channel blocking effects.[26] Lengthening of atrioventricular nodal refractoriness and noncompetitive adrenergic antagonism seem to be the main antiarrhythmic effects of intravenous amiodarone.[24] The ability of amiodarone to lower the ventricular response rate in the presence of supraventricular tachycardia has been previously shown.[27]

The detection of all supraventricular tachycardias in the first five postoperative days is consistent with other reports. Although not conclusively shown, the delayed occurrence of these arrhythmias in the amiodarone group may reflect their suppression particularly by the intravenous infusion given over the first 24 hours.

The incidence of potentially serious ventricular arrhythmias detected by Holter monitoring was reduced by amiodarone. Prolongation of the duration of the action potential is a potent antifibrillatory mechanism and amiodarone is known to be highly effective in preventing recurrent ventricular tachycardia or ventricular fibrillation resistant to other antiarrhythmic drugs. Ventricular arrhythmias that required intervention occurred rarely in our study, and it was therefore not possible to show any advantage of amiodarone for the prevention of these, but salvos of ventricular tachycardia recorded by Holter monitoring were considerably reduced.

A significant decline in heart rate occurred during infusion of amiodarone, suggesting non-competitive sympathetic blockade or slowing of phase 4 depolarisation within the sinus node.[12 13] This effect of slowing of sinus rhythm particularly in patients already on β blockers may preclude routine use of amiodarone in patients undergoing coronary artery surgery and there was some increased need for chronotropic support in the first 24 hours. In this series, however, heart rate was sufficiently slow to have to end the treatment in only one patient.

The development of acute sinus node dysfunction in another patient was not considered to be drug related by an independent cardiologist as it occurred shortly after surgery, did not improve after the end of the infusion, and required insertion of a permanent pacemaker. Two patients did not wish to continue the study after nightmares, a known side effect of amiodarone and therefore possibly drug related.

The difference in frequency of arrhythmias between age groups suggests that amiodarone may be less effective as prophylaxis in those over 60 years. There is also some evidence that the use of β-blockers for the prevention of atrial fibrillation or flutter is less effective with increasing age.[28] Several studies have now established that increasing age is the most important known risk factor for the development of supraventricular tachycardia after coronary artery surgery.[28 29] That this was not found in our placebo group may be explained by the relatively small size of the population.

In conclusion, amiodarone reduced the incidence of clinically important arrhythmias. In the supraventricular subgroup, its effect appeared to be mainly due to a decrease in the ventricular response rate rather than overall prevention of arrhythmias. An increased incidence of bradycardia is a potential disadvantage that deters us from advocating the routine use of amiodarone for the prophylaxis of tachycardia after coronary artery surgery.

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