Intravenous amiodarone or magnesium sulphate is not cost-beneficial prophylaxis for atrial fibrillation after coronary artery bypass surgery

M. M. Treggiari-Venzi[1]*, J.-L. Waeber[1], T. V. Perneger[2], P. M. Suter, R. Adamec[3] and J.-A. Romand[1]*

[1]Division of Surgical Intensive Care, Department of Anaesthesiology, Pharmacology and Surgical Intensive Care, [2]Institute of Social and Preventive Medicine and [3]Cardiology Centre, University Hospital of Geneva, Switzerland

**Corresponding authors: Division of Surgical Intensive Care, University Hospital of Geneva, CH-1211 Geneva 14, Switzerland*

Our aims were to examine whether the administration of amiodarone or magnesium sulphate after coronary artery bypass graft surgery (CABG) could reduce the occurrence of atrial fibrillation, and to identify the risk factors associated with atrial fibrillation after CABG. Patients scheduled for elective CABG (n=155) were allocated randomly, in a controlled double-blind study, to receive immediately after surgery a 72-h infusion of amiodarone (900 mg per 24 h), magnesium (4 g per 24 h) or placebo (0.9% NaCl; 50 ml per 24 h) intravenously. A 72-h Holter ECG was recorded concomitantly. The primary end-point was the prevention of atrial fibrillation; its onset was considered as prophylactic failure. An interim safety analysis was performed in 147 patients. The cumulative occurrence of atrial fibrillation was 27% in the placebo group, 14% in the amiodarone group (P=0.14) and 23% in the magnesium group (P=0.82). Although amiodarone delayed the onset of the first tachyarrhythmic episode (P=0.02), it was associated with the need for longer periods of vasoactive drug infusion and invasive monitoring and a longer stay in the intensive care unit. Variables associated with the onset of atrial fibrillation were older age (odds ratio 1.9) and a plasma magnesium concentration at 24 h of less than 0.95 mmol litre^{-1} (odds ratio 6.7). Postoperative administration of amiodarone reduced the occurrence of atrial fibrillation after elective CABG surgery, but was associated with a longer duration of cardiovascular instability and longer need for intensive care; magnesium prophylaxis had no effect. Advanced age and a low plasma magnesium concentration are risk factors for postoperative atrial fibrillation.

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Cardiac arrhythmias occur in 11–40% of patients after coronary artery bypass graft (CABG) surgery, atrial fibrillation (AF) being the most common supraventricular arrhythmia.[1 2] Postoperative AF has a negative effect in terms of perioperative morbidity (myocardial infarction, stroke), 30-day and 6-month mortality, stay in the intensive care unit (ICU) and hospital costs.[3–7] Perioperative intravenous[8 9] or oral amiodarone[10] has been shown to decrease the occurrence of AF after cardiac surgery. Magnesium prophylaxis for postoperative AF has also been reported, with conflicting conclusions.[11–14] The aim of the present study was to evaluate the effects of postoperative administration of intravenous amiodarone or magnesium sulphate in preventing AF and on postoperative recovery. In addition, variables predisposing to postoperative AF were assessed.

Methods

Patients scheduled for elective coronary bypass grafting (CABG) were allocated randomly in a double-blind, placebo-controlled study. The study protocol was approved by our institutional ethics committee and all patients gave written consent the day before surgery. Exclusion criteria

were refusal of consent, chronic AF, second- or third-degree atrioventricular block, pacemaker dependence, amiodarone treatment in the year preceding the operation, thyroid disease, other associated heart surgery, valvular disease, chronic renal failure (defined as a creatinine clearance rate less than 30 ml min^{-1}) and liver dysfunction (prothrombin time <50% and/or bilirubin >35 μmol $litre^{-1}$ and/or the presence of ascites).

Preoperative and postoperative management

Before transfer to the operating room, all patients received premedication with diazepam and morphine, and chronic β-blocker therapy was replaced with metoprolol by mouth. General anaesthesia was induced and maintained with midazolam, fentanyl and pancuronium bromide, adjusted to body weight and elimination half-time. Systemic hypothermic (28°C) cardiopulmonary bypass (CPB; aortic and right atrium cannulation) associated with repeated cold cardioplegic-induced cardiac arrest was used. At the end of the surgical procedure, the patients were transferred to the ICU.

Weaning from mechanical ventilation and tracheal extubation were done as early as possible. Weaning from catecholamine infusion was guided by standard haemodynamic criteria. The pulmonary artery catheter was removed when there was no evidence of cardiac dysfunction and no need for catecholamine infusion. Patients were discharged from the ICU to the ward as soon as their haemodynamic and respiratory condition was stable.

Study design

The randomization procedure was accomplished by the Pharmacy Department using colour-coded spheres extracted from an opaque container. Additional patients were allocated to compensate for technical drop-outs. Patients were allocated to one of three groups, to receive a 72-h continuous intravenous infusion of amiodarone 900 mg per 24 h (Cordarone; Sanofi-Winthrop, Basel, Switzerland) or magnesium sulphate 4 g (16 mmol, 32 mEq) per 24 h (Bichsel, Interlaken, Switzerland) or placebo (0.9% NaCl), starting within 1 h of arrival in the ICU. The study drugs were prepared daily in an opaque syringe and tubing (Perfusor; Braun, Melsungen, Germany) by an independent observer. Throughout the 72-h infusion period, a Holter ECG recording (Cardiocorder three-channel recorder, model 459; Delmar Avionics, Irvine, California, USA) was obtained. Additional 12-lead ECGs were recorded every 12 h.

The primary end-point of the study was the prevention of AF. If AF occurred, the prophylaxis was considered to have failed and the study was terminated; the drug code was opened and the patient was treated as appropriate. The Holter ECG recording was analysed on completion of the 72-h study period or earlier if the study was terminated because of arrhythmia. Supraventricular arrhythmia episodes were then detected visually and printed for accurate diagnosis by two of the investigators. Considering the potential adverse effect of acute amiodarone infusion,[15] an intermediate safety analysis was planned after the inclusion of half of the patients.

Definitions of supraventricular arrhythmia

Supraventricular tachycardia was defined as an arrhythmia of more than three narrow QRS complexes at a rate greater than 100/b.p.m. and lasting more than 30 s. Atrial fibrillation was defined as totally irregular atrial rhythm leading to irregular ventricular rhythm.

Data collection

Relevant patient characteristics, associated medical conditions, concomitant treatment, pulmonary and renal function tests were recorded. Also recorded were perioperative variables, including aortic cross-clamping and CPB duration, the number and type of coronary bypasses performed, and treatment at weaning from CPB. After surgery, heart rate, mean arterial pressure, central venous pressure and, when available, mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index (triplicate normal saline injection at room temperature, thermodilution technique) and stroke volume index were recorded 6-hourly. Arterial blood gases and electrolytes (Na^+, K^+ and Ca^{2+}) were also measured at the same intervals. Total plasma magnesium concentrations were measured 12-hourly. Additional recorded variables included postoperative complications and drug-related side-effects. Data obtained from the Holter ECG recording were the number of isolated or paired supraventricular ectopic beats and the number of supraventricular tachycardia runs, with their ventricular response rate and the respective count of QRS complexes. To adjust for the variability in the number of beats per hour of the ECG Holter recordings, the number of abnormalities was normalized to 1000 recorded beats.

Statistical analysis

Continuous variables were expressed as mean (SD) unless otherwise specified. The two intervention groups were compared with placebo using the unpaired *t*-test when dealing with approximately normally distributed variables and the Mann–Whitney test otherwise. The χ^2 test was used for categorical variables. Kaplan–Meier analysis was used to analyse the delay in the onset and the duration of arrhythmia in the three groups. Potential predictors of the development of AF included patient characteristics, perioperative myocardial infarction and plasma magnesium concentration. Logistic regression was used to assess univariate associations between predictor variables and the onset of AF. All predictor variables that exhibited

Table 1 Baseline clinical characteristics (n=147). Values are mean (SD) unless indicated otherwise. LVEF, left ventricular ejection fraction; FEV_1/FVC, forced expiratory volume at 1 s/forced vital capacity; ACE, angiotensin converting enzyme

	Patient group		
	Amiodarone (n=49)	**Placebo (n=51)**	**Magnesium (n=47)**
Age (yr)	65 (44–78)	65 (37–88)	65 (46–81)
Sex (M/F)	43/6	43/8	42/5
Weight (kg)	78 (11)	76 (12)	76 (10)
Myocardial infarction <6 months (n)	9	9	3
Myocardial infarction >6 months (n)	20	14	15
History of supraventricular arrhythmias (n)	1	2	1
Hypertension (n)	24	17	19
Diabetes (n)	13	6	6
Creatinine clearance (ml min^{-1})	75 (20)	72 (23)	71 (20)
History of stroke (n)	1	2	2
Previous heart surgery (n)	2	4	3
LVEF (mean %)	58 (14)	57 (13)	62 (15)
Diseased vessels [median (range)]	3 (1–3)	3 (1–3)	3 (1–3)
FEV_1/FVC (% predicted)	92 (11)	95 (10)	91 (12)
Concomitant cardiac medication			
Nitrate derivatives (n)	45	41	40
β–Adrenergic blocker (n)	27	33	24
Calcium channel blocker (n)	12	15	16
Digoxin (n)	1	2	0
ACE inhibitor (n)	13	10	8
Diuretic (n)	9	4	4
Coronary bypass grafts [median (range)]	3 (1–5)	3 (1–5)	3 (1–5)
Duration of CPB (min)	157 (54)	148 (47)	140 (38)
Duration of aortic cross-clamping (min)	100 (39)	103 (39)	91 (26)

significant univariate associations with AF (P<0.05) were tested in multivariate models; the final model included only statistically significant predictors (at the P<0.05 level).

Sample size and power

The frequency of AF detected by Holter ECG monitoring after CABG surgery is about 40%.[16] From previous studies on AF prophylaxis after CABG surgery,[8 17 18] we expected a reduction of 50% in the occurrence of AF. Ninety-one patients per group would have been needed to detect such a difference with a power of 80% and α=5%. An interim analysis was planned after inclusion of 50 patients in each group.

Results

Study population

The first 155 patients meeting our inclusion criteria were studied over an 18-month period. During this period, 299 patients were admitted to our 20-bed surgical Intensive Care Unit after elective CABG. Six patients were excluded from the analysis because of early withdrawal due to haemodynamic instability [four in the amiodarone group: hypotension (1), major bradycardia (2), third-degree atrioventricular block (1); one in the magnesium group (cardiac arrest) and one in the placebo group (pacemaker dependence); P=0.2 between groups)]; two additional patients (one in the placebo and one in the magnesium group) were excluded because of incomplete data availability due to technical failure of the Holter ECG recording. The final number of patients included in the interim data analysis was 147 (amiodarone 49, magnesium 47, placebo 51).

The mean age of evaluable patients was 65 yr (range 37–88). The three groups were similar in baseline characteristics and surgical procedure (Table 1). Variables recorded on arrival at the ICU, including haemodynamics, laboratory and electrocardiograph findings, were similar among the three groups (data not shown).

Tachyarrhythmias

The frequency of AF longer than 30 s was 27% in the placebo group, 14% in the amiodarone group (P=0.14) and 23% in the magnesium group (P=0.82) (Table 2). The time to onset of AF after the start of the prophylactic infusion is illustrated in Figure 1 (log-rank test: amiodarone versus placebo P=0.17, magnesium versus placebo P=0.5). Among patients who developed AF, its onset was significantly delayed in the amiodarone group compared with the placebo group (Table 2).

Predictors of postoperative arrhythmia

The univariate analysis identified the following six variables that were positively associated with the subsequent onset of postoperative atrial fibrillation at the level of P<0.05: age; history of supraventricular tachycardia; creatinine clearance; perioperative myocardial infarction; duration of pulmonary artery catheter monitoring; and plasma magnesium concentration 24 h after the operation <0.9 mmol $litre^{-1}$. From the multivariate logistic regression model,

Table 2 Occurrence and number of episodes of atrial fibrillation. *Difference between amiodarone and placebo. †Difference between magnesium and placebo. HR, heart rate

	Patient group				
	Amiodarone (*n*=49)	***P****	**Placebo (*n*=51)**	***P*†**	**Magnesium (*n*=47)**
AF					
Occurrence [*n* (%)]	7 (14%)	0.14	14 (27%)	0.82	11 (23%)
Delay in onset after start of infusion [h; mean (SD)]	54 (10)	0.02	42 (12)	0.37	45 (14)
Episodes [*n* (max. number of episodes/patient)]	11 (5)	0.28	14 (1)	0.88	17 (3)
HR during AF [b.p.m.; mean (SD)]	140 (18)	0.12	153 (18)	0.26	146 (9)

independent predictors were older age (OR=1.9 for every 10 yr) and plasma magnesium concentration <0.9 mmol litre^{-1} 24 h after the operation (OR=6.7). This model classified correctly 82% of all observations.

Postoperative course

Haemodynamics, blood gas and electrolytes

No differences in haemodynamic values were found compared with placebo, except that patients receiving intravenous amiodarone had slower heart rates from 18 h after starting the infusion (Fig. 2). No differences were observed in pH, Pa_{CO_2} and Pa_{O_2}, or in blood concentrations of potassium and ionized calcium. In the magnesium group, higher plasma magnesium levels compared with baseline and the placebo group (P<0.01) were detected 12 h after starting the infusion and thereafter.

Postoperative complications

The incidences of myocardial infarction, cardiac arrest, requirement for surgical haemostasis and prolonged tracheal intubation (>72 h) were similar among the three groups. The occurrence of AF was not associated with attributable morbidity.

Compared with the placebo group, patients in the amiodarone group required a longer period of catecholamine infusion [placebo 19 (13), amiodarone 32 (18) h; P<0.01] and concomitant invasive monitoring with an indwelling pulmonary artery catheter [placebo 31 (14) h, amiodarone 42 (16) h; P<0.01]. In the magnesium group, neither the duration of catecholamine infusion [10 (11) h, not significant] nor the duration of invasive monitoring [31 (10) h, not significant] was different from the values for the placebo group.

The length of stay in the ICU was significantly longer in patients receiving amiodarone (median 4 days, range 2–9 days) than in the placebo group (3, 2–7 days; P<0.05). The median length of stay in the ICU in the magnesium group was 3 days (2–21). In the placebo group, patients with sustained AF stayed longer in the ICU (5, 4–7 days) than patients maintaining a sinus rhythm (3, 2–6 days; P<0.05).

One patient in the amiodarone group died 3 days after surgery from acute myocardial infarction and cardiogenic shock and a patient in the placebo group died 5 days after surgery.

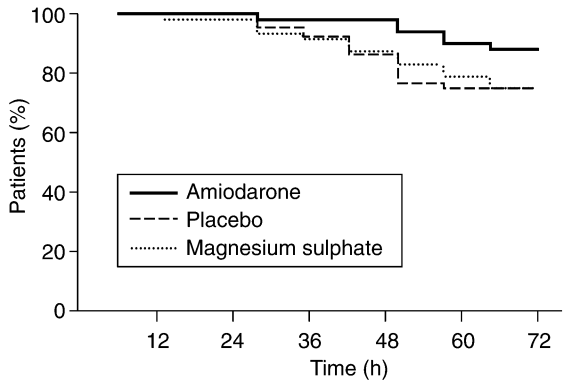

Fig 1 Percentage of patients without AF and delay in AF onset in patients receiving intravenous amiodarone, placebo or magnesium sulphate.

Discussion

The interim analysis did not demonstrate the effectiveness of either amiodarone or magnesium for the prophylaxis against postoperative AF. Although amiodarone halved the rate of occurrence of AF, as shown previously,[10] it was associated with a longer need for catecholamine infusion and invasive monitoring and a longer stay in the ICU. The adverse haemodynamic effect seen in our series has already been described.[19] Concerning the longer ICU stay observed in the amiodarone group, if we extrapolate to 1000 post-CABG patients, AF will prolong ICU stay by 2 days per patient, and an occurrence of 27% will result in 540 AF-attributable ICU patient days. Prophylaxis with amiodarone will increase ICU stay by 1000 patient days, whereas the avoidable risk of AF of 13% will reduce the ICU stay by only 260 days. Thus, the avoidance of prophylaxis will save 740 patient days in the ICU. In addition, patients in the amiodarone group experienced a slightly higher rate of adverse events, which may have been attributable to the study drug; these events included hypotension, atrioventricular block and bradycardia, and led to study termination in four of the patients. Intravenous magnesium did not reduce the occurrence of AF. On the basis of the present intermediate analysis, we judged it futile to proceed with further patient recruitment, because there was no evidence of effectiveness from prophylaxis in patients undergoing

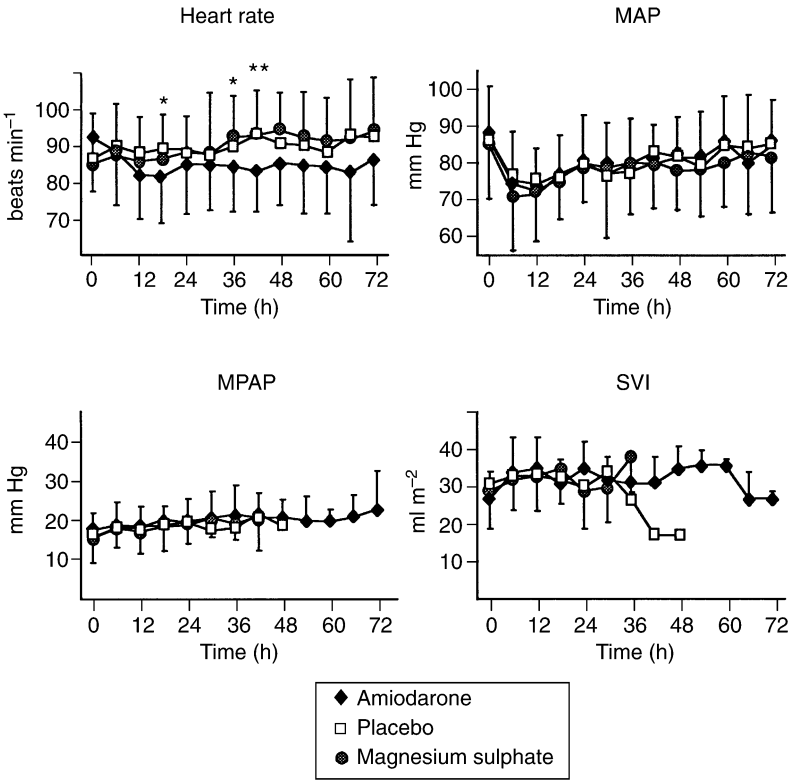

Fig 2 Six-hourly postoperative time course of heart rate, mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP) and stroke volume index (SVI) in patients receiving intravenous amiodarone, placebo or magnesium sulphate. *P<0.05, amiodarone versus placebo.

elective CABG surgery and no additional morbidity attributable to the occurrence of AF.

Prophylaxis against AF in cardiac surgery may still be indicated in selected populations such as patients presenting with valvular disease, which is complicated by a higher incidence of AF. Furthermore, as shown in our study, older patients are at higher risk of developing AF and may also benefit from prophylaxis.

The relevance of the delayed onset of AF with amiodarone remains questionable.

In our study, as shown by England and colleagues,[20] although magnesium sulphate prophylaxis was ineffective in preventing AF, patients presenting with plasma magnesium levels higher than 0.95 mmol litre^{-1} were protected from the development of AF. Variables predictive of postoperative AF onset were older age, and plasma magnesium concentrations in the low normal range (<0.95 mmol litre^{-1}) regardless of replacement therapy. Previous retrospective and observational studies emphasized the importance of age as an important independent predictor of AF after CABG.[21–24] Other predictors were chronic obstructive pulmonary disease, right coronary artery stenosis, preoperative β-adrenergic blockers and digoxin and chronic renal failure.[21–24] Among the variables we studied, our results confirm the increased risk associated with older age, with a 2-fold increase for each 10-yr interval.

In conclusion, perioperative administration of amiodarone intravenously required prolonged vasoactive and inotropic support, longer invasive monitoring and a longer stay in the ICU. The decision to administer amiodarone prophylaxis should be made cautiously, taking account of the increased risks of arrhythmia associated with, for example, age and mitral valve surgery, and the side-effects associated with this drug. Postoperative magnesium supplementation was ineffective in reducing the occurrence of AF.

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