SURGERY FOR ACQUIRED HEART DISEASE

LOW-DOSE AMIODARONE-RELATED COMPLICATIONS AFTER CARDIAC OPERATIONS

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Objective: High-dose preoperative amiodarone therapy has been implicated as a risk factor for serious complications after cardiac operations. To investigate the effect of preoperative low-dose amiodarone treatment on early postoperative outcome after cardiac operations, we prospectively studied 88 patients. **Methods:** Forty-four patients were receiving amiodarone (mean daily dose $\pm$ standard deviation, 205 ± 70 mg/day) and 44 patients were controls matched in pairs. The following parameters were recorded after the operation in all patients: (1) the ratio of oxygen tension to inspired oxygen fraction on arrival in the intensive care unit and 2, 4, 6, 10, 14, 18, and 22 hours thereafter; (2) the occurrence of acute respiratory distress syndrome; (3) early postoperative cardiac complications; and (4) the type and number of inotropic agents or vasopressors (or both) needed. **Results:** No difference in the ratio of oxygen tension to inspired oxygen fraction was noted at the various time intervals between amiodarone-treated patients and control patients. Overall, only one patient had acute respiratory distress syndrome in the amiodarone group, but he had multiple other factors known to predispose to acute lung injury. Several cardiac complications, such as pulmonary edema, temporary pacing, and need for intraaortic balloon pump counterpulsation, were observed more frequently in amiodarone-treated patients than in control patients. In addition, amiodarone-treated patients required more frequent inotropic support (73% vs 43%, $p = 0.003$) and more inotropic drugs or vasopressors (or both) per patient than did control patients (1.4 ± 1.1 vs 0.6 ± 0.8 , $p = 0.002$). **Conclusion:** Preoperative low-dose amiodarone therapy does not seem to be related to significant postoperative lung toxicity, but it is associated with various cardiac complications and an increased need for more intense inotropic support after cardiac operations. These findings may be related to the drug's depressant effect on the myocardium. (J Thorac Cardiovasc Surg 1997;114:31-7)

Amiodarone is an iodinated benzofuran derivative that has been proved effective in the control of supraventricular and ventricular arrhythmias refrac-

tory to other antiarrhythmic drugs.¹ Its use has been complicated by the frequent development of adverse effects, the most serious of which is pulmonary toxicity occurring in 5% to 10% of patients, rare proarrhythmic effects, worsening of cardiac failure, conduction disturbances, and hepatic dysfunction.^{2, 3} Surgical intervention in patients treated with amiodarone is commonly required, and several reports have suggested that these patients may be at particular risk for cardiopulmonary complications, including rapidly progressive adult respiratory distress syndrome (ARDS). Such complications have been described after cardiac operations or endocardial resection,⁴⁻⁹ lung resection,¹⁰ operations for

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Table I. Perioperative data

	<i>Amiodarone group (n = 44)</i>	<i>Control group (n = 44)</i>	<i>p Value</i>
Type of operation (No.)			
CABG	28	28	
VR	9	9	
CABG+VR	5	5	
ASD	1	1	
ALV	1	1	
Surgical teams			
Team 1 (No. of patients)	25	25	
Team 2 (No. of patients)	13	13	
Team 3 (No. of patients)	6	6	
Bypass time (min)	107 ± 52*	94 ± 32*	0.07
Crossclamp time (min)	61 ± 40*	55 ± 28*	0.6

ALV, Aneurysmectomy of the left ventricle; ASD, atrial septal defect; CABG, coronary artery bypass grafting; VR, valve replacement.

*Mean ± standard deviation.

implantation of an automatic cardioverter-defibrillator,^{9,11} pulmonary angiography,¹² and even after abdominal surgery.⁴ The side effects of amiodarone, especially pulmonary toxicity, are thought to be dose and time related¹³; indeed, in all previous studies in which amiodarone toxicity has been documented, amiodarone-treated patients had received high maintenance doses (375 to 685 mg/day), usually for a prolonged time. Low-dose amiodarone therapy (200 to 300 mg/day) is mostly used in Europe, and it has been shown to be safe and effective.¹⁴ The current study was undertaken to prospectively evaluate the early postoperative cardiopulmonary complications of patients undergoing cardiac operations who had received a low-dose amiodarone regimen in the preoperative period.

Methods

Study population. Between October 1994 and March 1996, three different surgical teams performed cardiac operations on 1971 patients at Onassis Cardiac Surgery Center. Data were collected prospectively from all consecutive patients ($n = 44$) who were receiving amiodarone before the operation, as well as from control patients who were operated on during the same time interval but had not received amiodarone. Control and amiodarone-treated patients were matched in pairs, in terms of the following parameters: age (mean ± standard deviation [SD], 61 ± 9 vs 61 ± 9 years); sex (88% male in each group); smoking history (85% smokers in each group); extent of cardiac disease (single-, double-, or triple-vessel disease, 7% vs 9%, 43% vs 31%, and 46% vs 59%); New York Heart Association classification as regards angina (class I, 45% vs 39%; class II, 38% vs 43%; and classes III to IV, 17% vs 18%), and preoperative left ventricular ejection fraction ($44\% \pm 12\%$ vs $41\% \pm 13\%$). On the basis of routine clinical examination, no patient in either

group was preoperatively believed to have chronic obstructive pulmonary disease. The two groups were also matched for type of operation, the surgical team performing the operation, and bypass and aortic crossclamp times (Table I). Treating physicians were not aware that the patients were included in a clinical study.

In the preoperative period, patients were treated with various medications, such as digoxin, β -blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, nitrates, antiplatelet agents, and diuretics. Amiodarone-treated patients were using β -blockers less frequently than control patients (25% vs 53%, $p = 0.009$). The duration of amiodarone therapy ranged from 7 to 1440 days (mean ± SD, 231 ± 269 days), the daily maintenance dose from 100 to 420 mg (mean ± SD, 205 ± 70 mg), and the total dose from 3 to 430 gm (mean ± SD, 45 ± 68 gm). Fifteen patients were receiving amiodarone for atrial fibrillation, 14 for refractory multifocal premature ventricular beats, three for previous episodes of ventricular tachycardia, four for previous ventricular fibrillation, two for atrial flutter, and six for ill-defined reasons. None of the amiodarone-treated patients had apparent pulmonary toxicity and none had discontinued his or her treatment before the operation.

Cardiopulmonary bypass with a membrane oxygenator was applied with moderate systemic hypothermia (28° to 30° C) and hemodilution at a flow rate of 2 L/min per square meter. Ninety-one percent of the amiodarone-treated patients and 93% of the control patients received blood cardioplegia, whereas 7% and 5% of patients, respectively, received cold crystalloid cardioplegia (St. Thomas' Hospital II solution). In one patient in each group, cardiac arrest was achieved with fibrillation without cardioplegia.

Protocol. The following parameters were recorded after the operation in all patients:

1. The ratio of oxygen tension to inspired oxygen fraction (PO_2/FiO_2 ratio) on arrival in the intensive care unit (ICU) and 2, 4, 6, 10, 14, 18, and 22 hours after the operation while in the ICU, to index the degree of hypoxemia.

2. The occurrence of adult respiratory distress syndrome (ARDS). Amiodarone-related ARDS was defined according to the Joint European-American Consensus Conference on ARDS: (a) oxygenation: $PO_2/FiO_2 \leq 200$, regardless of positive end-expiratory pressure; (b) chest x-ray film: bilateral infiltrates seen on frontal chest x-ray film; and (c) pulmonary artery wedge pressure: 18 mm Hg or less when measured or no clinical evidence of left atrial hypertension according to chest x-ray film and other clinical data.¹⁵

3. The postoperative cardiac complications observed.

4. The type and number of inotropic drugs or vasopressors (or both) administered. These agents were introduced in the operating room or in the ICU (or both) on the basis of the following criteria: (a) difficulty to wean from cardiopulmonary bypass; (b) hypotension (mean systemic arterial pressure < 60 mm Hg) unresponsive to fluid administration; and (c) cardiac index < 2.2 L/min per square meter after optimization of volume status, heart rate, and rhythm.

Table II. Postoperative cardiac complications

	Amiodarone group (n = 44)	Control group (n = 44)
Atrial fibrillation	6	2
Ventricular tachycardia	0	1
Temporary pacing	5	2
Intraaortic balloon pump	2	0
Myocardial infarction	2	0
Pulmonary edema	4	0
Total	19*	5*

* $p = 0.004$.

Thermodilution cardiac output catheters (Swan-Ganz catheters, Baxter Healthcare Corp., Edwards Division, Santa Ana, Calif.) were inserted routinely before the operation if the preoperative ejection fraction was less than 35%, if left main coronary artery disease was present, or if patients had had a recent myocardial infarction. In addition, a thermodilution catheter was introduced during the operation or in the ICU for difficulties in restoring arterial blood pressure or in monitoring inotropic support.

In our institution the first-line inotropic agents used are dobutamine or adrenaline, depending on the patient's response. If cardiac output or blood pressure remain marginal, despite moderate doses of one drug (dobutamine 8 to 10 $\mu\text{g/kg}$ per minute, adrenaline 0.3 $\mu\text{g/kg}$ per minute), the second is added. In patients with pulmonary hypertension we usually use milrinone, alone or in combination with the aforementioned inotropic drugs. Dopamine is often used in renal dose (2 to 3 $\mu\text{g/kg}$ per minute), unless severe hypotension ensues. Vasopressors (norepinephrine or phenylephrine hydrochloride [Neo-Synephrine]) are used during the rewarming period in the ICU for significant hypotension with low systemic vascular resistance unresponsive to fluid resuscitation. If hemodynamic stability cannot be achieved with inotropic support, an intraaortic balloon pump is inserted.

Statistical analysis. Values for continuous variables are expressed as the mean $\pm$ SD of the mean. So that comparisons could be made between amiodarone-treated patients and control patients, Student's t test, paired t test, the Wilcoxon matched-pairs signed rank test, the Mann-Whitney rank sum test, and the Mantel-Haenszel test were performed where appropriate with the use of Sigma-stat (Jandel Corporation, San Rafael, Calif.) and SPSS statistical software (SPSS, Inc., Chicago, Ill.). Differences were considered statistically significant if the p value was less than 0.05.

Results

Postoperative oxygenation—ARDS—lung complications. No difference in oxygenation was observed between amiodarone-treated patients and control patients, as expressed by the Po_2/Fio_2 ratio, at the various time intervals (Fig. 1). Overall, only one patient had ARDS: he had a long-standing history of coronary artery disease, his preoperative

Fig. 1. Po_2/Fio_2 ratio in amiodarone-treated control patients on arrival in the ICU and at various time intervals after the cardiac operation (mean $\pm$ SD). Not all patients stayed in the ICU for the entire 22-hour period.

left ventricular ejection fraction was 50%, and he had been receiving amiodarone (200 mg/day) for about 3 months before the operation for atrial fibrillation. This patient had an extensive intraoperative myocardial infarction necessitating a prolonged bypass time (6 hours) and multiple transfusions. Postoperatively, he required multiple inotropic drugs and intraaortic balloon pump support to maintain adequate blood pressure. He remained intubated for 10 days requiring high concentrations of inspired oxygen (Fio_2) and finally died of multi-organ failure and sepsis.

Three patients, all in the amiodarone group, had left lower lobe atelectasis on radiologic examination, which resolved after intense physiotherapy and bronchodilator use.

Cardiac complications. Overall, postoperative cardiac complications observed in the ICU (Table II) were more frequent in the amiodarone-treated group than in the control group (19 vs 5 complications, $p = 0.004$, $\chi^2 = 8.45$, odds ratio [OR] = 5.67, and 95% confidence intervals (CI) of OR 1.76 to 18.25). Four of the 44 amiodarone-treated patients

Fig. 2. Percent of patients with inotropic agents or vasopressors. *dobu*, Dobutamine; *adre*, adrenaline; *dopa*, dopamine; *milr*, milrinone; *vaso*, vasopressors.

had pulmonary edema. Two of them had this complication while in the ICU and had high pulmonary capillary wedge pressure (>20 mm Hg). The other two patients were readmitted from the ward to the intermediate care unit, 2 and 3 days after the operation, with dyspnea and tachypnea, rales, distention of internal jugular veins, hypoxemia (PO_2 50 and 55 mm Hg, respectively, with the patients breathing room air), and radiologic findings consistent with mild pulmonary interstitial edema (redistribution of blood flow and Kerley B lines). We did not insert a thermodilution catheter in these two patients, because they were in hemodynamically stable condition and showed prompt response to treatment with oxygen and diuretics. None needed intubation and mechanical ventilatory support, and they were discharged to the ward after 1 and 2 days, respectively, without experiencing any further complications. They did not need bronchodilators or steroids at any time.

Perioperative support with inotropic drugs or vasopressors (or both). More amiodarone-treated patients required inotropic drugs or vasopressors (or both) than did control patients (73% of patients vs 43% of patients, $p = 0.003$, $\chi^2 = 8.65$, OR = 5.56, and 95% CI of OR 1.77 to 17.42). All inotropic agents and vasopressors were used more frequently in amiodarone-treated patients (Fig. 2), but only the

use of dobutamine reached statistical significance (55% of patients vs 25% of patients, $p = 0.008$, $\chi^2 = 7.04$, OR = 3.8, and 95% CI of OR 1.42 to 10.19). The duration of dobutamine infusion was longer in the amiodarone group (mean 31 ± 34 hours, median 20 hours, 25th to 75th percentiles 15 to 40, vs mean 15 ± 13 hours, median 15 hours, 25th to 75th percentiles 2 to 20 hours, $p = 0.049$), as was the maximum dose administered (mean 7 ± 3 $\mu\text{g/kg}$ per minute, median 5 $\mu\text{g/kg}$ per minute, 25th to 75th percentiles 4 to 8 $\mu\text{g/kg}$ per minute, vs mean 4 ± 1 $\mu\text{g/kg}$ per minute, median 4 $\mu\text{g/kg}$ per minute, 25th to 75th percentiles 3 to 5 $\mu\text{g/kg}$ per minute, $p = 0.009$). More inotropic agents and vasopressors per patient were required in the amiodarone group than in the control group (mean 1.4 ± 1.1 , median 1, 25th to 75th percentiles 0 to 2, vs mean 0.6 ± 0.8 , median 0, 25th to 75th percentiles 0 to 1, $p = 0.002$).

In most cases, in 88% and 84% for amiodarone and control groups, respectively, inotropic agents were introduced in the operating room. Thirty-five of the 51 patients who received inotropic drugs had a thermodilution catheter. The mean cardiac index and systemic vascular resistance measured before sternotomy were 2.2 ± 0.6 L/min per square meter and 1333 ± 580 dynes $\cdot$ sec $\cdot$ cm $^{-5}$, respectively.

Except for the patient who died and his matched control, the mean postoperative intubation time was 16 ± 11 hours in the amiodarone-treated group and 12 ± 4 hours in the control group (median 12 hours, 25th to 75th percentiles 11 to 18 hours, vs median 11 hours, 25th to 75th percentiles 10 to 14 hours, $p = 0.03$), whereas the time spent in the ICU was 39 ± 30 and 27 ± 14 hours (median 28 hours, 25th to 75th percentiles 24 to 43 hours, vs median 24 hours, 25th to 75th percentiles 19 to 28 hours, $p = 0.02$). However, causes of prolonged intubation and ICU stay were not related to the use of amiodarone and included bleeding with surgical reexploration, shivering with metabolic acidosis necessitating prolonged sedation and muscle relaxation, agitation, and impaired consciousness. The mean hospital stay both in the amiodarone and in the control group was 8 ± 2 days (median 8 days, 25th to 75th percentiles 7 to 9 days, vs median 7 days, 25th to 75th percentiles 6 to 8 days, $p = 0.09$).

Discussion

In this prospective study we found that patients receiving long-term low-dose amiodarone therapy did not have significant lung toxicity after cardiac operations, as assessed by impairment in oxygen-

ation or occurrence of ARDS. However, they had more frequent cardiac complications and required more intense inotropic support in the early postoperative period than did matched paired control patients.

Amiodarone is an effective antiarrhythmic agent with potentially serious side effects, which may limit its clinical utility.^{1,2} Of particular interest are case reports and small series of patients suggesting that amiodarone can induce significant pulmonary and hemodynamic complications in patients undergoing various cardiac operations.¹⁶ Acute lung injury, with all the characteristics of ARDS, may occur in the immediate postoperative period or occasionally 3 to 5 days after the operation^{8, 10, 11, 17} and results in prolonged ventilatory support and high mortality.^{4, 7, 8, 10} Although the mechanism by which amiodarone may elicit acute lung toxicity after cardiac operations remains unknown, prolonged pump-oxygenator time, anesthetic agents, congestive heart failure, preoperative amiodarone pulmonary toxicity, superimposed pulmonary infection, and exposure to high FiO_2 have all been implicated as predisposing factors.^{18, 19} Most previous studies examining amiodarone's adverse effects after cardiac operations are retrospective and include patients receiving high preoperative doses of the drug (350 to 720 mg/day), for prolonged time intervals.

Our study was prospective and involved, to our knowledge, the largest number of amiodarone-treated patients who underwent cardiac operations. Our patients were matched for age, sex, smoking history, ejection fraction, type of operation performed, duration of cardiopulmonary bypass, and duration of aortic crossclamping. We did not find any difference in the oxygenation status between amiodarone-treated patients and control patients during a 22-hour interval after the operation. Although we did not routinely record our patients' arterial blood gases after they left the ICU, we believe we would have detected any serious respiratory complication thereafter, because such complications would have resulted in readmission to the ICU or intermediate care unit. Only one of the 44 amiodarone-treated patients had ARDS, but he had numerous other predisposing factors known to contribute to the development of acute lung injury. Our finding that lung toxicity is not as frequently observed as described in previous studies is probably related to the low-dose regimen (205 mg/day) and the low total dose of amiodarone (less than 50 gm) administered. However, this finding should be cau-

tiously interpreted, because our study involves a relatively small number of patients and the possibility of a type II error cannot be excluded, given the very low incidence (1/88) of ARDS in our study. Our study did not investigate extensively the occurrence of atelectasis in the two groups of patients by examining chest x-ray films according to a certain atelectasis score. We identified only three amiodarone-treated patients who had lobar atelectasis necessitating specific therapy. Postoperative atelectasis after cardiac operations has been associated with many other factors, such as decreased clearance of secretions, decreased mobility, gastric distention, intraoperative lung contusion, or phrenic nerve hypothermic injury.²⁰ Therefore we believe that further studies are needed to test the hypothesis that postoperative atelectasis might be related to the preoperative use of amiodarone.

The cardiovascular complications of amiodarone may result from the accentuation of its pharmacologic, hemodynamic, and electrophysiologic actions. The drug has an α -antagonist and a β -antagonist activity, which results from inhibition of adenylyl cyclase formation, reduction in the number of β -adrenergic receptors, and inhibition of the inward calcium ion current.²¹ From the hemodynamic point of view, amiodarone increases coronary blood flow by dilating coronary arteries, and it decreases systemic blood pressure and afterload by peripheral arterial vasodilation. In addition, amiodarone may reduce ventricular contractility through a mild direct negative inotropic effect on the myocardium.^{1, 3} An increased incidence of postoperative low cardiac output syndrome has been observed in amiodarone-treated patients who undergo cardiac operations, and the drug has been implicated as a possible etiologic factor.²² Other studies have shown that these patients more often required intraaortic balloon pump support to be weaned from cardiopulmonary bypass and that, in rare cases, angiotensin, a potent arterial vasoconstrictor, was used.²³ In terms of electrophysiology, amiodarone reduces sinus node and junctional automaticity, increases the conduction time and refractoriness of the atrioventricular node, prolongs the QT interval, and reduces conduction velocity in the myocardium and Purkinje tissue.²⁴ Accordingly, postoperative atropine-resistant or β -agonist-resistant bradycardia or complete atrioventricular block (or both), requiring atrioventricular sequential pacing, have been described in amiodarone-treated patients. Therefore some inves-

tigators suggest that the drug has to be used prudently in candidates for cardiac operations.^{5,6}

In accordance with the aforementioned reports, our study demonstrates that patients who receive low-dose amiodarone in the preoperative period are more likely to have postoperative cardiac complications, such as pulmonary edema, need for temporary pacing, and intraaortic balloon pump counterpulsation. These findings are even more significant when the less frequent preoperative use of β -blockers by our patients is taken into account.

Acute reversible myocardial dysfunction occurs commonly after elective cardiac operations. This condition is termed "stunned myocardium" and has been associated with the ischemic injury induced by cardioplegia—the cardioplegic arrest and the reperfusion injury. This situation has been described even in patients with good preoperative left ventricular performance. The appropriate treatment is the introduction of inotropic drugs.²⁵ Breisblatt and associates²⁶ reported that 71% of their patients needed inotropic drugs in the postoperative period, despite a mean preoperative ejection fraction of 58%. Royster and coworkers²⁷ defined a critical value of ejection fraction, 55%, which differentiated patients who require more intense inotropic support from those who do not. In the present study, amiodarone-treated patients required inotropic agents more often than their matched controls, with dobutamine reaching statistical significance, because this is the first-line inotropic drug used in our institution. Therefore our data suggest that preoperative amiodarone therapy may accentuate transient myocardial stunning after cardiac operations. In contrast, in a recent study, Mickleborough and associates⁸ found that amiodarone-treated patients undergoing cardiac operations did not differ from control patients in terms of inotropic support. However, they reported a trend toward more frequent adrenaline use in the amiodarone group to treat low systemic vascular resistance and to maintain adequate perfusion pressures.⁸ In that study the impact of amiodarone on postoperative myocardial depression, based on the need for inotropic support, is difficult to assess because all patients had poor preoperative left ventricular function (ejection fraction 23% to 33%) and long pump times (246 to 254 minutes), and the majority would have needed inotropic drugs anyway. Additionally, Mickleborough and associates⁸ used inotropic agents in a slightly higher percentage than we did (83% vs 74% of amiodarone-treated and non-amiodarone-treated groups,

respectively, received dopamine with or without dobutamine and 14% vs 0%, respectively, received adrenaline). With this high percentage and with their smaller patient numbers, statistical significance would be more difficult to achieve.

In conclusion, in contrast to previous reports that revealed an association between high-dose amiodarone treatment and ARDS, long-term low-dose amiodarone therapy does not seem to be related to a high risk for acute lung toxicity after cardiac operations. However, it is associated with a more prolonged intubation time and ICU stay and an increased incidence of postoperative cardiac complications. In addition, our study is the first to point out that low-dose amiodarone may increase the need for inotropic support after cardiac operations. These findings may be ascribed to the accentuation of amiodarone's adverse electrophysiologic and hemodynamic actions after cardiac surgery. Therefore we suggest that amiodarone should be used with caution in candidates for cardiac operations, even if the drug is administered in a low dose.

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