

Cardiopulmonary effects of chronic amiodarone therapy in the early postoperative course of cardiac surgery patients

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We compared the early postoperative course of 28 consecutive patients who underwent cardiac surgery while on amiodarone therapy (group 1) with the consecutive 28 patients who underwent similar surgery and were later given amiodarone (group 2). Group 1 patients received a cumulative dose of 373.6 ± 546.2 mg/kg amiodarone over a period of 60.5 ± 107.5 days. Preoperatively, sustained ventricular tachycardia ($P < .01$) and sudden cardiac death ($P < .01$) were significantly more common in group 1 than in group 2. Postoperatively, incidences of congestive heart failure, low cardiac index, bradycardia necessitating pacing, ventricular arrhythmias, and myocardial infarction were similar in the two groups. Postoperative respiratory failure was more common in group 1 and led to longer intubation and longer intensive care unit (ICU) stays. Four patients with respiratory failure had significantly lower PaO_2 and higher (A-a) PO_2 values preoperatively compared with the 24 group 1 patients without respiratory failure. Subclinical amiodarone pulmonary toxicity may be the underlying cause of significantly higher incidence of postoperative respiratory failure, leading to longer intubation and ICU periods. Arterial blood gas analysis may help differentiate high-risk patients before cardiac surgery.

Index term: Amiodarone, adverse effects

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Oral amiodarone has recently been approved for clinical use in the United States. Oral and intravenous amiodarone have been marketed in Europe and South America since the early 1970s. Although a variety of new antiarrhythmic agents have been developed, none perhaps has attracted as much clinical and experimental attention as amiodarone.

This interest is because of its potent antiarrhythmic property and wide-ranging multisystem side effects. Adverse effects of chronic amiodarone therapy in postoperative cardiac surgical patients have been addressed in a few case reports,¹⁻³ in clinical studies,^{4,5} and in anecdotal communications.^{6,7}

We reported the preliminary results of our study in 1986⁸ and noted increased incidence of respiratory failure following open heart surgery in patients who were receiving amiodarone. Feinberg et al⁴ in a controlled study concluded that patients receiving oral amiodarone preoperatively had a greater need for postoperative inotropic support as well as longer time to extubation. Gallagher et al¹ stated that any patient who has received amiodarone within the 45 days preceding surgery may be at risk for atropine-resistant bradycardia as well as decreased peripheral resistance and diminished contractility of the left ventricle. Elliot et al⁵ in a prospective study

showed that hemodynamic responses to general anesthesia did not differ in patients taking amiodarone and a control group.

We undertook this study to define the possible cardiopulmonary effects of chronic amiodarone therapy in the early postoperative phase of cardiac surgery.

Methods

All cardiac surgical patients who began amiodarone therapy at the Cleveland Clinic Foundation between January 1, 1982, and July 1, 1985, were included in this study. We retrospectively studied various preoperative cardiopulmonary parameters of patients who received amiodarone for seven or more days and then underwent cardiac surgery. We compared the results with similar postoperative variables in patients who were not receiving amiodarone therapy at the time of surgery but who started amiodarone ther-

Table 1. Parameters analyzed

Variable type	Variable
PREOPERATIVE	
Physical	age sex weight height body surface area
Respiratory	history of chronic obstructive pulmonary disease history of smoking abnormal chest radiograph PaO ₂ (partial pressure of arterial oxygen) (A-a) PO ₂ (alveoloarteriolar oxygen difference)
Cardiovascular	history of myocardial infarction history of congestive heart failure history of sustained ventricular tachycardia history of sudden cardiac death left ventricular function left ventricular ejection fraction left ventricular end diastolic pressure high-grade AV block or bundle-branch block indication for amiodarone therapy
PERIOPERATIVE	type of surgery total anesthesia time extracorporeal bypass time cross clamp time blood transfusion within 24 hours of surgery
POSTOPERATIVE	congestive heart failure low cardiac index respiratory failure bradycardia necessitating pacing ventricular arrhythmias perioperative MI length of intubation duration of intensive care unit stay

apy later. Group 1 (amiodarone group) consisted of 28 consecutive patients who were receiving amiodarone at the time of cardiac surgery. The control group (group 2) consisted of the 28 consecutive patients who underwent cardiac surgery and began amiodarone therapy after surgery. In both groups, amiodarone was given after several conventional and/or investigational drugs had either failed to control spontaneous or electrically induced arrhythmias or had not been tolerated. Demographic, preoperative, perioperative, and postoperative respiratory and cardiovascular variables analyzed in all patients are shown in *Table 1*.

Blood gas values were obtained while the patient was breathing room air. Alveoloarteriolar oxygen difference ((A-a) PO₂) was calculated using the formula proposed by Martin.⁹ The following findings were accepted as abnormal chest radiographic findings for this study: patchy alveolar infiltrates, pleural effusions, pleural adhesions, and prominent interstitial markings. Radiocontrast left ventriculograms were reviewed by one angiographer for left ventricular function and graded as normal or mildly, moderately, or severely impaired. Left ventricular ejection fraction was calculated from ventriculograms by using Dodge's formula.¹⁰ Left-ventricular end diastolic pressure was measured during catheterization of the left side of the heart before angiography. Chronic obstructive pulmonary disease was determined by pulmonary function tests when available and by clinical and radiographic findings. Postoperative de novo congestive heart failure or marked deterioration in preoperative heart failure was determined by clinical findings (tachycardia, third heart sound, basilar inspira-

tory rales) as well as hemodynamic measurements (increased pulmonary capillary wedge pressure and decreased cardiac index). Low cardiac index was defined as cardiac index <2 L/min/m² persisting more than 24 hours. Significant respiratory failure was defined as hypoxia (PaO₂ <60 mmHg) and requirement for intubation for more than two days. Sustained ventricular tachycardia was defined as ventricular tachycardia lasting longer than 30 seconds or necessitating immediate intervention. Sudden cardiac death was defined as instantaneous cardiovascular collapse requiring cardiopulmonary resuscitation.

Data obtained in both groups were analyzed by Student's *t* test, Wilcoxon rank sum test, and Fisher's exact test.¹¹

Results

The mean age was 55.8 ± 7.9 years, ranging from 34 to 76 years in the amiodarone group (group 1) and 58.4 ± 9.2 years, ranging from 32 to 77 years, in the control group. There were 25 men and three women in group 1, and 23 men and five women in group 2. The two groups were also comparable for age, sex, body weight, and height (77.2 ± 11.6 kg vs 78.4 ± 12.5 kg and 173 ± 8 cm vs 174 ± 8 cm, respectively). In

Table 2. Amiodarone therapy in group 1

	Mean ± SD	Range
Loading dose (mg/day)	1079 ± 199	600–1200
Loading duration (days)	6.5 ± 1.0	3–7
Maintenance dose (mg/day)	471 ± 112	200–600
Duration of therapy (days)	60.5 ± 107.5	7–586
Cumulative dose/body weight (mg/kg)	374 ± 546	56–2965

SD = standard deviation.

Table 3. Preoperative clinical characteristics

	Amiodarone group (1)		Control group (2)		Significance of difference
	Patients	(%)	Patients	(%)	
Ventricular tachycardia as indication for amiodarone therapy	26	(93)	22	(79)	NS
Sustained ventricular tachycardia	26	(93)	14	(50)	<i>P</i> < .001
History of sudden cardiac death	18	(64)	8	(29)	<i>P</i> < .001
Chronic obstructive pulmonary disease	3	(11)	2	(7)	NS
History of myocardial infarction	21	(75)	19	(68)	NS
History of congestive heart failure	10	(36)	5	(18)	NS
History of smoking	24	(86)	22	(79)	NS
Incidence of conduction defect	10	(36)	7	(25)	NS
Abnormal chest radiographic findings	2	(7)	3	(11)	NS
Left ventricular dysfunction	23	(82)	22	(79)	NS

NS = not significant.

group 1 there were 24 patients with atherosclerotic heart disease, three with rheumatic heart disease, and one with primary myocardial disease. In group 2 there were 25 patients with atherosclerotic heart disease, one with hypertensive heart disease, one with hypertrophic obstructive cardiomyopathy, and one with atrial septal defect.

The dose and duration of therapy in group 1 patients are shown in *Table 2*. Indication for starting therapy was similar in the two groups (*Table 3*). Sustained ventricular tachycardia and the incidence of sudden death were the only two preoperative parameters that were significantly different between the two groups, both being more prevalent in amiodarone group than in the control group (26 vs 14 patients, $P < .001$ and 18 vs 8 patients, $P < .001$, respectively) (*Table 3*). The incidence of other preoperative and perioperative variables was similar in the two groups (*Tables 3 and 4*).

Types of surgery in both groups are shown in *Table 5*. Membrane oxygenators were used in all patients who underwent open heart surgery. In

operations for automatic implantable cardioverter defibrillator implantation only, the left thoracotomy approach was used.

The incidences of postoperative congestive heart failure, low cardiac index persisting more than 24 hours, perioperative myocardial infarction, life-threatening ventricular arrhythmias, and persistent bradycardia requiring a pacemaker were similar in the two groups (*Table 6*).

Four patients in group 1 had postoperative respiratory failure; none in group 2 had this complication. This difference was found to be marginally significant ($P = .056$). All four patients had moderate or severe left ventricular dysfunction preoperatively, all had a history of smoking, only one of the four had a history of chronic obstructive lung disease, and none had abnormal chest radiographic findings preoperatively. All four had sustained ventricular tachycardia and three of these four patients had a history of sudden cardiac death. Two of these patients had coronary artery bypass graft surgery, and the remaining two had ventricular aneurysm excision and endocardial resection.

Table 4. Preoperative and perioperative variables

	Amiodarone group (1) Mean \pm SD	Control group (2) Mean \pm SD	Significance of difference
PaO ₂ (mmHg)	72.4 \pm 10.4	75.1 \pm 9.7	NS
Alveoloarteriolar oxygen difference (mmHg)	28 \pm 10.5	25.2 \pm 8.4	NS
Left ventricular ejection fraction (%)	38.2 \pm 16.9	40.9 \pm 19.6	NS
Left ventricular end diastolic pressure (mmHg)	20 \pm 7.5	17 \pm 7.9	NS
Bypass time (min)	90.4 \pm 30.4	94.4 \pm 41.7	NS
Cross clamp time (min)	40.7 \pm 20.9	48.7 \pm 22.7	NS
Total anesthesia time (min)	234.3 \pm 64.1	248.6 \pm 83.8	NS
Blood transfusions (units)	1.2 \pm 2	1.3 \pm 1.8	NS

NS = not significant.

Table 5. Types of surgery

	Amiodarone group (1)		Control group (2)	
	Patients	(%)	Patients	(%)
Coronary artery bypass graft surgery	6	(21.4)	16	(57.2)
Coronary artery bypass graft surgery + endocardial resection	2	(7.1)	2	(7.1)
Coronary artery bypass graft surgery + ventricular aneurysm resection	2	(7.1)	2	(7.1)
Coronary artery bypass graft surgery + automatic cardioverter defibrillator implantation	2	(7.1)	—	
Coronary artery bypass graft surgery + aortic valve replacement	—		1	(3.6)
Ventricular aneurysm resection + endocardial resection	4	(14.4)	1	(3.6)
Mitral valve replacement	3	(10.8)	—	
Myectomy	—		1	(3.6)
Atrial septal defect repair	—		1	(3.6)
Automatic cardioverter defibrillator implantation	9	(32.1)	4	(14.2)

Duration of therapy and cumulative dose per body weight in the four patients with respiratory failure were greater than in the remaining 24 patients of group 1 who did not have respiratory failure (mean = 169 ± 278 d, range = 18–586 d vs mean = 42 ± 33 d, range = 7–125 d and mean = $854 \pm 1,411$ mg/kg, range = 56–2,965 mg/kg vs mean = 293 ± 209 mg/kg, range = 66–1,013 mg/kg, respectively). However, the differences were not statistically significant. All the preoperative and perioperative parameters of these four patients, except baseline PaO₂ and (A-a) PO₂, were similar to those of the remaining 24 patients in the amiodarone group. Those patients in the amiodarone group who had postoperative respiratory failure had significantly lower PaO₂ (57.5 ± 7.6 vs 75.2 ± 8.4 mmHg, $P < .001$) and higher (A-a) PO₂ values (43.5 ± 4.8 mmHg vs 25.0 ± 8.4 mmHg, $P < .001$) preoperatively than the remaining 24 patients.

Duration of intubation (2.3 ± 3.3 days in group 1 vs 1.1 ± 0.4 days in group 2, $P < .05$) and duration of intensive care unit stay (3.3 ± 1.0 days in group 1 vs 1.5 ± 1.1 days in group 2, $P < .05$) were significantly longer in the amiodarone group than in the control group (Table 6). Intubation period and intensive care unit stay in the four patients with respiratory failure were 8 ± 6 d (range 2–14 d) and 12 ± 7 d (range 5–18 d), respectively. When these four patients with respiratory failure were excluded from the amiodarone group, no significant differences were found between the remaining 24 patients receiving amiodarone and the control group.

Discussion

Amiodarone possesses several properties that may present problems intraoperatively and/or postoperatively in patients undergoing cardiac surgery. Atropine- and isoproterenol-resistant

bradycardia,¹ myocardial depression,⁴ peripheral vasodilation,¹² and long and variable half-life¹³ are some of the reported problems. Gallagher et al¹ reported a case of atropine- and isoproterenol-resistant bradycardia and complete AV block in a patient who underwent open heart surgery while he was receiving chronic amiodarone therapy. Navalgund et al² recently published a case report describing amiodarone-induced sinus arrest during general anesthesia.

Bradycardia effects of amiodarone are mainly due to lengthening of action potential duration in all cardiac tissues.^{14–17} Amiodarone is also known to inhibit automaticity¹⁸ and to exert antiadrenergic effects.¹⁹ We detected persistent bradycardia necessitating pacing in two patients. One of these patients was taking amiodarone at the time of surgery and the other was in the control group. In our study, persistent bradycardia was not a problem in patients receiving amiodarone before surgery.

Amiodarone has been reported to aggravate arrhythmias.^{20–23} In this study we found no significant difference in the postoperative incidence of ventricular arrhythmias. However, the wide range of factors contributing to the genesis of arrhythmias in the postoperative period hampers assessment of the proarrhythmic effect of amiodarone.

In animal²⁴ and clinical⁷ studies, intravenously administered amiodarone produced a mild and transient deterioration of left ventricular function. Negative inotropic effect of amiodarone infusion was attributed to the solvent of the intravenous solution,^{25,26} but this finding was not substantiated by others.⁷ Although the reported incidence of drug intolerance because of heart failure ranges from 1%²³ to 4%,²⁷ Schwartz et al⁷ and others²⁸ have shown that oral amiodarone therapy, unlike intravenous therapy, does not

Table 6. Postoperative parameters

	Amiodarone group (1)		Control group (2)		Significance of Difference
	Patients	(%)	Patients	(%)	
Congestive heart failure	7	(25)	6	(21.4)	NS
Low cardiac index	5	(17.9)	2	(7.1)	NS
Life-threatening ventricular arrhythmia	11	(39.3)	7	(25)	NS
Bradycardia requiring pacing	1	(3.6)	1	(3.6)	NS
Perioperative myocardial infarction	0	(0)	1	(3.6)	NS
Respiratory failure	4	(14)	0	(0)	$P = .056$
	Mean \pm S.D.		Mean \pm S.D.		
Intubation period (days)	2.3 ± 3.3		1.1 ± 0.4		$P < .05$
Intensive care unit stay (days)	3.3 ± 4.4		1.5 ± 1.1		$P < .05$

NS = not significant.

exert any deleterious effect on left ventricular function.

There are anecdotal communications from a number of authors regarding the negative inotropic effect of amiodarone in the perioperative and early postoperative periods of open heart surgery.⁶ MacKinnon et al³ reported a case in which profound myocardial depression and low cardiac output developed as the patient was weaned from cardiopulmonary bypass. Feinberg et al⁴ stated that patients who were receiving amiodarone therapy required greater inotropic support because of congestive heart failure.

In our study, postoperative incidence of congestive heart failure and a low cardiac output syndrome were more common in the amiodarone group than in the control group. However, this difference was not statistically significant. Chronic amiodarone therapy did not seem to contribute to the development of congestive heart failure in our patients in the postoperative phase.

There are increasing numbers of reports documenting the pulmonary toxicity of amiodarone.²⁹⁻³³ Pulmonary changes ranging from asymptomatic pulmonary infiltrates to advanced fibrosis and respiratory failure with fatal outcome have been reported.¹⁸ Feinberg et al⁴ studied 129 patients and found that patients taking amiodarone at the time of surgery had a significantly higher incidence of respiratory complications. The mechanism of amiodarone pulmonary toxicity remains unclear. Dose-dependent toxicity²⁹ and hypersensitivity to amiodarone³⁴ have been proposed as important factors in the mechanism of amiodarone toxicity.

In this study, the difference in incidence of postoperative respiratory failure between the amiodarone group and the control group was marginally significant ($P = .056$). None of the preoperative or perioperative factors except preoperative PaO_2 and (A-a) PO_2 were found to be significantly different in these four patients compared with the rest of the group or the control group. In several studies, pulmonary function tests in patients with amiodarone-related infiltrates have shown hypoxia and diffusion abnormalities.²⁹ It is possible that preoperative hypoxia and impaired pulmonary gas exchange predisposed these four patients to the postoperative respiratory failure. Hypoxia and increased (A-a) PO_2 in the four patients who were clinically stable were probably evidence of amiodarone pulmonary toxicity. Amiodarone is assumed to be re-

sponsible for these changes, although irrefutable evidence is lacking. However, no other cause could be found for the clinical outcome. None of the four patients had elevated pulmonary capillary wedge pressures over 20 mmHg or clinically overt pulmonary edema. No lung infection or sepsis could be identified. There were no predictive preoperative or perioperative factors except the blood gas values that indicated diffusion abnormalities. These findings suggest that clinically unsuspected pulmonary disease, presumably caused by chronic amiodarone therapy, led to the respiratory failure after surgery.

Several reports suggest that pulmonary toxicity is at least partially dose-dependent.⁶ The four patients in our study with postoperative respiratory failure had received higher doses of amiodarone for longer periods, though this difference was not statistically significant.

Another important finding in our study was the significant increase in the duration of intubation and cardiac intensive care unit stay in the amiodarone group. It is noteworthy that these differences were due to respiratory failure. When the four patients with respiratory failure were excluded, there were no differences between the remaining 24 patients and the control group. Feinberg et al⁴ also found longer intubation periods in patients receiving amiodarone and attributed this finding to the "stormier postoperative course" of these patients.

Amiodarone has been available in Europe for more than 20 years and has been used as an investigational drug extensively in the United States. However, there have been very few reports of the possible postoperative problems caused by chronic amiodarone therapy. This may be due to the different dose regimens used, the multifactorial character of the postoperative respiratory failure, and the relative infrequency of this complication. Because the problem is complex, caution must be exercised in interpreting clinical and laboratory findings before attributing the clinical picture partially or totally to amiodarone toxicity. On the other hand, the appearance of respiratory failure with infiltrates in the early postoperative phase without other clearly identifiable causes, such as cardiogenic pulmonary edema or infection, is a strong reason for further investigation.

For the present, it seems prudent to suggest that arterial blood gas analysis, together with clinical evaluation of patients who are candidates for cardiac surgery, may differentiate high-risk

patients who will need additional preoperative and perioperative attention. Prospective controlled trials with attempts at pathological documentation would help achieve a more thorough understanding of this problem.

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