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Intravenous Amiodarone in Treatment of Recent-Onset Atrial Fibrillation: Results of a Randomized, Controlled Study

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Objectives. **This study was designed to determine the efficacy of intravenous amiodarone in the management of recent-onset atrial fibrillation.**

Background. **The optimal approach for acute atrial fibrillation has not been established. Amiodarone is a unique antiarrhythmic agent with activity in both supraventricular and ventricular tachyarrhythmias, but its value for the restoration of sinus rhythm in patients with recent-onset atrial fibrillation has not been demonstrated.**

Methods. **Sample size was calculated to detect a 25% increase in reversion rate with amiodarone with a statistical power of 80%. One hundred consecutive patients with recent-onset (<1 week) atrial fibrillation and not taking antiarrhythmic agents were randomized to receive either intravenous amiodarone, 5 mg/kg body weight in 30 min followed by 1,200 mg over 24 h, or an identical amount of saline. Both groups received intravenous digoxin, 0.5 mg initially, followed by 0.25 mg at 2 h and 0.25 mg every 6 h thereafter, to complete 24 h while the ventricular rate was >100 beats/min. Amiodarone and digoxin blood levels were determined. Both groups were homogeneous regarding underlying heart disease, time from onset to treatment, initial ventricular rate and left atrial size.**

Results. **By the end of the 24-h treatment period, 34 patients (68%, 95% confidence interval [CI] 53% to 80%) in the amiodarone group and 30 (60%, 95% CI 45% to 74%) in the control group had returned to sinus rhythm (p = 0.532). Mean times (±SD) of conversion were 328 ± 335 and 332 ± 359 min, respectively (p = 0.957). Among patients who did not convert to sinus rhythm, treatment with amiodarone was associated with a slower ventricular rate (82 ± 15 beats/min in the amiodarone group vs. 91 ± 23 beats/min in the control group, p = 0.022). After restoration of sinus rhythm, atrial fibrillation recurred during a 15-day follow-up period in 4 (12%) of 34 patients (95% CI 3% to 27%) in the amiodarone group and in 3 (10%) of 30 (95% CI 2% to 26%) in the control group (p = 0.861).**

Conclusions. **Intravenous amiodarone, at the doses used in this study, produces a modest but not significant benefit in converting acute atrial fibrillation to sinus rhythm.**

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Recent-onset atrial fibrillation is a common occurrence, but its treatment is not settled. The pharmacologic approach in the acute phase consists of 1) slowing ventricular response and 2) restoring sinus rhythm. Many drugs have been used by the intravenous route with both aims. Digoxin (1), calcium antagonists (2) and beta-adrenergic blocking agents (3) slow the ventricular response, although they do not convert atrial fibrillation to sinus rhythm. The most promising drugs in restoration sinus rhythm are the class IC antiarrhythmic drugs flecainide and propafenone (4–7). Amiodarone is widely used in Europe to revert atrial fibrillation. Its conversion rate has been reported to range from 55% to 86% (8–12). Nevertheless, because many patients with atrial fibrillation revert spontaneously to sinus rhythm, only a randomized, placebo-controlled study can establish its real value.

The purpose of the present study was to determine, in a prospective, randomized, single-blind trial, whether intravenous amiodarone is superior to placebo in converting atrial fibrillation of recent onset to sinus rhythm.

Methods

Study patients. One hundred consecutive patients (55 men, 45 women; mean [±SD] age 61 ± 12 years, range 26 to 85) with atrial fibrillation of recent onset (<7 days) were recruited during a period of 18 months. All patients were seen in the emergency department, on the wards or on the coronary unit of our hospital. Confirmatory evidence of the arrhythmia was obtained by a 12-lead electrocardiogram in all patients. Criteria defining the onset of the arrhythmia included a documented onset in patients admitted to the hospital or, for those cases seen in the emergency department, an abrupt, well defined onset of symptoms, such as palpitations, chest discom-

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fort or dyspnea, in patients with no previous history of recurrent arrhythmias.

Exclusion criteria were 1) any previous antiarrhythmic treatment (digoxin included); 2) baseline systolic blood pressure <100 mm Hg; 3) baseline mean ventricular rate <120 beats/min; 4) moderate or severe clinical or radiologic signs of congestive heart failure (mild cases were accepted); 5) clinical or laboratory data indicative of severe impairment of left ventricular function; 6) obstructive hypertrophic cardiomyopathy; 7) renal insufficiency (urea nitrogen >120 mg/dl or creatinine >2.5 mg/dl); 8) goiter or thyroid dysfunction; 9) high degree atrioventricular block; 10) sick sinus syndrome; 11) pulmonary fibrosis; 12) hepatic dysfunction; and 13) refusal to participate.

Protocol. After informed consent was obtained, patients were randomized to receive intravenous amiodarone at the dosage of 5 mg/kg body weight over 30 min, diluted in 100 ml of saline, followed by 1,200 mg diluted in 500 ml of saline over 24 h. Patients in the placebo group received an identical amount of saline. To reduce the high ventricular rate, both amiodarone and placebo groups received intravenous digoxin, 0.5 mg initially followed by 0.25 mg at 2 h and 0.25 mg every 6 h thereafter to complete 24 h (this administration schedule was stopped if mean ventricular rate decreased to <100 beats/min).

Amiodarone was given by means of an infusion pump through either a peripheral vein or a central line. Patients were continuously monitored and received subcutaneous calcium heparin at a dosage of 2,500 IU/10 kg every 12 h. Intravenous infusion containing amiodarone or placebo was interrupted as soon as conversion to sinus rhythm was observed. When conversion did not occur, the infusion was maintained until the completion of 24 h. Blood samples were taken at the end of the treatment to determine amiodarone and digoxin blood levels. Amiodarone plasma levels were determined by high performance liquid chromatography (13), whereas digoxin serum levels were determined by radioimmunoassay. Afterward, patients were treated with oral digoxin alone and followed up for a 15-day period.

A Doppler–echocardiographic recording was performed within 72 h of the onset to determine ventricular function, atrial size and underlying heart disease.

Statistics. Statistical analysis was performed using commercially available software (SPSS PC+/v4.0). The study was intended to detect a large, clinically relevant effect of amiodarone. Therefore, sample size was calculated to provide alpha and beta probabilities of 0.05 and 0.20, respectively (statistical power of 80%) for a 25% increase in the rate of reversion to sinus rhythm with amiodarone, assuming a rate of reversion of 50% in the control group receiving only digoxin. Frequencies observed in the two groups of treatment were compared by means of the chi-square test. Differences in continuous variables were analyzed by means of the *t* test for independent samples. To identify which factors predicted conversion to sinus rhythm, patients recovering sinus rhythm were compared with patients not recovering sinus rhythm in a univariate analysis, and all variables presenting p values <0.10, as well as treatment allocation, were included into a stepwise multiple logistic regression analysis. A significance level of 0.05 was used for all comparisons. Continuous variables were expressed as mean value ± SD. Ninety-five percent confidence intervals were calculated for all frequencies by using the binomial distribution.

Table 1. Baseline Patient Data

	Amiodarone (n = 50)	Placebo (n = 50)
Age (yr)	60 ± 13	61 ± 11
Male/female	27/23	28/22
Previous atrial arrhythmias	5 (10%)	7 (14%)
Duration of AF (h)	25 ± 32	18 ± 35
Cardiac surgery	8 (16%)	9 (18%)
Heart failure	5 (10%)	6 (12%)
Ventricular rate (beats/min)	147 ± 24	141 ± 24
Systolic pressure (mm Hg)	138 ± 25	128 ± 30
Left atrial size (mm)	42 ± 7	42 ± 8
LVSF (%)	34 ± 7	32 ± 7
Cardiac disease/lone atrial fibrillation	22/28	30/20

Data presented are mean value (±SD) or number (%) of patients. AF = atrial fibrillation; LVSF = left ventricular shortening fraction.

Results

Patient characteristics. Of the 100 patients who were randomized, 76 were seen in the emergency department, 18 in the coronary unit and 6 in the wards. Regarding underlying cardiac disease, 27 patients had valvular, 18 coronary, 5 cardiomyopathy and 2 miscellaneous heart disease, whereas 48 patients had idiopathic atrial fibrillation. There were 17 patients in whom the arrhythmia occurred during the postoperative period after cardiac surgery. Atrial fibrillation was present for 21 ± 34 h (mean ± SD, range 3 min to 146 h). Table 1 shows the baseline data from all patients. There were no significant differences between the amiodarone and placebo groups regarding age, gender, previous history of atrial arrhythmias, duration of atrial fibrillation, postoperative period of cardiac surgery, mild or moderate heart failure, baseline ventricular rate, blood systolic pressure, left atrial size or left ventricular shortening fraction by echocardiography.

Reversion to sinus rhythm. By the end of the 24-h treatment period, 34 patients (68%, 95% confidence interval [CI] 53% to 80%) in the amiodarone group had reverted to sinus rhythm, whereas 30 patients (60%, 95% CI 45% to 74%) in the control group had reverted (p = 0.532) (Fig. 1). The mean times of conversion were 328 ± 335 and 332 ± 359 min, respectively (p = 0.957). At 2, 6 and 12 h 15 (30%), 24 (48%) and 28 (56%) patients, respectively, in the amiodarone group had converted versus 12 (24%), 23 (46%) and 25 (50%) patients, respectively, in the control group (Fig. 1).

In patients who did not revert to sinus rhythm, ventricular rate had decreased at the end of the 24-h period of treatment

to 82 ± 15 beats/min in the amiodarone group versus 91 ± 23 in the control group (p = 0.022). After restoration of sinus rhythm and interruption of intravenous drugs, atrial fibrillation recurred during a 15-day follow-up in 4 (12%) of 34 patients (95% CI 3% to 27%) in the amiodarone group and in 3 (10%) of 30 (95% CI 2% to 26%) in the control group (p = 0.861).

Drug blood levels and side effects. Mean digoxin serum levels were 1.21 ± 0.74 ng/ml in the amiodarone-digoxin group and 1.48 ± 1.05 in the placebo-digoxin group (p = 0.205). Mean amiodarone plasma levels in those patients who received the drug were 1.14 ± 0.97 μg/ml. Digoxin serum concentration was not different in patients reverting to sinus rhythm compared to those not reverting (1.41 ± 1.06 and 1.22 ± 0.57 ng/ml, respectively, p = 0.302). Similarly, among patients receiving amiodarone, plasma levels of this drug were not different in those reverting and not reverting to sinus rhythm (1.03 ± 1.05 and 1.66 ± 2.57 μg/ml, respectively, p = 0.411). Among side effects, hypotension below 100 mm Hg developed in four patients in the amiodarone group and in four patients in the control group, with good response to volume expansion with saline solution. Medication had to be interrupted in no cases. There were one case of nonsustained ventricular tachycardia and one case of phlebitis in the amiodarone group, and two cases of vomiting, one of atrial flutter and one of transient junctional rhythm in the control group.

Predictors of reversion. Patients reverting to sinus rhythm differed from those not reverting (Table 2) in that they had younger age (p = 0.027), less frequent previous history of supraventricular arrhythmias (p = 0.0226), a shorter duration of atrial fibrillation from the onset of the arrhythmia to the start of the treatment (p = 0.006), smaller left atrial size (p = 0.018) and less frequent congestive heart failure (p = 0.00023). Multiple logistic regression analysis retained absence of congestive heart failure (p = 0.0000), smaller left atrial size (p = 0.0095) and absence of previous history of supraventricular arrhythmias (p = 0.0191) as independent predictors of conversion to sinus rhythm, but not treatment allocation (p = 0.1947).

Figure 1. Proportion of patients who reverted to sinus rhythm (SR) in both amiodarone and control groups plotted against time from start of infusion.

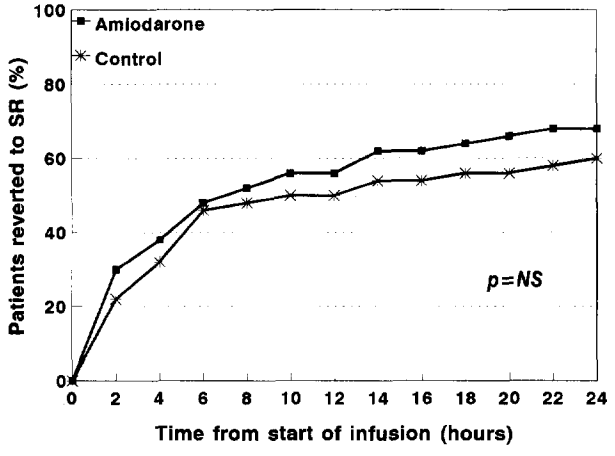

Table 2. Predictors of Reversion (univariate analysis)

	Reversion to SR		p Value
	Yes	No	
Age (yr)	59 ± 13	64 ± 10	0.027
Male	38 (69%)	17 (31%)	
Female	26 (58%)	19 (42%)	0.335
Baseline heart rate (beats/min)	143 ± 22	146 ± 28	0.590
Baseline SBP	129 ± 27	140 ± 28	0.055
Baseline DBP	79 ± 14	85 ± 83	0.052
Duration of AF (h)	11.7 ± 20.8	40.5 ± 46.3	0.006
Previous atrial arrhythmias			
Yes	5 (42%)	7 (58%)	0.023
No	59 (67%)	29 (33%)	(1 tail)
Left atrium (mm)	41 ± 7	44 ± 8	0.018
LVEDD (mm)	53 ± 7	53 ± 8	0.852
LVSF (%)	33 ± 7	32 ± 7	0.461
Heart failure			
Yes	2 (18%)	9 (81%)	
No	61 (77%)	18 (23%)	0.0002
Cardiac disease	29 (47%)	33 (53%)	
Lone AF	23 (66%)	12 (34%)	0.113

Data presented are mean value (±SD) or number (%) of patients. DBP = diastolic blood pressure; LVEDD = left ventricular end-diastolic diameter; SBP = systolic blood pressure; SR = sinus rhythm.

Discussion

When acute atrial fibrillation is associated with severe hemodynamic deterioration, electrical cardioversion is the treatment of choice. In a less urgent situation, there is room for a less aggressive strategy, and drug therapy can be considered. Digitalis is the drug most commonly used. However, as has been demonstrated by Falk et al. (1), digitalis does not increase the likelihood of reversion, although it helps to control ventricular rate. Large-scale randomized trials comparing the relative benefits of antiarrhythmic drugs have not been reported, and the optimal approach has not been established. The present study was conducted to test the efficacy and safety of intravenously administered amiodarone to revert acute atrial fibrillation.

Reversion to sinus rhythm. Amiodarone reverted 68% of cases within 24 h, a figure that compares with other uncontrolled trials employing the same drug by intravenous route (8–12). However, the control group obtained a not significantly different conversion rate of 60%. This latter figure illustrates the high spontaneous conversion of recent-onset atrial fibrillation (because digoxin has been shown ineffective in conversion [1]) and raises some concern as to whether the real conversion rate can be attributed to any drug intervention. Many factors are involved in the conversion of atrial fibrillation, some of which are highlighted by this study, including the presence of heart failure, left atrial size, previous history of supraventricular arrhythmias and duration of the arrhythmia. This explains the differences among series regarding conversion rates and emphasizes the need for controlled studies.

Comparison with other drugs. In reverting acute atrial fibrillation, intravenous amiodarone has been demonstrated to be superior to verapamil (11) and similar to procainamide (14), quinidine (15) and digoxin (16). Regarding class IC agents, comparative studies have not demonstrated any statistically significant superiority of either propafenone and flecainide over amiodarone in conversion rate (17,18). Nevertheless, it seems clear that both propafenone and flecainide are faster in achieving the conversion to sinus rhythm. In the study by Treglia et al. (17), the mean times of conversion for amiodarone and propafenone were 996 and 210 min, respectively ($p < 0.01$), and in the study by Capucci et al. (18), the mean times of conversion for amiodarone and flecainide were 705 and 190 min, respectively ($p < 0.001$).

Control of ventricular rate. In cases who did not convert, treatment with amiodarone was associated with a significantly lower ventricular rate compared with the control group ($p = 0.022$). This result could be expected because of the additive effects on the atrioventricular node of the two drugs, amiodarone and digoxin. Although fast and effective control of ventricular rate is desirable for reducing the symptoms caused by the arrhythmia, it is possible that the better control obtained with amiodarone could be achieved in a simpler manner by increasing the dosage of digoxin.

Dosage and rate of amiodarone administration. There are nearly as many dosages and rates of amiodarone infusion as studies in the literature, and none of them has been demonstrated to be clearly superior (8,11,12,14,16,17,19). Our trial utilized a dose that can be considered adequate at least from the point of view of achieving therapeutic levels and controlling ventricular rate, although we cannot rule out that other dosages could have obtained other results. Nevertheless, it has to be emphasized that higher doses are associated with more frequent side effects.

Study limitations. The differences obtained between the amiodarone and the control group in reversion rate (68% vs. 60%) were not significant, but there was a trend in favor of amiodarone (in fact, the amiodarone group had a conversion rate 13.3% superior to that of the control group). This raises the hypothetical possibility that with a larger sample, this difference could reach the significant level. This study was designed to detect a clinically relevant effect (>25%) of amiodarone in the reversion of acute atrial fibrillation, and the results allow us to rule out this effect with reasonably certainty. Moreover, a posteriori analysis revealed that the probability of obtaining the present results by a type I error in the presence of a true beneficial increase of 25% in the reversion rate was only 16%. If we consider such other data as the mean time of conversion (which was identical for both amiodarone and control group) and the number of recurrences of the arrhythmia (slightly superior in the amiodarone group), the present results allow us to conclude that amiodarone is of little if any help in the management of acute atrial fibrillation.

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