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Efficacy, Safety, and Determinants of Conversion of Atrial Fibrillation and Flutter With Oral Amiodarone

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Amiodarone is effective for long-term maintenance of sinus rhythm after electrical cardioversion of refractory atrial fibrillation or flutter. To examine its efficacy and safety for pharmacologic conversion of these arrhythmias, we studied 129 patients with refractory atrial fibrillation or flutter who had failed previous intensive conventional antiarrhythmic treatment. In anticipation of electrical cardioversion, patients were loaded with amiodarone, 600 mg/day during a 4-week period. The main outcome measure was pharmacologic conversion during this period. During the loading period, 23 patients (18%) converted to sinus rhythm. When analyzed in a multivariate model, conversion was related to desethylamiodarone plasma level ($p = 0.0006$), arrhythmia duration ($p = 0.04$), left atrial area ($p = 0.02$), and

concomitant treatment with verapamil ($p = 0.01$). During ongoing atrial fibrillation after loading, the ventricular rate decreased from 100 ± 25 to 87 ± 27 beats/min ($p < 0.001$). Amiodarone appeared to be safe and did not have to be discontinued because of intolerable side effects. Thus, amiodarone loading is safe and is still able to convert refractory atrial fibrillation or flutter. Conversion is related to increased desethylamiodarone plasma levels and concomitant treatment with verapamil. Because prolonged loading may increase desethylamiodarone plasma concentrations, this may enhance efficacy and obviate the need for electrical cardioversion. © 1997 by Excerpta Medica, Inc.

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Concerns have been raised regarding the safety of drugs with class III properties in patients with atrial fibrillation with respect to the possibility of bradycardia-dependent torsade de pointes occurring after conversion to sinus rhythm. Also, it has never been investigated whether amiodarone is safe in outpatients for the control of heart rate or bradyarrhythmias during ongoing atrial fibrillation. The present prospective study investigates the efficacy and safety of amiodarone for pharmacologic conversion of atrial fibrillation or atrial flutter in 129 patients with refractory arrhythmia and relates patient characteristics and drug plasma levels to the conversion rate.

METHODS

Patients: One hundred twenty-nine consecutive patients with chronic atrial fibrillation or flutter were considered candidates for preparatory amiodarone treatment in anticipation of electrical cardioversion. Eighty-nine of these patients participated in a study described previously.¹ Criteria for prophylactic treatment with amiodarone were also described previously by Crijns et al.² In short, amiodarone was administered only as a "last resort" drug in patients who failed to maintain sinus rhythm after previous cardioversions despite serial antiarrhythmic drug

treatment. Furthermore, it was used in patients in whom other antiarrhythmic drug treatment was contraindicated or in whom it was not possible to restore sinus rhythm during a previous electrical cardioversion. Exclusion criteria were (1) paroxysmal atrial fibrillation, (2) myocardial infarction or unstable angina within 6 months before entry into the study, (3) sick sinus syndrome or atrioventricular conduction disturbances without artificial pacemaker, and (4) hyperthyroidism. In all patients, the arrhythmia was symptomatic. All patients had undergone electrical cardioversion at least once before (median 2, range 1 to 8). Ninety-six patients had failed long-term maintenance of sinus rhythm after cardioversion despite serial cardioversion treatment and serial administration of an average of 2.0 ± 0.7 antiarrhythmic drugs. In the remaining 33 patients, treatment with other antiarrhythmic drugs was contraindicated, mainly because of impaired left ventricular function. In 14 patients, previous electrical cardioversion was not successful. The clinical characteristics of the patients are presented in Table I.

This study was approved by the institutional review board, and informed consent for participation in the study was obtained from all patients.

Amiodarone loading regimen and study protocol: Before starting amiodarone, all antiarrhythmic drugs were discontinued for at least 5 half-lives. Atrioventricular nodal blocking drugs, instituted to obtain adequate ventricular rate control (digoxin, calcium antagonists, or β blockers), were allowed during the loading period. Because of the known interaction of amiodarone with digitalis, the dose of the latter was reduced by 50% after initiating amiodarone treat-

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TABLE I Characteristics of the 129 Study Patients	
Age (yrs)	64 ± 10
Men/women	81/48
Atrial fibrillation/flutter	107/22
Underlying heart disease (%)*	
Coronary artery disease	39
Rheumatic valve disease	16
Mitral valve disease	26
Aortic valve disease	19
Systemic hypertension	24
Congenital heart disease	2
Dilated cardiomyopathy	11
"Lone" arrhythmia	9
Arrhythmia history	
Median duration, range (mo)	53, 1–348
Previous electrical cardioversions	1.9 ± 1.4
Previous antiarrhythmic drugs	2.0 ± 0.7
Concomitant negative chronotropic medication (%)	
Digitalis	40
Verapamil	29
Both digitalis and verapamil	20
Beta blocker	14
New York Heart Association class (%)	
I	23
II	52
III–IV	25
Echocardiographic variables	
Left atrial size, long-axis view (mm)	47 ± 7
Left atrial size, apical view (mm)	70 ± 7
Left atrial area (mm ²)	2,600 ± 530
Right atrial size	61 ± 7
Left ventricular end-diastolic diameter (mm)	54 ± 8
Left ventricular end-systolic diameter (mm)	39 ± 10
Fractional shortening (%)	29 ± 10

* >1 disease entity per patient.

ment. Patients received oral anticoagulation therapy to maintain an international normalized ratio between 2.4 and 4.8. A 12-lead electrocardiogram, chest x-ray, and 24-hour Holter monitoring were performed at baseline. Two-dimensional echocardiography was used to determine end-systolic and end-diastolic diameters. Left atrial area was calculated from 2 left atrial diameters (long-axis and apical view) using the following formula³: Left atrial area = (0.5 × left atrium long axis) × (0.5 × left atrium apical view) × π .

Routine clinical laboratory tests, including thyroid function tests, were performed. Amiodarone was initiated on an outpatient basis at a loading dose of 600 mg/day for 4 weeks. At the end of this period, patients visited the outpatient department. A 12-lead electrocardiogram was repeated to determine cardiac rhythm and to compare heart rate, QRS, QT, and QT_c intervals before and after loading. Blood was obtained for the determination of amiodarone and desethylamiodarone plasma levels using high-pressure liquid chromatography. Patients who were still in atrial fibrillation at that time underwent direct-current electrical cardioversion.

Definition of terms: "Chronic atrial fibrillation or flutter" was defined as repeatedly documented arrhythmia, without intercurrent sinus rhythm, on routine 12-lead electrocardiograms recorded at consecutive outpatient visits before inclusion. To exclude patients with paroxysmal (stress-induced) adrenergic

atrial fibrillation during these visits, we performed 24-hour Holter monitoring. "Underlying heart disease" was determined from the patient's history and physical examination, as well as from chest x-ray, echocardiography, and, if available, coronary angiography. "Total arrhythmia duration" was defined as the duration of arrhythmia history from the first episode of chronic atrial fibrillation or flutter. "Proarrhythmia" was defined according to the criteria proposed by Horowitz et al.⁴

Statistical analysis: The main outcome measure of the study was conversion to sinus rhythm within 1 month after the start of the loading period. Data are reported as mean ± 1 SD. Median values were used in cases of a nonuniform distribution of variables. For the comparison of 2 groups, continuous, normally distributed variables were tested by 1-way analysis of variance. Variables with a nonuniform distribution were tested with Wilcoxon's 2-sample test. Frequencies were compared by Fisher's exact test for equality of proportions. To determine parameters related to conversion, logistic regression was performed. Linearity of the continuous variables in relation to conversion was assessed by evaluating the coefficients of the quartiles of their distributions. In cases of a linear trend of the estimated coefficients of the different groups, the variable was introduced as continuous. If no linearity was apparent, the variable was categorized by taking together the quartiles with similar coefficients. A p value <0.05 was considered statistically significant; a p value between 0.05 and 0.10 was considered marginally significant.

RESULTS

During an amiodarone loading phase of 30 ± 3 days, patients received a mean total dose of 18 ± 2 g. Twenty-three patients (18%) converted to sinus rhythm, whereas the remaining 106 patients were still in atrial fibrillation or flutter after this period. The latter patients underwent subsequent electrical cardioversion, which was successful in 92 (87%). QRS duration increased from 96 ± 18 ms to 105 ± 20 ms (p <0.001). QT and QT_c intervals increased from 372 ± 46 to 409 ± 45 ms (p <0.001) and from 444 ± 66 to 467 ± 51 ms (p = 0.09), respectively. In the 106 patients who were still in atrial fibrillation or flutter, heart rate at rest decreased from 100 ± 25 to 87 ± 27 beats/min (p <0.001).

Clinical variables associated with conversion during oral amiodarone therapy: Tables II and III compare the clinical characteristics of patients who converted pharmacologically while receiving amiodarone with those who did not. Analyzed in a univariate model, amiodarone and desethylamiodarone plasma levels were associated with conversion to sinus rhythm. Furthermore, in the group of patients who converted during the loading period, there were significantly more patients treated with verapamil. On the other hand, a long total arrhythmia duration was an unfavorable factor. When analyzed in a multivariate model, amiodarone plasma level did not maintain statistical significance. In contrast, independent pre-

TABLE II Clinical Characteristics Associated With Pharmacologic Conversion During Amiodarone Loading: Univariate Analysis

Characteristic	Conversion (n = 23)	No Conversion (n = 106)	p Value
Age (yrs)	66 ± 9	63 ± 10	NS
Men/women (%)	61/39	63/37	NS
Atrial fibrillation/flutter (%)	87/13	82/18	NS
Underlying heart disease (%)*			
Coronary artery disease	52	37	NS
Rheumatic valve disease	13	17	NS
Mitral valve disease	22	26	NS
Aortic valve disease	17	19	NS
Systemic hypertension	39	21	NS
Congenital heart disease	0	2	NS
Dilated cardiomyopathy	13	10	NS
"Lone" arrhythmia	9	9	NS
Arrhythmia history			
Median duration, range (mo)	20, 2–161	34, 1–348	0.02
Previous electrical cardioversions	1.7 ± 1.0	2.0 ± 1.5	NS
Previous antiarrhythmic drugs	2.1 ± 0.7	1.9 ± 0.7	NS
Concomitant negative chronotropic medication during loading (%)			
Digitalis	43	35	NS
Verapamil	35	16	0.09
Both digitalis and verapamil	22	7	0.06
Beta blocker	9	3	NS
New York Heart Association class (%)			
I	22	24	NS
II	57	51	NS
III–IV	21	25	NS
Amiodarone level (μg/ml)	2.0 ± 0.8	1.4 ± 0.7	0.0003
DEA plasma level (μg/ml)	1.4 ± 0.7	1.0 ± 0.5	0.00001

*More than 1 disease entity per patient.
DEA = desethylamiodarone.

TABLE III Relation Between Echocardiographic and Electrocardiographic Characteristics and Conversion During Amiodarone Loading*

Variable	Conversion (n = 23)	No Conversion (n = 106)
Echocardiographic variables		
Left atrial size, long-axis view (mm)	47 ± 5	47 ± 7
Left atrial size, apical view (mm)	68 ± 6	71 ± 7
Left atrial area (mm ² , calculated)	2,502 ± 475	2,620 ± 540
Right atrial size (mm)	60 ± 6	61 ± 7
LVEDD (mm)	52 ± 7	55 ± 8
LVESD (mm)	37 ± 9	39 ± 11
Fractional shortening (%)	30 ± 9	29 ± 11
Electrocardiographic variables before amiodarone		
Heart rate (beats/min)	99 ± 20	100 ± 25
QRS (ms)	94 ± 12	96 ± 19
QT (ms)	386 ± 49	368 ± 45
QT _c (ms)	456 ± 75	440 ± 64

*Univariate analysis revealed no significant differences.
LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; QT_c = corrected QT time.

dictors of conversion were desethylamiodarone plasma level ($p = 0.0006$), arrhythmia duration ($p = 0.04$), left atrial area ($p = 0.02$), and concomitant treatment with verapamil ($p = 0.01$) (Table IV). There were no significant differences in the clinical characteristics or drug plasma levels between patients treated with or without verapamil.

Amiodarone and its metabolite:

Figure 1 shows the amiodarone and desethylamiodarone plasma concentrations in all patients 1 month after initiation of amiodarone therapy. Patients who converted pharmacologically tended to have higher amiodarone and desethylamiodarone plasma levels than those who failed to convert. Although there was a considerable overlap in plasma levels between the groups, conversion was unlikely to occur when the amiodarone level was $<1.2 \mu\text{g/ml}$ or desethylamiodarone was $<0.9 \mu\text{g/ml}$.

Heart rate at rest: In the 106 patients who failed to convert during loading, the heart rate at rest fell significantly after 1 month of amiodarone treatment from 100 ± 25 to 87 ± 27 beats/min ($p < 0.001$). Of note, in anticipation of a major reduction in ventricular rate during ongoing atrial fibrillation, the administration of β blockers or verapamil was stopped in 63 of these patients, in addition to the 50% reduction in the dose of digitalis. Figure 2 depicts the correlation between the reduction in heart rate at rest and drug plasma concentrations

in the 43 patients in whom the dose of concomitant negative chronotropic medication was unchanged. There appeared to be a significant relation between rate reduction and amiodarone serum concentrations (Figure 2A, $p = 0.007$). No relation between heart rate reduction and desethylamiodarone serum levels was found (Figure 2B, $p = 0.76$).

Adverse events: During the loading period, 3 patients (2%) suffered from minor gastrointestinal complaints, which disappeared spontaneously. No adverse effects necessitating drug discontinuation occurred. There were no proarrhythmic events, either in patients converting to sinus rhythm or in patients remaining in atrial fibrillation.

DISCUSSION

The importance of amiodarone for long-term arrhythmia outcome after cardioversion of atrial fibrillation or flutter is well known.^{1,5–10} Amiodarone is also useful for pharmacologic conversion of atrial fibrillation, with success rates ranging from 27% to as high as 86%,^{6–9,11–13} depending upon patient characteristics and drug administration. The present study showed that even in a highly selected group of patients refractory to antiarrhythmic treatment, amiodarone was still able to restore sinus rhythm in 18% of the patients, obviating the need for electrical cardioversion. This is quite a remarkable number; pharmacologic conversion by oral amiodarone was considered very unlikely to occur in our patient

TABLE IV Multivariate Analysis: Parameters Related to Successful Pharmacologic Conversion

Variable	Odds Ratio	95% CI	p Value
Desethylamiodarone level >1.3 mg/L*	11.259	2.8–45.2	0.0006
Arrhythmia duration <60 mo	5.745	1.1–30.8	0.0414
Use of verapamil	5.566	1.5–20.6	0.0103
Left atrial area <2,689 mm ^{2†}	4.728	1.3–17.0	0.0176

*Third quartile.

†Median.

CI = confidence interval.

FIGURE 1. Amiodarone and desethylamiodarone plasma concentrations after 1 month of amiodarone loading in all 129 patients, comparing patients who converted pharmacologically (open triangles) and those who did not (closed circles). Patients with an amiodarone concentration <1.2 mg/L or a desethylamiodarone level <0.9 mg/L were unlikely to convert (dashed lines).

group because of a very long arrhythmia duration, large left atrial area, and proven refractoriness to previously instituted antiarrhythmic therapy.

The relation between plasma concentrations of amiodarone and desethylamiodarone and clinical efficacy is not well established. Especially concerning supraventricular arrhythmias, very limited data are available.^{14,15} Several investigators have demonstrated only a weak or even an absent concentration-effect relation.^{16–20} Others found a clear concentration-related effect of amiodarone on QT-interval prolongation, slowing of heart rate, and suppression of ventricular arrhythmias.^{21–23} The present study showed that for conversion of atrial fibrillation, plasma concentrations of desethylamiodarone were more important than those of the parent compound. This is in agreement with previous studies²⁴ and is possibly related to a high myocardium/plasma concentration ratio in the case of desethylamiodarone.²⁵ In contrast, reduction of the ventricular rate during

FIGURE 2. Reduction in resting heart rate by amiodarone in 43 patients with a stable dose of negative chronotropic medication during ongoing atrial fibrillation. **A**, there was a significant correlation between the reduction in heart rate at rest and the plasma amiodarone concentration (Pearson's correlation coefficient = -0.40 , $p = 0.007$). **B**, no significant relation between plasma desethylamiodarone concentration and heart rate reduction could be found (Pearson's correlation coefficient = -0.08 , $p = 0.62$). bpm = beats per minute.

ongoing atrial fibrillation was clearly correlated with plasma levels of amiodarone itself. Because plasma levels of desethylamiodarone only increase gradually with prolonged therapy, reaching approximately 80% of that of amiodarone in several months,^{26,27} conversion is expected to occur later, whereas effects on rate control will occur early after instituting ther-

apy.^{28,29} Whether prolonged oral amiodarone loading is also accompanied by an increase in the number of patients who undergo conversion remains to be established.

A positive interaction between amiodarone and verapamil has not been reported before. This could be explained by a pharmacokinetic drug interaction or by selection bias. However, amiodarone plasma levels were not increased in patients using verapamil, and there were no differences in patient characteristics between patients with and without concomitant treatment with verapamil. This preliminary finding will have to be confirmed in a randomized, placebo-controlled study.

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