

Clinical Investigations

Amiodarone in Restoration and Maintenance of Sinus Rhythm in Patients with Chronic Atrial Fibrillation after Unsuccessful Direct-Current Cardioversion

GRZEGORZ OPOLSKI, M.D., PH.D., JOLANTA STANISŁAWSKA, M.D., PH.D., ALEKSANDER GÓRECKI, M.D., PH.D., GRAŻYNA ŚWIĘCICKA, M.D., ADAM TORBICKI, M.D., PH.D.,* TADEUSZ KRASKA, M.D., PH.D.

Department of Cardiology and *Department of Hypertension and Angiology, Medical Academy of Warsaw, Warsaw, Poland

Summary

Background: When direct-current (DC) cardioversion is used, sinus rhythm can be restored, at least temporarily, in 80–90% of patients with atrial fibrillation. However, there is a small but significant group of patients with chronic atrial fibrillation in whom DC cardioversion has failed to restore sinus rhythm. The value of antiarrhythmic drug pretreatment before DC cardioversion is still controversial.

Hypothesis: The aim of our study was to assess (1) the effectiveness of repeat DC cardioversion in patients with chronic atrial fibrillation after pretreatment with amiodarone, and (2) the efficacy of amiodarone in maintaining sinus rhythm after repeat cardioversion.

Methods: Forty-nine patients with chronic atrial fibrillation after ineffective DC cardioversion were included in the study. Repeat DC cardioversion was performed after loading with oral amiodarone, 10–15 mg/kg body weight/day for a period necessary to achieve the cumulative dose of over 6.0 g.

Results: Spontaneous conversion to sinus rhythm during amiodarone pretreatment was achieved in 9 of 49 patients (18%). Direct-current cardioversion was performed in 39 patients and sinus rhythm was achieved in 23 of these patients (59%). Mean heart rate decreased from 95 beats/min before to 68 beats/min after DC cardioversion ($p < 0.001$). Systolic blood pressure significantly ($p < 0.05$) decreased from 126 ± 23 to 108 ± 25 mmHg. Complications occurring in four patients just after electroconversion were well tolerated and of

short duration. After 12 months, 52% of patients maintained sinus rhythm on low dose (200 mg/day) amiodarone therapy.

Conclusion: Pretreatment with amiodarone and repeat DC cardioversion allows for restoration of sinus rhythm in about 65% of patients with chronic atrial fibrillation after first ineffective DC cardioversion. Direct-current cardioversion can be performed safely with the use of standard precautions in patients who are receiving amiodarone. At 12 months' follow-up, more than 50% of patients maintain sinus rhythm on low-dose amiodarone after successful repeat cardioversion.

Key words: amiodarone, chronic atrial fibrillation, repeat cardioversion

Introduction

When direct-current (DC) cardioversion is used, sinus rhythm can be restored, at least temporarily, in 80–90% of patients with atrial fibrillation.^{1–3} However, there is a small but significant group of patients with chronic atrial fibrillation in whom DC cardioversion has failed to restore sinus rhythm. The value of antiarrhythmic drug pretreatment before DC cardioversion is still controversial.

The long-term results of maintaining sinus rhythm after successful electroversion, however, are more discouraging without prophylactic antiarrhythmic therapy. After a successful DC shock, only about 25% of patients remain in sinus rhythm for 12 months.^{4,5} Maintenance therapy with class I antiarrhythmic drugs, such as quinidine, is commonly employed, yet despite this therapy, 50% of patients will revert to atrial fibrillation within 1 year.⁵ In addition, class I antiarrhythmic drugs are not without risks, including proarrhythmia (especially in patients with structural heart disease), heart failure exacerbation, and noncardiac toxicities.^{5,6} These concerns have revived interest in the use of amiodarone for suppression of atrial fibrillation.^{7–13} Relatively low doses of amiodarone can be effective in controlling atrial arrhythmias and have lower toxicity.

The aim of our study was to assess (1) the effectiveness of repeat DC cardioversion in patients with chronic atrial fibril-

Address for reprints:

Grzegorz Opolski, M.D., Ph.D.
Dept. of Cardiology
Medical Academy of Warsaw
Banacha str 1a
02-097 Warsaw, Poland

Received: August 27, 1996

Accepted with revision: January 10, 1997

lation after pretreatment with amiodarone, and (2) the efficacy of amiodarone in maintaining sinus rhythm after repeat cardioversion.

Methods

Study Population

Between January 1993 and June 1995, 49 of 70 patients with chronic atrial fibrillation (duration > 7 days) and ineffective DC cardioversion were included in the study. The etiology of atrial fibrillation could be either unassociated with heart disease and lone atrial fibrillation, or it may be associated with ischemic heart disease and hypertension.

Exclusion criteria were age >75 years, thyrotoxicosis, pregnancy, acute myocarditis, uncompensated heart failure (NYHA class III), hypertension of diastolic blood pressure (115 mmHg), known pulmonary hypertension, unstable hepatic or renal function, amiodarone therapy within last 12 months, and heart rate at rest < 90/min; also excluded were patients with sick sinus syndrome, bundle-branch block, and QT prolongation [i.e., corrected QT (QTc) > 0.45 s].

Informed consent was obtained before beginning either study agent, using a protocol approved by the Committee for the Protection of Human Subjects from Research Risks at the Medical Academy of Warsaw.

Patient records were scanned for the following clinical data: age, gender, duration of atrial fibrillation, history of hypertension, ischemic heart disease, and congestive heart failure. Left atrial anteroposterior size and left diastolic diameter of the left ventricle were determined by M-mode echocardiographic tracing. Antiarrhythmic drugs (except beta blockers) administered before inclusion in the study were discontinued ≥ 5 half-lives before treatment with amiodarone.

The clinical characteristics of patients in the study group are shown in Table I.

TABLE I Clinical characteristics of study group patients

No. of patients	49
Age (years)	62 \pm 11
Sex (M/F)	28/21
Mean duration of atrial fibrillation (months)	4 \pm 3.8
Underlying heart disease ^a	
Hypertension	22
Ischemic heart disease	19
Congestive heart failure	7
Cardiomyopathy	5
Lone AF	5
Left atrial size (mm)	
Long axis view	46 \pm 7
LVEDD (mm)	53 \pm 4

^a More than one disease entity per patient.

Abbreviations: AF = atrial fibrillation, LVEDD = left ventricular end-diastolic dimension.

Study Design

All patients underwent loading with oral amiodarone 10–15 mg/kg body weight/day for a period necessary to achieve the cumulative dose of >6.0 grams). Loading duration varied from 1 to 2 weeks. If sinus rhythm was not restored after achieving the cumulative dose of amiodarone, patients qualified for repeat DC cardioversion. All patients were receiving acenocoumarol anticoagulation 3 weeks before and at least 4 weeks after successful repeat cardioversion to maintain an international normalized ratio of 2.0–3.0.

After restoration of sinus rhythm, amiodarone therapy was continued at doses of 200 to 400 mg/day (mostly 200 mg/day). Antiarrhythmic agents other than digitalis and beta blockers were not given as concomitant medication.

Follow-up visits were scheduled at 1 week and at 1, 3, 6, and 12 months after DC cardioversion if sinus rhythm was maintained. Electrocardiograms were taken before and after conversion to sinus rhythm and during follow-up visits. Plasma levels of fT4 and TSH were measured at 6 and 12 months of treatment.

Statistical Analysis

The quantitative variables were given as mean \pm standard deviation (SD) unless specified as percent (%). Quantitative variables were compared with Student's *t*-test or chi-square test with Yates correction, when appropriate. A *p* value of <0.05 was considered statistically significant.

Results

Restoration of Sinus Rhythm

Spontaneous conversion to sinus rhythm during amiodarone pretreatment was achieved in 9 of 49 patients (18%). One patient with persistent atrial fibrillation was withdrawn because he had clinically significant bradycardia < 50/min. Direct-current cardioversion was performed in 39 patients, with sinus rhythm achieved in 23 patients (59%). Pretreatment with amiodarone and repeat DC cardioversion resulted in restoration of sinus rhythm in 32 of 49 patients (65%).

There were significant changes in heart rate and systolic blood pressure before and immediately after DC cardioversion (Table II).

Complications just after electroconversion were well tolerated and of short duration. One patient had idioventricular rhythm with hypotension that reverted within 5 min after intravenous administration of 1 mg atropine. Three patients had premature ventricular beats that subsided after lidocaine administration.

Follow-Up

At 6 months' follow-up sinus rhythm was maintained in 21 of 32 patients (66%) on amiodarone therapy; after 12 months,

TABLE II Changes in heart rate and blood pressure before and immediately after successful DC repeat cardioversion of chronic atrial fibrillation in 23 patients on amiodarone pretreatment.

	Before DC cardioversion		After DC cardioversion
Heart rate (beats/min)	95 ± 18	p < 0.001	68 ± 15
Systolic blood pressure (mmHg)	126 ± 23	p < 0.05	108 ± 25
Diastolic blood pressure (mmHg)	85 ± 14	NS	77 ± 17

Abbreviations: DC = direct current, NS = not significant.

16 of 31 patients (52%) maintained sinus rhythm. The mean dose of amiodarone was 212 ± 56 mg/day. Repeat cardioversion after amiodarone pretreatment maintained sinus rhythm in 8 of 9 patients. Comparison of patients who maintained sinus rhythm and those in whom atrial fibrillation recurred on amiodarone therapy during 12 months' follow-up is shown in Table III.

One patient had clinically significant sinus bradycardia after 1 month of therapy and was treated with DDD pacemaker implantation. One patient was withdrawn after 8 months due to hyperthyroidism.

Discussion

Our results indicate that amiodarone pretreatment and repeat DC cardioversion in patients with chronic atrial fibrillation after ineffective DC cardioversion is a safe procedure and

TABLE III Comparison of patients who maintained sinus rhythm and those with recurrence of atrial fibrillation on amiodarone therapy during 12 months' follow-up

	Group I	Group II
No. of patients	n = 16	n = 15
Age (years)	63 ± 9	61 ± 10
Sex (M/F)	7/9	9/6
Mean duration of AF (months)	4 ± 3.9	5 ± 4.7
Underlying heart disease ^a		
Hypertension	9	8
Ischemic heart disease	8	9
Congestive heart failure	2	3
Cardiomyopathy	1	2
Lone AF	2	2
Left atrial size (mm)		
Long axis view	45 ± 4.3	46 ± 4.9
LVEDD (mm)	53 ± 5.2	54 ± 4.0
Pharmacologic repeat cardioversion	8 (50%)	1 (7%) ^b

^a More than one disease entity per patient.

^b p < 0.05.

Abbreviations as in Table I.

allows for restoration of sinus rhythm in about 65% of patients. This observation confirmed the results of a previous study showing that the complications just after electroconversion are well tolerated and of short duration.¹⁴ Sagrista-Sauleda *et al.* analyzed the effect of amiodarone administration on the effectiveness and complications of electrical cardioversion of atrial fibrillation.¹⁴ They concluded that electrical cardioversion of supraventricular arrhythmias can be safely performed in patients on long-term oral or intravenous amiodarone therapy provided that usual precautions are observed.

It is interesting that spontaneous conversion to sinus rhythm during amiodarone pretreatment was achieved in 18% of our patients. In prior published experiences, 16–71% of patients converted to sinus rhythm during oral amiodarone loading.^{7–13} In our protocol, amiodarone pretreatment time was rather short (1–2 weeks). Some authors do not recommend electrical cardioversion until after 4–6 weeks therapy to allow time for spontaneous conversion and to maximize antiarrhythmic benefits following restoration of sinus rhythm.¹⁵ Gosselink *et al.* studied factors determining conversion of difficult-to-treat atrial fibrillation with oral amiodarone.¹⁵ In anticipation of electrical cardioversion, patients were loaded with 600 mg amiodarone daily for about 30 days (mean total dose 18 ± 2 g). At the end of this period, 15% patients were in sinus rhythm. Analyzed multivariately, only DEA serum level and arrhythmia duration maintained significance.

The efficacy of amiodarone for atrial fibrillation in the setting of nonrheumatic cardiac disease has been investigated in several trials.^{7–13} In the majority of these investigations, amiodarone has been administered as a drug of last resort, in a nonrandomized fashion, to patients with paroxysmal or chronic atrial fibrillation refractory to multiple trials of conventional antiarrhythmic agents. Low-dose amiodarone was successful in maintaining sinus rhythm in 53–79% of patients during a mean follow-up of 15–27 months. In our select group of patients undergoing DC repeat cardioversion on amiodarone therapy, sinus rhythm was maintained in 52% at 1 year. It is interesting that restoration of sinus rhythm on amiodarone pretreatment was maintained in most patients during 12 months follow-up.

Gosselink *et al.* administered low-dose amiodarone (204 ± 66 mg/day maintenance) to 89 patients with chronic atrial fibrillation following cardioversion.¹² Actuarial 3-year sinus rhythm maintenance was 53%. Only one patient withdrew because of intolerable side effects, and proarrhythmia did not occur. In another large retrospective study by Chun *et al.*¹⁶ the probability of patients with chronic atrial fibrillation remaining in sinus rhythm after cardioversion without recurrence of atrial fibrillation was 87, 70 and 55% at 1, 3, and 5 years, respectively.

The relatively small group of patients and the lack of a control group limited our study.

Conclusion

Pretreatment with amiodarone and repeat DC cardioversion allows for restoration of sinus rhythm in about 65% of

patients with chronic atrial fibrillation after ineffective DC cardioversion. Direct-current cardioversion can be safely performed with the use of standard precautions in patients who are receiving amiodarone. Amiodarone has a high rate of long-term efficacy in maintaining sinus rhythm in patients with refractory atrial fibrillation on first DC cardioversion. Restoration of sinus rhythm on amiodarone pretreatment is a predictor of sinus rhythm maintenance.

References

1. Lown B: Electrical reversion of cardiac arrhythmias. *Br Heart J* 1976;29:469-489
2. Mancini J, Goldberg AI: Cardioversion of atrial fibrillation: Consideration of embolization, anticoagulation, prophylactic pacemaker and long term success. *Am Heart J* 1982;104:617-621
3. Ewy GA, Ulfers L, Hager HD, Rosenfeld AR, Roeske WR, Goldman S: Response of atrial fibrillation to therapy: Role of etiology and left atrial diameter. *Electrocardiology* 1980;13:119-124
4. Lundstrom T, Ryden L: Chronic atrial fibrillation: Long term results of direct current conversion. *Acta Med Scand* 1988;223:53-59
5. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC: Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990;82:1106-1116
6. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin J: Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. *J Am Coll Cardiol* 1992;20:527-532
7. Brodsky MA, Allen BJ, Walker CJ, Casey TP, Luchet CR, Henry WL: Amiodarone for maintenance of sinus rhythm after conversion of atrial fibrillation in the setting of a dilated left atrium. *Am J Cardiol* 1987;60:572-575
8. Gold RL, Haffajee CI, Charos K, Sloan K, Baker K, Baker S, Alpert JS: Amiodarone for refractory atrial fibrillation. *Am J Cardiol* 1986;57:124-127
9. Horowitz LN, Spielman SR, Greenspan AM, Mintz GS, Morganroth J, Brown R, Brady PM, Kay HR: Use of amiodarone in the treatment of persistent and paroxysmal atrial fibrillation resistant to quinidine therapy. *J Am Coll Cardiol* 1985;6:1402-1406
10. Crijns HJ, Van Gelder IC, Van Gilst WH, Hillege H, Gosselink AM, Lie KI: Serial antiarrhythmic drug treatment to maintain sinus rhythm after electrical cardioversion for chronic atrial fibrillation or atrial flutter. *Am J Cardiol* 1991;68:335-341
11. Grayboys TB, Podrid PJ, Lown B: Efficacy of amiodarone for refractory supraventricular tachyarrhythmias. *Am Heart J* 1983;106:870-876
12. Gosselink ATM, Crijns HJGM, Van Gelder IC, Hillege H, Wiesfeld ACP, Lie KI: Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. *J Am Med Assoc* 1992;267:3289-3293
13. Middlekauff HR, Wiener J, Stevenson WG: Low-dose amiodarone for atrial fibrillation. *Am J Cardiol* 1993;72:75F-81F
14. Sagrista-Sauleda J, Permanyer-Mirada G, Soler-Soler J: Electrical cardioversion after amiodarone administration. *Am Heart J* 1992;123:1536-1542
15. Gosselink ATM, Crijns HJGM, Hillege H, Lie KI: Factors determining conversion of difficult-to-treat atrial fibrillation and flutter on oral amiodarone (abstr). *J Am Coll Cardiol* 1993;21:202A
16. Chun SA, Sager PT, Stevenson WG, Nademanee K, Middlekauff R, Singh BN: Long-term efficacy of amiodarone for the maintenance of normal sinus rhythm in patients with refractory atrial fibrillation or flutter. *Am J Cardiol* 1995;76:47-50