Clinical Investigations

Rate of Conversion and Recurrence after Sotalol Treatment in Patients with Direct Current-Refractory Atrial Fibrillation

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Summary

Background: A number of patients with persistent atrial fibrillation (AF) will not have sinus rhythm (SR) restored by direct current (DC) cardioversion.

Hypothesis: In patients with DC-refractory AF, oral pretreatment with sotalol increases the success rate at DC cardioversion.

Methods: Consecutive patients with persistent AF, refractory at a first DC cardioversion, were prospectively included. A comparative group of patients with AF not refractory at DC cardioversion was studied. Oral sotalol treatment was started after unsuccessful DC cardioversion and given at least 7 days before renewed cardioversion. Four weeks after cardioversion, an electrocardiogram was performed.

Results: In all, 53 patients were enrolled in the study. Forty-three (81%) in the sotalol group regained sinus rhythm (SR); 10 (19%) of these converted pharmacologically and 33 (62%) after a second DC cardioversion; SR was never restored in 10 patients (19%). After 4 weeks, SR was maintained in 29 patients (67%). The comparative group included 132 patients and differed significantly from the DC-refractory patients only with regard to weight. After 4 weeks, SR was maintained by 50 patients (37%) in this group.

Conclusions: In patients with persistent AF refractory to DC cardioversion, oral pretreatment with sotalol results in a high rate of SR restoration, either pharmacologically or by DC cardioversion. Maintenance of SR at 4 weeks is of sufficient clinical relevance to consider this treatment option in patients with AF refractory to DC cardioversion.

Key words: atrial fibrillation, cardioversion, sotalol, arrhythmias

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and the prevalence increases with age.¹ The general treatment strategy of persistent, symptomatic AF has been restoration and maintenance of sinus rhythm (SR). Direct current (DC) cardioversion remains the technique of choice in patients with symptomatic persistent AF, with a success rate ranging from 65 to 90%.² Recently, the conversion success rate has further improved due to the use of a biphasic shock wave form, reaching 90 to 95%;³ however, 5 to 35% do not convert to SR, that is, they have DC-refractory AF. In these patients, internal low-energy cardioversion has been successful in restoring SR, with a conversion rate between 75 and 90%.⁴ An alternate strategy is pretreatment with antiarrhythmic agents of class I or III (Vaughan Williams classification), preceding a second DC cardioversion. This strategy has shown convincing results for intravenous treatment with ibutilide and amiodarone.^{5,6}

Sotalol is a class II and III antiarrhythmic agent, with the properties of a common beta blocker and an antiarrhythmic effect. In experimental dog models, sotalol decreases defibrillation energy requirement in ventricular tachycardias.⁷ In a study by Dorian and Newman, oral sotalol treatment lowered defibrillation energy requirement in patients treated with implanted cardioverter defibrillators.⁸ The present study was designed to evaluate the effect of pretreatment with oral sotalol in patients with refractory AF, determining the success rate at renewed DC cardioversion and maintenance of SR.

This study was supported by a grant from the Swedish Heart and Lung Foundation.

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Received: February 22, 2005

Accepted with revision: October 10, 2005

Methods

Patients

Consecutive patients who failed conventional monophasic DC cardioversion were enrolled in this study. Direct current-refractory AF was defined as less than three heart beats in SR after the attempt to cardioversion. Inclusion criteria were a clinical diagnosis of symptomatic, persistent AF for at least 1 month without any current treatment with class I or III antiarrhythmics. Exclusion criteria were contraindication for sotalol, including renal insufficiency, sick sinus syndrome, bradycardia (< 50 beats/min), hypotension (< 90 mmHg), untreated congestive heart failure, hyperthyroidism, and myocardial infarction or cardiac surgery within the preceding 2 months. In an attempt to determine the duration of AF, a careful medical history was taken and a review of available electrocardiograms (ECG) was performed in all patients. All patients underwent transthoracic echocardiography prior to the first cardioversion.

A comparative group of 132 patients with persistent AF, without treatment with class I or III antiarrhythmics, not refractory at DC cardioversion, was studied to determine conditions that might influence conversion success rate. These were consecutive patients sent to our clinic and managed by the same clinicians.

Study Treatment

Treatment with oral sotalol was initiated directly after the failed electrocardioversion, starting with 80 mg twice daily and with a maximum dose 160 mg twice daily. No other antiarrhythmic drug treatment was allowed. Pretreatment with sotalol was continued at least 7 days before a renewed attempt of cardioversion in order to establish the highest tolerable dose with regard to heart rate, QT interval, and blood pressure. All patients were treated with warfarin, with the International Normalized Ratio (INR) ranging between 2.0 and 3.0, for at least 3 weeks before and for 4 weeks after cardioversion.

Cardioversion

Direct current cardioversion was performed on an elective basis according to clinical practice. Light general anesthesia with propofol was induced intravenously. Paddles were placed in the right second intercostal space and in a left-sided lateral position along the mid-axillary line. Delivery of shocks (monophasic wave form) started with 200 J and, if unsuccessful, was increased to at least two attempts at 360 J. In patients with rapid ventricular rate or high blood pressure, selective beta₁-blockers were given intravenously according to the clinician's decision. Successful outcome after pretreatment with sotalol was defined as SR after DC cardioversion, and also verified SR on electrocardiogram (ECG) 2 h after cardioversion. All patients underwent clinical examination and 12-lead ECG 4 weeks after cardioversion.

Statistics

According to earlier reports, a conversion success rate of 8% might be expected in patients with DC-refractory AF undergoing a second cardioversion with no change in therapy.⁵ To detect an increase in conversion rate from 15 to 40% with sotalol, using the patients as their own controls, with $\alpha = 0.05$ and $\beta = 0.8$, it was calculated that at least 49 patients were required. We enrolled 53 patients.

Continuous variables are given as mean values $\pm$ standard deviation (SD). The unpaired *t*-test was used for analysis of statistical differences in variables between the groups. In comparison of the two proportions, Pearson's chi-square test was used, and in the case of small numbers, Fisher's exact test was used. When comparing the DC-refractory group with the comparative group, stepwise multiple regression analysis was performed. A *p* value < 0.05 was considered statistically significant. Calculations were performed with the statistical computer package Statistica 6.0 (StatSoft Inc., Tulsa, Okla., USA).

Ethics

The study was approved by the Local Ethics Committee of Karolinska Institute, and all patients gave their informed consent to participate.

Results

Patient Characteristics

In all, 53 patients were enrolled in the study. Baseline clinical data for all patients are summarized in Table I. The mean ($\pm$ SD) administrated dose of sotalol at cardioversion was 255 (± 53) mg daily. Baseline clinical data for the comparative group are summarized in Table I. In univariate analysis, the comparative group differed significantly from the DC-refractory group as far as age, weight, duration of AF, and LA and LV dimension were concerned (Table I). However, after stepwise multiple regression analysis, only the difference in patients' mean ($\pm$ SD) body weight remained statistically significant.

Cardioversion

In total, 43 patients (81%) in the sotalol group converted to SR. Of these, 10 (19%) converted to SR after initiated sotalol treatment and before scheduled DC cardioversion, that is, pharmacologic cardioversion. An additional 33 patients (62%) restored SR with DC cardioversion, and all of these patients maintained SR at discharge from the clinic. The mean ($\pm$ SD) cumulative energy delivered was significantly lower than the cumulative energy delivered at the first unsuccessful cardioversion, that is, 788 (± 549) J versus 1344 (± 527) J, $p < 0.001$. An intravenous beta₁-blocker was administered in 33 patients (73%) on the first unsuccessful occasion. Significantly fewer patients ($n = 14$) (37%), received a beta blocker

TABLE I Baseline characteristics

Characteristic	Study group (n = 53)	Comparative group (n = 132)	p Value
Male	38 (71)	87 (66)	NS
Age (years)	63.4 ± 10.5	67.8 ± 9.5	<0.01
Weight (kg)	88.4 ± 15.0	77.2 ± 12.1	<0.01
AF duration (months)	5.9 ± 3.0	4.4 ± 2.3	<0.01
AF, unknown duration	16 (30)	40 (30)	NS
Hypertension	15 (28)	41 (30)	NS
Ischemic heart disease	5 (9)	14 (11)	NS
Congestive heart failure	5 (9)	3 (2)	0.03
Corrected thyroid disease	3 (6)	9 (7)	NS
Valvular heart disease	8 (15)	26 (20)	NS
Lone AF ^a	25 (47)	53 (40)	NS
LA dimension (mm)	44.6 ± 5.5	42.5 ± 5.3	<0.01
LV dimension (mm)	50.7 ± 6.4	48.3 ± 5.6	<0.01
EF (%), mean (range)	45 ± 9.5	47.3 ± 8.7	NS

^a Defined as the absence of any of the above mentioned diseases.

Values are expressed as means ± standard deviation or number (%) of patients.

Abbreviations: EF = ejection fraction, LA = left atrium, LV = left ventricular, AF = atrial fibrillation.

intravenously at the second attempt of DC cardioversion ($p < 0.001$). The patients ($n = 8$) who were refractory to the second DC cardioversion received a significantly lower mean (SD) dose of sotalol than the patients who restored SR at DC cardioversion, that is, 206 (± 63) mg vs. 268 (± 71) mg ($p = 0.04$). There was no significant difference in any clinical characteristic such as age, weight, duration of AF, LA dimension, or ejection fraction (EF).

Maintenance of Sinus Rhythm

Of the 43 patients who restored SR after pretreatment with sotalol, 29 patients (67%) maintained SR after 4 weeks. Of the total study population of 53 patients, 29 (55%) had SR at follow-up. (Fig. 1) Maintenance of SR at 4 weeks was more common among patients who had pharmacologic cardioversion than among patients who restored SR after DC cardioversion (90 vs. 60%, $p = 0.03$). Ten patients (19%) went through the study with persistent AF. In the comparative group of 132 patients, 50 patients (37%) maintained SR after 4 weeks.

Adverse Effects

Sotalol treatment was withdrawn in four patients because of side effects, occurring in two patients before cardioversion. These two patients never underwent a second cardioversion. In another two patients, treatment with sotalol was withdrawn 2 weeks after their second cardioversion because of side effects, and sotalol was replaced by diltiazem. Both these patients maintained SR at 4 weeks follow-up. During the study period, there were no signs of proarrhythmias, such as torsade de pointes, in the study population.

Discussion

In the present study, we demonstrate that patients with DC-refractory AF may be successfully converted following oral sotalol pretreatment. In addition, a group of patients will convert pharmacologically after initiation of sotalol treatment. Patients converted after oral sotalol treatment remained in SR to a no lesser extent than those with nonrefractory AF.

Cardioversion

The most frequently applied method for restoration of SR is DC cardioversion, although the success rate ranges from 65 to 95%.^{2,3} Several factors are known to predict the success

FIG. 1 Sinus rhythm (SR) at direct current cardioversion and maintenance of SR at 4 weeks of follow-up. 1 = Percentage of patients in sotalol group with SR after cardioversion ($n = 43$, 81%). 2 = Percentage of patients in sotalol group with SR at 4 weeks ($n = 29$, 55%). 3 = Percentage of patients with SR at 4 weeks, control group ($n = 132$, 37%). ▨ = pharmacologic cardioversion, □ = electrocardioversion.

rate at DC cardioversion. The duration of AF has most consistently been found to correlate with an impaired success rate. Other factors such as age, the presence of underlying heart disease, functional New York Heart Association class, mitral valve disease, or left ventricular enlargement all show inconsistent results.^{9–11} Apart from a short duration of AF, the patients' body weight has been shown to be an independent predictor of successful cardioversion.^{12, 13} This fact suggests that successful cardioversion depends on the amount of energy delivered to the heart, consistent with the higher efficacy of internal cardioversion.¹⁴ In our study, refractory patients had a mean ($\pm$ SD) weight of 88.4 ($\pm$ 15) kg, and no patient had duration of AF for less than 1 month. Compared with the control group, earlier findings are confirmed, especially as far as weight is concerned. This parameter remained statistically significant after stepwise multiple regression analysis, indicating that our patients with DC-refractory AF constituted a representative group.

Direct Current-Refractory Atrial Fibrillation

There is no consensus on the definition of refractory AF. Our patients were defined to have refractory AF if there were <3 heart beats in SR after conventional monophasic DC cardioversion. This is in accordance with study protocols used earlier. However, the amount of cumulative energy delivered before considering refractory AF varies from 360 up to 1200 J.^{4–6} Our patients were refractory despite the fact that they received a high amount of delivered energy at their first unsuccessful cardioversion.

Antiarrhythmic pretreatment with class I or III antiarrhythmics (Vaughan Williams classification) preceding DC cardioversion has shown convincing results for intravenous treatment with ibutilide and amiodarone.^{5, 6} One problem with ibutilide is, however, that since most recurrence of AF occurs during the first weeks after cardioversion, pretreatment with an oral class III agent in order to achieve steady-state at the time of cardioversion would be preferable, but it is not possible to combine this treatment with ibutilide. The effects of class I-antiarrhythmic drugs have been inconsistent in earlier studies.^{15–17}

Sotalol Effect

The mode of action of sotalol in increasing the conversion rate at DC cardioversion remains unclear. In several studies, sotalol treatment has been shown to reduce the defibrillation threshold in ventricular arrhythmias, and it has been hypothesized that this could be due to a greater degree of synchronization of adjacent myocardial elements, resulting from a prolongation of refractoriness.^{7, 8} A similar mechanism has been suggested for the AF threshold, with data indicating that sotalol decreased the atrial defibrillation energy requirement by increasing atrial refractoriness.¹⁸

In the present study, the patients who had SR after renewed DC cardioversion received a significantly higher dose of sotalol than those in whom SR was not restored. This may

reflect a dose-dependent effect of sotalol on the success rate at cardioversion.

In our study, 10 patients (19%) converted pharmacologically after induction of sotalol treatment. This is in accordance with earlier studies of oral sotalol treatment in patients with persistent AF.^{19, 20} According to our study, it seems difficult to predict which patients will convert pharmacologically. However, our results emphasize the importance of adequate anticoagulation treatment, since approximately one of five patients converts after the initiation of class III antiarrhythmic treatment.

Maintenance of Sinus Rhythm

The maintenance of SR at 4 weeks of follow-up was high (67%) among patients in whom SR was restored either by DC cardioversion or pharmacologic conversion. In all, 55% of all patients enrolled in the study had SR at 4 weeks of follow-up. These results compare well with earlier results of sotalol treatment after DC cardioversion.^{19, 21} This is particularly striking, considering that our patients had a relatively long duration of AF (mean 5.9 [$\pm$ 3.0] months) and that the duration of AF was unknown in 30% of the patients. Patients who converted pharmacologically had a low AF relapse rate. To our knowledge, this has not been described earlier, but could, of course, be a chance finding because of the small number of patients and needs to be evaluated further.

In the comparative group of patients, the incidence of SR at 4 weeks was lower (37%). However, no comparison should be made, although the patients with nonrefractory AF received no prophylactic antiarrhythmic therapy.

Side Effects

Sotalol treatment was well tolerated overall. Only a total of four patients interrupted the sotalol treatment because of subjective adverse effects (tiredness, dizziness, and shortness of breath). We found no ventricular proarrhythmias or episodes of syncope in our study population. This could be because of the relatively small number of patients, but might also depend on selection bias; our patients had at most a moderate decrease in left ventricular function and a relatively low frequency of other risk factors for proarrhythmias.

Study Limitations

This study was not a randomized placebo-controlled study. This choice was made since the success rate of renewed DC cardioversion, without change of therapy, in patients with DC-refractory AF seems to be extremely low, and partly because of ethical reasons this study design was abandoned. This is, of course, a major limitation, and randomization prospectively would be of need in further studies to confirm our results. However, the rate of conversion (81%) after pretreatment with sotalol seems high to be random, considering that all patients had one failed DC cardioversion prior to study inclusion. Another limitation is the lack of prespecified proto-

col for the maximum cumulative amount of delivered energy. Due to this fact, it is not possible to draw any conclusions concerning the effect of sotalol on the DC-cardioversion threshold. In our study, we did not distinguish between patients with refractory AF and those with immediate reinitiation of AF, defined as at least one sinus beat and reinitiation of AF within 2 min. Using the definition < 3 beats in SR for refractory AF, our result might underestimate success rate at DC cardioversion. Another limitation is the use of monophasic shock wave-form; however, this was the clinical routine at the time for this study. It is also important to point out that the follow-up period is limited to 4 weeks in this study.

Conclusions

In patients with persistent AF refractory to DC cardioversion, oral pretreatment with sotalol results in a high rate of SR restoration, by either pharmacologic or DC cardioversion. Maintenance of SR at 4 weeks is of sufficient clinical relevance to consider this treatment option in patients with AF refractory to DC cardioversion.

Acknowledgment

The authors thank Ms. Rigmor Hårdén for skilled assistance and also express their gratitude to Professor Mårten Rosenqvist for valuable and constructive criticism of the manuscript.

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