Does flecainide regain its antiarrhythmic activity after electrical cardioversion of persistent atrial fibrillation?

Robert G. Tieleman, MD, PhD,* Isabelle C. Van Gelder, MD,† Hans A. Bosker, MD,‡ Tsjerk Kingma, MSc,† Arthur A.M. Wilde, MD,§ Charles J.H.J. Kirchhof, MD,* Johan H. Bennekers, MD,‖ Frank A.L.E. Bracke, MD,¶ Nic J.G.M. Veeger, MSc,† Jaap Haaksma,PhD,† Maurits A. Allessie, MD, PhD, Harry J.G.M. Crijns, MD***

*From University Hospital Maastricht, Maastricht, The Netherlands,
†University Hospital Groningen, Groningen, The Netherlands,
‡Rijnstate Hospital Arnhem, Arnhem, The Netherlands,
§A.M.C. Amsterdam, Amsterdam, The Netherlands,
‖Martini Hospital, Groningen, The Netherlands,
¶Catharina Hospital Groningen, Groningen, The Netherlands, and
**Department of Physiology, University of Maastricht, Maastricht, The Netherlands.

OBJECTIVES The purpose of this study was to evaluate the hypothesis that presumed reversion of electrical remodeling after cardioversion of atrial fibrillation (AF) restores the efficacy of flecainide.

BACKGROUND Flecainide loses its efficacy to cardiovert when AF has been present for more than 24 hours. Most probably, the loss is caused by atrial electrical remodeling. Studies suggest electrical remodeling is completely reversible within 4 days after restoration of sinus rhythm (SR).

METHODS One hundred eighty-one patients with persistent AF (median duration 3 months) were included in this prospective study. After failure of pharmacologic cardioversion by flecainide 2 mg/kg IV (maximum 150 mg in 10 minutes) and subsequent successful electrical cardioversion, we performed intense transtelephonic rhythm monitoring three times daily for 1 month. In case of AF recurrence, a second cardioversion by flecainide was attempted as soon as possible.

RESULTS AF recurred in 123 patients (68%). Successful cardioversion by flecainide occurred only when SR had been maintained for more than 4 days (7/51 patients [14%]). Failure to cardiovert was associated with a prolonged duration of the recurrent AF episode and concurrent digoxin use. Multivariate logistic regression confirmed that successful cardioversion was determined by digoxin use (odds ratio [OR] 0.093, $P = .047$) and by the interaction between the duration of SR and the (inverse) duration of recurrent AF (OR 6.499, $P < .001$). When flecainide was administered within 10 hours after AF onset and the duration of SR was greater than 4 days, the success rate was 58%.

CONCLUSIONS Flecainide recovers its antiarrhythmic action after cardioversion of AF. However, successful pharmacologic cardioversion occurs only after SR has lasted at least 4 days and is expected only for recurrences having duration of a few hours. Immediate pharmacologic cardioversion of AF recurrence may be a worthwhile strategy for management of persistent AF.

KEYWORDS Atrial fibrillation; Antiarrhythmic agents; Remodeling; Cardioversion

(Heart Rhythm 2005;2:223–230)

Introduction

Pharmacologic cardioversion has proved to be a successful therapy for atrial fibrillation (AF) of short duration. One of

This study was supported by Grant 95.184 from the Netherlands Heart Foundation, The Hague, The Netherlands. Dr. Van Gelder was supported by Grant 94.014 from The Netherlands Heart Foundation, The Hague, The Netherlands. Dr. Tieleman is supported by an unrestricted research grant from Medtronic Bakken Research, Maastricht, The Netherlands.

A list of the participating clinical centers is given in the Appendix.

Address reprint requests and correspondence: Dr. Robert G. Tieleman, Department of Cardiology, University Hospital Maastricht, P. Debyelaan 25, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.

E-mail address: r.tieleman@fys.unimaas.nl.

(Received July 26, 2004; accepted November 11, 2004.)

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2004.11.014

the most effective drugs is the class IC agent flecainide (success rate 77–93%),[1–4] followed by the class III drug ibutilide (success rate 34–60%).[5,6] However, flecainide in particular loses its efficacy when the arrhythmia has been present for more than 1 day (success rate 0–40%).[2,3] Ibutilide also has lower conversion rates for AF of longer duration, with 35% conversion to sinus rhythm (SR) for AF that has lasted for more than 3 days.[5] The loss of efficacy of antiarrhythmic drugs is suggested to result from AF-induced atrial electrical remodeling,[7] which causes shortening of the atrial refractory period and creates a more vulnerable substrate for perpetuation of AF within 24 to 48 hours after arrhythmia onset.[8] In patients after cardioversion of long-lasting AF, atrial electrical remodeling is completely reversible within 4 days.[9] We hypothesized that if the loss of efficacy of cardioversion by flecainide resulted from electrical remodeling, then flecainide would regain its efficacy after 4 days of SR. This hypothesis was tested in patients with persistent AF who were undergoing electrical cardioversion.

Methods

Patients

The present study was a prospective multicenter study performed in 13 hospitals in The Netherlands. The study protocol was approved by the medical ethical committee of each participating center, and all patients gave written informed consent. Patients awaiting electrical cardioversion of persistent AF with a duration between 1 month and 1 year were evaluated for inclusion in the study. The duration of the arrhythmia was estimated using all ECGs available in the patient's chart, including routinely obtained 24-hour Holter ECG recordings. None of the patients had paroxysmal AF.

Routinely, all patients had undergone echocardiographic evaluation, laboratory tests, and proper anticoagulation (international normalized ratio 2.0–3.5) during the 4 weeks prior to cardioversion. Patients with untreated hyperthyroidism, significant valvular disease, left ventricular dysfunction with an ejection fraction $<50\%$, or contraindications to flecainide were excluded from the study. Patients with only minimal heart disease, such as grade 1 mitral regurgitation (color Doppler jet area $<25\%$ of the left atrial surface area), grade 1 aortic regurgitation (jet area $<20\%$ of the left ventricular outflow tract), left ventricular hypertrophy <11 mm, or asymptomatic coronary artery disease after treatment were allowed to participate in the study. Use of oral class IC or III antiarrhythmic medication was not allowed during the 4 weeks before to 4 weeks after electrical cardioversion.

Study protocol

Before electrical cardioversion, all patients were pretreated with infusion of flecainide 2 mg/kg IV (maximum 150 mg in 10 minutes) in an attempt to cardiovert AF. Flecainide did not restore SR within 1 hour after starting infusion in any of the patients (success rate 0%). All patients subsequently underwent electrical cardioversion. If SR was maintained for at least 4 hours after cardioversion, the patients received a transtelephonic monitoring device to record their heart rhythm three times per day for 1 month. Recordings were made at fixed time points between 8:00 and 10:00 hours, 16:00 and 18:00 hours, 22:00 and 24:00 hours, and at the time of symptoms. The patient transmitted the recordings daily to the central core-monitoring laboratory after the first (morning) and second (afternoon) recording. Using this technique, the time of onset of an eventual AF recurrence could be estimated. In symptomatic patients, the time of recurrence was defined as the time at which AF was recorded because of symptoms. In asymptomatic recurrences, the median time point between the last recording in SR and the first recording with AF was taken as the time of recurrence. Subsequently, the duration of SR after electrical cardioversion and the duration of the second AF episode could be calculated.

If AF recurrence was detected by either the patient or the transtelephonic monitoring laboratory, the patient was asked to come to the hospital as soon as possible to receive a second infusion of flecainide. Pharmacologic cardioversion was considered successful if SR was restored within 1 hour after starting flecainide infusion.

In total, 196 patients were studied using this approach. To minimize confounding factors, concomitant medication was left unchanged after the first electrical cardioversion, that is, rate-control medication was continued, and no class I and III antiarrhythmic drugs were started. Fifteen patients were excluded from the analysis because of protocol violations, mainly the prescription of a prophylactic antiarrhythmic drug after inclusion in the study, leaving a study population of 181 patients.

Statistical analysis

Data are presented as mean $\pm$ SD. Median values were used in case of nonuniform distribution. For comparison of groups, continuous and normally distributed variables were tested using one-way ANOVA. Nonuniform variables were tested using the Wilcoxon two-sample test. Frequencies were tested using the Fisher exact test for equality of proportions. Parameters possibly related to AF recurrence were evaluated by multiple Cox regression analysis. Stepwise backward logistic regression was performed to analyze parameters related to a successful cardioversion of recurrent AF using flecainide. The following characteristics were included: age, symptoms, echocardiographic parameters, medication, duration of AF before first cardioversion, duration of SR after cardioversion, and duration of the recurrent AF episode. Parameters with $P < .20$ were included in multiple logistic regression analysis. $P < .05$ was considered significant. Analyses were performed using SAS statistical software (version 6.11, SAS Institute, Cary, NC, USA).