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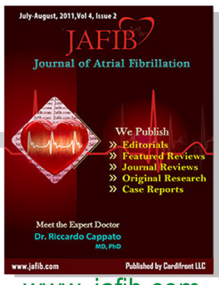

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Quinidine for Pharmacological Cardioversion of Long-lasting Atrial Fibrillation

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Abstract

Background

In the daily clinical practice, patients with atrial fibrillation (AF) lasting more than 48h (or not datable at all) are not uncommon. In long-lasting AF changes in electrophysiological features (electrical remodeling) can occur, resulting in a loss of sensibility to most antiarrhythmic drugs. There is strong evidence that the main mechanism involved in electrical remodeling is a global shortening in refractory period. To assess safety and efficacy of quinidine in pharmacological cardioversion of long-lasting AF, compared with propafenone and amiodarone.

Methods and Results

Ninety consecutive patients with AF lasting more than 6 weeks were randomized to amiodarone (5mg\kg bolus, then 15mg\kg in 24h) , propafenone (2 mg\kg bolus then 0.007mg\kg for 2h), and quinidine (275mg of quinidine arabogalattan sulphate per os every 2h for 8h maximum) for pharmacologic cardioversion. All patients had been previously treated with adequate oral anticoagulation and had been submitted to transthoracic echocardiogram. The 3 groups of patients did not differ for baseline and echocardiographic characteristics. Sinus rhythm was restored in 16 patients treated with quinidine (53%), compared with 6 patients (20%) in the amiodarone and propafenone groups ($p<0.01$). No major adverse effect was reported during the treatment.

Conclusions

Quinidine seems to be safe and effective in pharmacological cardioversion of long-lasting AF.

Introduction

Atrial fibrillation (AF) is a very common arrhythmia and its management remains a challenge. Recent data show that AF affects about 1-2% of general population and its prevalence seems to have an increasing trend.[1] At present, electrical cardioversion is the most effective way to restore sinus rhythm and is largely used in hospital setting. Unfortunately, this procedure requires conscious sedation or anesthesia. On the other hand, pharmacological cardioversion does not require patients' sedation but is less efficacious than electrical cardioversion. It also appears to be most effective when initiated within 7 days after the onset of AF. Drugs mainly used in pharmacological cardioversion such as amiodarone (Vaughan Williams' class III) and propafenone or flecainide (class IC) are known to be very effective in the first hours from the onset of the arrhythmia,[2,3] while their ability to restore sinus rhythm decreases later in time. Though simpler to be performed,

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pharmacological cardioversion still presents some disadvantages, including the risk of drug-induced torsade de pointes ventricular tachycardia or other serious arrhythmias.

In the daily clinical practice, patients with long-lasting (>48 hours) AF are not uncommon. In these cases, the fast activation of atrial miocardiocytes causes a complex pattern of electrophysiological alterations, called "electrical remodeling",[4] which is able to change the pharmacological sensibility of the arrhythmia, mainly through a slowdown of atrial tissue's conduction velocity and a global shortening of its refractory period. This might, in part, explain why class IC and, partially, class III drugs, which slow conduction speed, have only limited efficacy when the arrhythmia persists in time.[5] Quinidine is a class IA antiarrhythmic drug, mainly acting on the refractory period and is able to restore sinus rhythm in about 80-90% of patients when used in the first hours of arrhythmia, an efficacy comparable to class IC drugs.[6] Few data are available regarding the role of quinidine in pharmacological cardioversion of long-lasting AF. The aim of the present study was to assess safety and efficacy of quinidine in pharmacological cardioversion of long-lasting AF, compared with propafenone and amiodarone.

MATERIALS AND METHODS

In this open-label trial, 90 consecutive patients with AF lasting more than 6 weeks were enrolled in the study. Patients matching inclusion criteria were randomized to quinidine, amiodarone, and propafenone.All patients provided informed written consent to the study. The local ethical committee had approved the content of the study.

Inclusion and exclusion criteria:

Patients hospitalized for cardioversion of long lasting atrial fibrillation were evaluated for this study. Long lasting AF was defined as the presence of the arrhythmia for a period of time superior to 6 weeks (documented by Holter recording or at least two basal ECGs). Patients should have had more than 18 years and should have been in proper anticoagulation range (INR between 2 and 3) for at least 4 weeks. We excluded patients already in therapy with antiarrhythmic drugs for any reason. Patients with hemodynamic instability (SBP lower than 90 mmHg, signs of shock), NYHA class III or IV heart failure, II or III degree atrioventricular block, ventricular pre-excitation (positive history and\or delta wave at ECG), long QT (corrected QT > 480ms or measured QT > 500ms), acute coronary syndrome on admission or in the previous three months, history of hypersensitivity to iodine compounds, COPD, liver cirrhosis (Child class B or C) or myasthenia gravis were also excluded.

Baseline assessment:

Recorded patients' data included sex, age (in years) and duration of atrial fibrillation (in weeks). We considered the onset of the arrhythmia as the date of the first ECG or Holter recording of atrial fibrillation if not followed by others in sinus rhythm.

Before treatment, all patients underwent transthoracic echocardiographic examination to measure atrial and ventricular telediastolic diameters. Both values were taken on parasternal long axis view with M-mode, considering the frame before mitral valve opening.

In order to identify any possible cause of AF, careful medical history was collected for all patients. Where no underlying heart disease was found, the arrhythmia was classified as "lone AF". All patients underwent 12 leads ECG examination to verify the presence of the arrhythmia and rule out exclusion criteria. Blood analyses were also performed and electrolytic disorders were excluded or corrected before treatment (in particular, potassium level was recorded considering a safety value within the range 4.0 – 5.0 mEq\L).

Continuous wireless ECG monitoring during drug infusion and for the following 24 hours was provided in all patients to look for interruption criteria (see below) or sinus rhythm restoration. A final QTc measurement was taken at the end of observation period.

Interruption criteria:

Every major side effect of the three drugs was considered as criteria for treatment interruption. In particular, clinical and instrumental observation

was aimed to find any episode of bradyarrhythmia (sinus arrest, advanced atrioventricular block, symptomatic bradicardia), tachyarrhythmia (torsade de pointe, ventricular tachycardia, ventricular fibrillation), nausea and vomit conditioning electrolytic disorders, symptomatic hypotension, cinconism, allergic reaction (e.g. cutaneous rash) or QTc prolongation (> 550ms or QRS widening over 25%).

Drug protocols:

Amiodarone was administered intravenously with an initial bolus of 5mg\kg in 100ml of dextrose 5% solution followed by a maintenance infusion of 15 mg\kg in the following 24 hours.

Quinidine was administered orally as quinidine arabogalattan sulphate (Longachin)®. Each capsule contains 275mg of this slow-release molecule, equivalent to 165mg of quinidine sulphate. An experimental protocol was developed consisting of the administration of 1 capsule of the drug every two hours until sinus rhythm restoration or up to 4 capsules.

Propafenone was administered intravenously. After a bolus of 2mg/kg, the drug was infused at 0.007mg\kg in 2h or up to sinus rhythm restoration.

Endpoints and follow-up:

Primary endpoint was considered as the conversion to sinus rhythm within 24 hours after administration of drugs. Patients were monitored for pharmacological side effects for the same period of time, regardless to sinus rhythm restoration. AF relapses within the first 24h were considered

Table 1 Baseline Clinical Characteristics.

Clinical Characteristics	Amiodarone	Quinidine	Propafenone	p-value
Male/Female	17/13	17/13	14/16	0.7
Age	63±6	64±8	65±10	0.4
Atrial Diameter	47±7	46±4	45±3	0.2
Ventricular Diameter	56±3	53±6	54±5	0.2
LV-EF	59±2	58±3	58±1	0.3
Serum potassium	4.2±0.2	4.2±0.3	4.3±2	0.3
AF duration in weeks (range)	17(8-72)	21,5(10-100)	14(9-67)	0.9
AF etiology:				
Hypertension	12	13	15	NS
Disthyroidism	0	2	1	NS
VHD	4	2	5	NS
CAD	7	3	1	NS
DCM	3	2	0	NS
Lone AF	4	8	8	NS

LV-EF: left ventricular ejection fraction
AF: atrial fibrillation, CAD: coronary artery disease, DCM: dilatative cardiomiopathy,
VHD: Valvular Heart Disease

as failures in the procedure. Patients resulted in sinus rhythm were prescribed long-term AF prophylaxis according to clinical indications and current guidelines. Quinidine was not used for this purpose

Patients not responding to therapy (including early relapses) were addressed to electrical cardioversion the day following the procedure.

Statistical analysis:

Categorical data are presented as absolute values, whereas continuous data are summarized as mean value±SD. Chi-square and Fisher's exact test were used for comparison of categorical variables as appropriate. Comparison of continuous variables was performed by mean variance analysis (ANOVA) or Kruskar-Wallis test, where appropriate. A multivariate analysis was performed to find associations between drugs' efficacy and studied parameters. Statistical significance was inferred as $p<0.05$. In addition, ROC analysis was used for an exploratory evaluation of eventual cutoff point of AF duration to predict loss of efficacy of pharmacologic cardioversion.

Results

Patient characteristics:

Ninety consecutive patients (48 males, 53%) were enrolled in the trial. Thirty patients were randomly assigned to each group. Table 1 lists the clinical characteristics of each treatment group. Mean duration of the arrhythmia was 26 weeks (range 8 to 72) and mean age was 64±8 years. Echocardiographic parameters were homogeneous among group: mean atrial diameter was 46±5mm and mean ventricular diameter was 54±5mm. Mean left-ventricular ejection fraction was 58%±2. Mean serum potassium level was 4.4±0.4 mEq\L.

Patients' comorbidities are reported in table 1.

Conversion rate:

By the end of the study, 28 patients (31%) were converted in sinus rhythm: 6 patients were treated with amiodarone (20%), 16 patients with quinidine (53%) and 6 patients with propafenone (20%) ($p=0.006$) (Figure 1). Relative risk of cardioversion with quinidine compared to amiodarone or propafenone was 2.67.

Predictors of success:

No significant predictors for sinus rhythm restoration was found. In particular, AUCs of ROC analysis for atrial diameter, ventricular diameter, age and AF duration were constantly between 0.50 and 0.60. Albeit not statistically significant, propafenone group showed a trend toward a loss of efficacy after 3 months of AF. For this group, mean AF duration for cardioverted patients was lower than those with resistant AF (15 vs 27 weeks, $p=0.2$)

Adverse effects:

ECG monitoring showed no statistical differences in QTc duration (Table 2) among the groups. No difference was found before and after the administration within the groups. No adverse effects requiring drug discontinuation occurred, in particular there were no syncope or sustained ventricular tachycardia or torsade de pointe.

Discussion

Study Limitations:

Pharmacological cardioversion of atrial fibrillation is an evolving topic and current opinion tends to consider recent-onset and long-lasting atrial fibrillation as two different entities, separated by

Table 2 Corrected QT before drug administration and after observation period

Antiarrhythmic Drug	Before	After	p-value
Amiodarone	420±30 ms	430±30 ms	0.4
Quinidine	420±30 ms	410±10 ms	0.6
Propafenone	410±10 ms	420±30 ms	0.5

"electrical remodeling" phenomenon. At the time of design of this study, current ACC/AHA/ESC guidelines' revision for management of atrial fibrillation (2006)7 considered this evidence, with different recommendations for rhythm control of recent-onset and long-lasting AF. In this second case, amiodarone had IIa recommendation class while propafenone and quinidine were in class IIb. The reason of such a weak recommendation was that "quinidine is used less frequently than other pharmacological agents, due to the perception that it is less efficacious and has more frequent side effects, although direct comparative studies are lacking".

The present report is the first one directly comparing these three drugs on this particular subset of patients and our population is bigger than previous papers on pharmacological cardioversion of long-lasting AF, even if the size of our study is not comparable to major pharmacological trials.

The main finding in this study is that conversion rate of patients treated with quinidine is more than twice that "conventional" drugs (53% vs. 20% $p<0.01$). There wasn't any statistically significant difference among groups for parameters potentially predicting an increased risk of ADR or failure of cardioversion. In particular, atrial diameters weren't significantly different among groups suggesting that anatomical remodeling (another important factor concurring to stabilize atrial fibrillation when it persists in time) did not influence our analysis, even considering the limitations of this method to estimate the phenomenon.

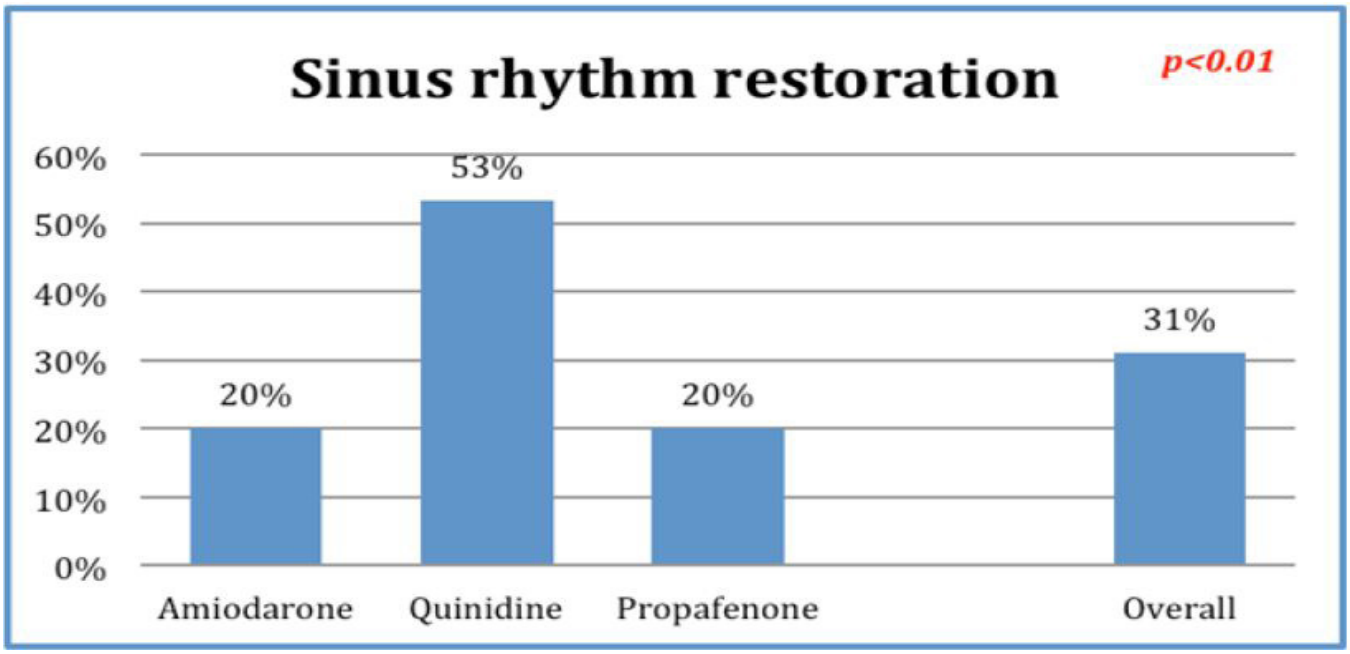
Multivariate in-group analysis did not find any correlation between historical or echocardiographic data and success rate for the procedure, showing that antiarrhythmic drug for pharmacologic cardioversion can probably be chosen considering its efficacy (and contraindications) only. The observation, albeit not statistically significant, of the trend to efficacy loss of propafenone with longer-lasting AF can be interpreted as a further confirmation that this drug should be kept for paroxysmal AF only. About quinidine's side effects, acute oral loading of this molecule did not cause any significant adverse effect in studied patients. In particular, no case of tachyarrhythmia or syncope was recorded, neither any disturbance requiring the suspension of the therapy.

Concerns about quinidine began with the observation of "quinidine syncopes"[8] associated with torsade the pointe and sudden cardiac deaths due to paroxysmal ventricular fibrillation. First described in 1848 by Van Heymingen and named by Pasteur in 1853, quinidine (class IA) has a long history as an antiarrhythmic. It has been used for decades for maintenance of sinus rhythm after cardioversion with an efficacy comparable to flecainide, but it has been progressively abandoned after the discovering of its proarrhythmic effect causing torsade de pointes and ventricular fibrillation, even if evidence is controversia.[19] In 1990s several meta analyses posed severe doubts about safety of quinidine in chronic usage10,11, showing an increased risk of death if compared to other antiarrhythmics and placebo, leading to progressive discontinuation of this drug. Several recent trials[12,13] and meta-analyses (including one from Cochrane collaboration14) noticed that fixed association of low dose quinidine and verapamil wasn't inferior to sotalol in term of safety and efficacy, even if the second one is widely used for long-term sinus rhythm maintenance.

Concerning acute loading of quinidine for pharmacological cardioversion, there is no report in literature of a higher risk for patients than other antiarrhythmic drugs. Moreover, a recent retrospective analysis proved quinidine's efficacy and safety on a large group of 501 patients with recent-onset atrial fibrillation.[15] Also in this case, no life-threatening ADR associated with this kind of administration was reported and diarrhea was the only frequent side effect (13% of patients). In addition, quinidine is being studied for prevention of sudden death in Brugada syndrome[16] as well as short QT syndrome[17] and idiopathic ventricular fibrillation.[18]

There were two previous studies in literature comparing quinidine and amiodarone.[19,20] Both showed similar conversion rates between drugs, but quinidine dose was not adequate and the studied populations were very small (40 and 30 patients respectively). Di Benedetto and colleagues compared propafenone with quinidine[21] finding a clear superiority of the second one (24% vs. 84%)

Figure 1: Efficacy comparison among the studied drugs



but patients enrolled had atrial fibrillation lasting no longer than six months. In another study,[22] quinidine was compared to another IC drug (flecainide) in a population with a wide variability in duration of the arrhythmia. This last work did not find any significant difference within the two drugs but quinidine seems to have a higher conversion rate in the subset of patients with atrial fibrillation lasting more than 10 days.

During the writing of this paper a new revision of ESC guidelines for management of atrial fibrillation was released1. In this new edition, pharmacological cardioversion is considered for recent-onset cases only, while for the others DC shock is kept as the only recommended way to restore sinus rhythm. In our opinion, aside from patient's major comfort, there are several situations (e.g. general medicine or geriatric departments, rehabilitation clinics, small structures etc.) where a monitored pharmacological approach can be a preferable solution, especially if drugs can be administered orally. Also, the absence of electrical shock avoids every risk of discomfort and device damage in paced patients. In conclusion, quinidine proved to be safe and effective for pharmacological cardioversion of atrial fibrillation and can be considered a first-line drug for this purpose.

Limitations

Although at present this is the first study directly comparing these 3 drugs for long-lasting AF, larger sample size studies are warranted in order to confirm the present data. Moreover, present study was addressed to assess quinidine's efficacy in hospital setting, which is usually limited to few hours of observation after drug administration, so mid and long term follow-up was not considered in this report. Ultimately, the unavoidable switch from quinidine to another drug for recurrences prophylaxis could be a source of misinterpretation for follow-up data.

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