

Pretreatment with intravenous amiodarone improves the efficacy of ibutilide treatment on cardioversion rate and maintenance time of sinus rhythm in patients with persistent atrial fibrillation

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Abstract. The aim of the present study was to assess the efficacy and safety of the pharmacological conversion of persistent atrial fibrillation (AF) using amiodarone or/and ibutilide. Seventy-nine consecutive patients (48 males and 31 females; mean age, 64.6 ± 11.2 years; range, 40-80 years) with non-valvular chronic AF lasting >7 days (range, 7-97 days) that were admitted to hospital for elective pharmacological cardioversion were randomly assigned to receive treatment with intravenous ibutilide (1 mg plus an additional 1 mg if required; $n=39$) or intravenous amiodarone (300 mg) plus intravenous ibutilide (1 mg; $n=40$). Success rates of cardioversion were 51.3% (20/39 patients) for ibutilide alone and 71.8% (28/39 patients) for amiodarone + ibutilide ($P<0.05$). A comparable increase in the QTc interval was observed in the two groups. It was observed that the co-administration of amiodarone and ibutilide was safer than ibutilide alone with regard to the risk of ventricular arrhythmia. Forty-eight patients of successful cardioversion were personally contacted for follow-up. The result indicated that the sinus rhythm maintenance time of the amiodarone + ibutilide group (4.36 ± 2.44 months) was significantly higher than that of the ibutilide group (2.34 ± 1.75 months; $P<0.01$). In conclusion, pretreatment with intravenous amiodarone + ibutilide for pharmacological cardioversion of persistent AF is considered to be more effective and safer than treatment with ibutilide alone.

Introduction

Atrial fibrillation (AF) is a highly prevalent disease encountered in clinical practice, which results in cardiovascular morbidity and mortality (1), and is difficult to treat (2). AF patients are treated using certain therapeutic strategies, such as electrical cardioversion, tissue ablation and pharmacological therapy. However, electrical cardioversion and tissue ablation require anesthesia, which may be associated with periprocedural complications. Pharmacological therapy is considered to be the most important treatment of AF, particularly in elderly populations. However, currently available pharmacological therapeutic modalities for terminating AF or maintaining sinus rhythm are only moderately effective. Furthermore, these drugs may induce ventricular pro-arrhythmia (3). Therefore, the development of effective and safe therapeutic strategies to treat AF is important. An improved understanding of the anti-arrhythmic mechanisms of the effective drugs may facilitate the improvement of therapeutic strategies. Drugs are conventionally grouped according to their anti-arrhythmic mechanism of action, such as: i) Na^+ channel blockade, ii) β -adrenoceptor antagonism, iii) action potential prolonging, and iv) Ca^{2+} channel blockade. Certain drugs have various classes that act to inhibit AF, such as amiodarone, a class III drug, has multiple actions for blocking numerous ion currents (I_{Na} , $I_{\text{Na/Ca}}$, I_{CaL} , I_{CaT} , I_{to} , I_{Kur} , I_{Kr} , I_{KS} , I_{K1} and I_{KACh}) and adrenergic/cholinergic receptors. The current therapeutic strategies for the management of AF recommend the administration of specified drugs for rate control depending on the patient's state (4). Amiodarone is recommended for treating recent onset or persistent AF and preventing AF recurrence. When other methods are unsuccessful for rate control, amiodarone is an alternative approach. However, amiodarone has serious side effects, and may adversely affect numerous organs and tissues (5,6). The other class III drug, ibutilide, is recommended for treatment of AF or atrial flutter, although there is a risk of ventricular pro-arrhythmia, most likely due to inhibition of I_{Kr} , which induced QT prolongation (4). Amiodarone and ibutilide are two of the most effective class III antiarrhythmic drugs for cardioversion of acute onset AF; however, their efficacy in persistent AF of long duration is limited (7-9).

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Thus, the aim of the current study was to investigate whether the combination of amiodarone and ibutilide with different treatment processes improves the treatment success rates in persistent AF. In the present study, the efficacy and safety of treatment with amiodarone plus ibutilide, vs. ibutilide alone, on cardioversion of persistent AF and maintenance time of sinus rhythm was compared.

Materials and methods

Patients. The study recruited 79 patients (48 males and 31 females; mean age, 64.6 ± 11.2 years; range, 40–80 years) with non-valvular chronic AF lasting >7 days (range, 7–97 days) who had been referred to The First Affiliated Hospital of Harbin Medical University (Harbin, China) for cardioversion of persistent AF between June 2013 and April 2014. Exclusion criteria for the study were as follows: Patients with i) acute coronary syndrome; ii) severe structural heart disease; iii) ventricular arrhythmia; iv) ventricular rate <50 times per min; v) left ventricular ejection fraction (LVEF) <35%. Written informed consent was obtained from all patients for the present study, which involved internal atrial defibrillation, electrophysiology studies, and intravenous administration of amiodarone and/or ibutilide. The study was approved by the Clinical Research Committee of The First Affiliated Hospital of Harbin Medical University.

Study protocol. Treatment with antiarrhythmic drugs (excluding *Digitalis*, β -blockers and calcium channel antagonists) was discontinued at least 5 half-lives prior to the study. Patients that had already been treated with amiodarone were not included in the current study. A placebo was administered to 39 patients, and amiodarone (Sanofi Winthrop Industrie, Floirac, France) was administered intravenously (dose, 300 mg) to 40 patients, then 30 min later ibutilide (Feng Yuan Pharmaceutical Co., Ltd., Maanshan, China) was administered (dose, 1 mg) to all patients, resulting in an ibutilide treatment group (ibutilide alone; $n=39$) and an amiodarone + ibutilide co-treatment group (amiodarone + ibutilide; $n=40$). The administered quantities were based on typical clinical doses.

Electrocardiography recordings were obtained prior to administration of the drugs and subsequently at 30, 60, 75, 95, 105 and 120 min. The electrocardiography (ECG) recording speed was 25 mm/sec and the voltage was 1 mV/cm. Noise was minimized using a digital filter. Analyses of the ECG waves were performed to calculate heart rate (HR; bpm), QRS duration (msec), QT interval (msec) and PR interval (msec). Corrected QT for HR was established using Bazett's formula: $[QTc = QT / (\text{square root of RR interval})]$. For each data point, measurements were obtained at three non-consecutive, randomly selected points in every 5-min recording. The results are presented as the mean of three randomly selected segments.

Follow-up. At baseline and at the follow-up visits, patients underwent physical examination, transthoracic echocardiography, resting electrocardiogram, blood pressure measurement, and assessment of quality of life and symptoms. For those who were not followed up at The First Affiliated Hospital of Harbin Medical University, attempts were made to contact the patients or their relatives. In addition, hospital records were reviewed

and all cardiac events were confirmed by a review of hospital records.

Statistical analysis. Values are expressed as means \pm standard deviation. The clinical characteristics of the patients were analyzed using the Mann-Whitney U test. Differences between pre- and post-treatment HR, effective refractory period and QTc within each group were analyzed using the Wilcoxon signed-rank test. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS 13.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics of the patients. The current study included 79 patients (48 males and 31 females), which were divided into two groups, the ibutilide treatment group (ibutilide alone; $n=39$) and the amiodarone + ibutilide co-treatment group (amiodarone + ibutilide; $n=40$). No significant differences were identified between the two groups with regard to clinical characteristics and basic diseases (Table I).

Cardioversion rate. A total of 48 patients were successfully converted to sinus rhythm, there were 20 patients from the control group (ibutilide treatment alone; rate of cardioversion, 51.3%) and 28 from the study group (co-treatment of amiodarone + ibutilide; rate of cardioversion, 71.8%). A significant difference in the number of patients successfully converted to SR was identified between the two groups ($P < 0.05$; Fig. 1A). There were 10, 9 and 1 patients successfully converted to sinus rhythm in 75, 95 and 120 min, respectively, in the ibutilide treatment group. There were 4, 8, 8, 4 and 4 patients successfully converted to sinus rhythm in 60, 75, 95, 105 and 120 min, respectively in the amiodarone and ibutilide co-treatment group (Fig. 1B). The timing of conversion to sinus rhythm in the two groups displayed two distinct peaks at 75 and 95 min after the onset of drug administration (Fig. 1B). Furthermore, no significant differences in demographic and clinical characteristics were identified between the patients who successfully converted to sinus rhythm and those who continued to exhibit AF.

QTc interval prolongation. The QTc interval was significantly prolonged in the two groups, from 440.7 ± 38.1 to 520.6 ± 69.3 msec ($P < 0.05$) in the ibutilide group and from 447.7 ± 39.4 to 484.8 ± 61.4 msec ($P < 0.05$) in the amiodarone + ibutilide group. As shown in Fig. 2, although the QTc interval of the two groups was prolonged following the application of the drug, the extent of the prolongation was similar, and the QTc of each group demonstrated no significant difference between the time points that were close together. Furthermore, the QTc interval of the amiodarone + ibutilide co-treatment group was identified to be shorter than the QTc of the ibutilide alone group at 120 min ($P < 0.05$).

Complications and safety profile. There were no patients exhibiting frequent premature ventricular contractions, non-sustained ventricular tachycardia, sustained ventricular tachycardia or ventricular fibrillation in the

Table I. Baseline characteristics of the two groups.

Variable	Ibutilide (n=39)	Amiodarone + ibutilide (n=40)	P-value
Age (years)	65.64±8.59	61.73±12.34	0.147
Male/female	22/17	26/14	0.558
Atrial fibrillation duration (days)	26.31±24.38	29.97±28.67	0.641
Coronary artery disease (%)	51.31	47.11	0.861
Hypertension (%)	56.41	61.12	1.002
Diabetes (%)	5.11	6.24	0.580
Heart failure (%)	29.71	28.35	1.030
Potassium ion (mM)	4.52±0.37	4.43±0.31	0.993
Magnesium ion (mM)	0.81±0.09	0.91±0.11	0.755
Left atrial size (mm)	40.86±4.12	40.97±4.24	0.963
LV end-diastolic dimension (mm)	50.23±6.31	51.17±7.31	0.981
LV ejection fraction (%)	57.34±9.73	56.66±9.19	0.187

Values are expressed as means ± standard deviation. LV, left ventricular.

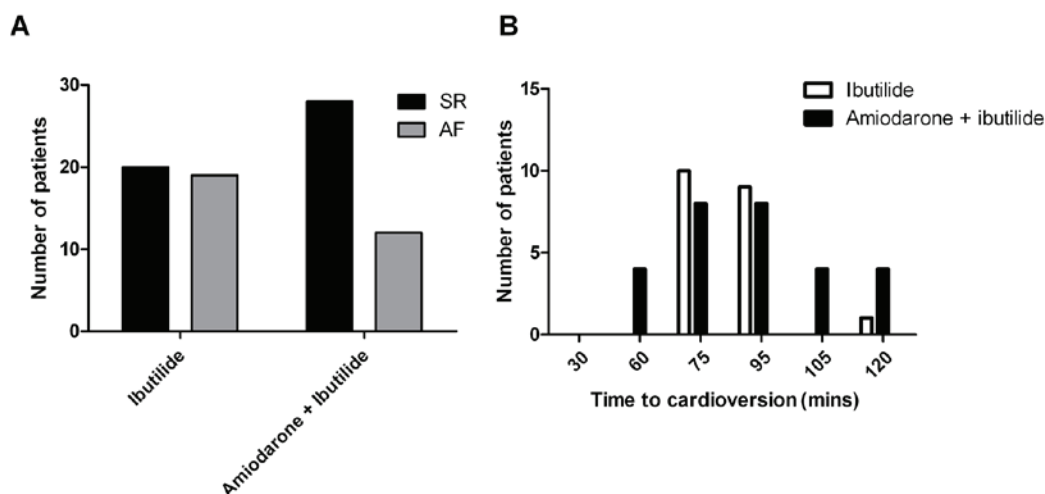


Figure 1. Effects of intravenous administration of ibutilide alone or amiodarone + ibutilide on cardioversion in patients with persistent AF. (A) Number of patients successfully converted to SR. (B) Timing of conversion to SR (expressed in time after initiation of drug administration) in patients that received treatment with ibutilide or amiodarone + ibutilide. AF, atrial fibrillation; SR, sinus rhythm.

amiodarone + ibutilide co-treatment group. There were 13 patients exhibiting frequent premature ventricular contractions, 7 patients with non-sustained ventricular tachycardia and 3 patients with sustained ventricular tachycardia and ventricular fibrillation (the 3 patients underwent emergency electrical defibrillation therapy for conversion of sinus rhythm) in the ibutilide alone group. It was observed that the co-administration of amiodarone + ibutilide was safer than the ibutilide alone with regard to the risk of ventricular arrhythmia. In addition, 9 patients exhibited sinus bradycardia in the amiodarone + ibutilide group and 5 patients exhibiting sinus bradycardia in the ibutilide group.

Long-term outcome. The patients of successful cardioversion were personally contacted for an updated follow-up. After a median follow-up period of 19.84±8.50 months, the result demonstrated that the mean sinus rhythm maintenance time

of the amiodarone + ibutilide group was 4.36±2.44 months. Furthermore, the mean sinus rhythm maintenance time of the ibutilide group was 2.34±1.75 months. The mean sinus rhythm maintenance time of the amiodarone + ibutilide group was significantly higher than that of the ibutilide group ($P<0.01$).

Discussion

For the refractory treatment of AF, AF patients are managed with electrical vs. chemical cardioversion. At present, the majority of patients with persistent AF of long duration are treated with electrical direct current cardioversion, which is associated with high success rates and reduced monitoring times. However, electrical conversion requires general anesthesia and may be associated with periprocedural complications. Thus, the development of effective and safe therapeutic strategies to treat AF is important (10,11). In the

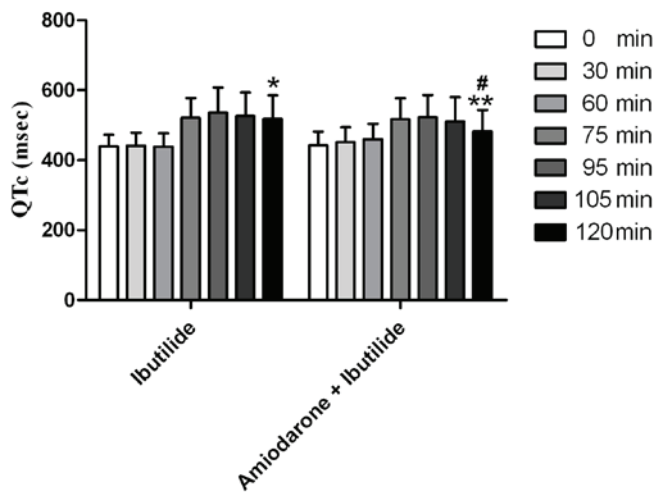


Figure 2. Effects of treatment with intravenous ibutilide or amiodarone + ibutilide on QTc interval prolongation. Timing of QTc in patients who received ibutilide or amiodarone + ibutilide. Data are presented as means \pm standard deviation. * $P < 0.05$ vs. ibutilide 0 min; ** $P < 0.05$ vs. amiodarone + ibutilide 0 min; # $P < 0.05$ vs. ibutilide 120 min group.

current study, the pharmacological effects of a combination of amiodarone and ibutilide on cardioversion of persistent AF were determined.

Ibutilide is administered for the acute cardioversion of AF and atrial flutter. It is used as a first-line drug in the treatment of recent-onset AF and atrial flutter. In rapid onset (3–48 h), the cardioversion rate of atrial flutter with ibutilide was 87%, and the cardioversion rate of AF with ibutilide was 77% (12). However, the efficacy of treatment of ibutilide in the cardioversion of persistent AF is not as effective as the curative effect for acute AF. A previous study indicated that the conversion rate of persistent AF (duration, >30 days) with ibutilide was 48% (13). Furthermore, ibutilide may induce QT interval prolongation and increase the risk of torsade de pointes, as a result of prolonging the action potential duration (APD) by increasing the slow inward sodium current and blocking the delayed rectifier potassium current (14–16). Amiodarone has a complex electrophysiological characteristic (12,17). With long-term administration, amiodarone markedly prolongs the ventricular action potential and the QT interval (13); however, the incidence of torsade de pointes is low (18,19). Long-term amiodarone therapy is commonly used for the maintenance of sinus rhythm for patients with recent-onset AF. Thus, the conventional antiarrhythmic drugs, used for persistent AF of long duration, have shown limited efficacy. In the current study, the electrophysiological effects of amiodarone and ibutilide on the atrium in patients with persistent AF were evaluated. A total of 48 patients were successfully converted to sinus rhythm; with 20 patients from the ibutilide treatment group (rate of cardioversion, 51.3%), and 28 patients from the ibutilide and amiodarone co-treatment group (rate of cardioversion, 71.8%). The rate of cardioversion was significantly different between the two groups ($P < 0.05$; Fig. 1).

The most serious proarrhythmic side effect of class III agents is torsade de pointes. Class IA and class III antiarrhythmic agents induced prolongation of APD and the QTc interval, which are associated with an increased risk of

torsade de pointes. As shown in Fig. 2, the QTc interval was significantly prolonged in the two groups, from 440.7 ± 38.1 to 520.6 ± 69.3 msec ($P < 0.05$) in the ibutilide treatment group and from 447.7 ± 39.4 to 484.8 ± 61.4 msec ($P < 0.05$) in the amiodarone + ibutilide co-treatment group. However, the QTc interval of the co-treatment group was identified to be shorter than the QTc of the ibutilide group at 120 min. In the current study, there were 13 patients with frequent premature ventricular contractions, 7 patients with non-sustained ventricular tachycardia, and 3 patients with sustained ventricular tachycardia and ventricular fibrillation in the ibutilide treatment group. The incidence of sustained torsade de pointes was 10.1% (3/31 patients). This result was relatively consistent with previous ibutilide studies. In a study of 180 patients who received ibutilide treatment for cardioversion, the incidence of torsade de pointes was reported to be up to 8.3% (20). There were no patients with frequent premature ventricular contractions, non-sustained ventricular tachycardia, or sustained ventricular tachycardia and ventricular fibrillation in the amiodarone + ibutilide co-treatment group in the present study. The low incidence of ventricular fibrillation with amiodarone + ibutilide therapy may be multifactorial. Previous studies indicate that the dispersion of repolarization was a critical factor in the maintenance of torsade de pointes (13,18). The ventricular myocardium normally displays heterogeneity of refractoriness, with the M (or middle) cells displaying the longest APD of the ventricular subtypes. Amiodarone prolongs the APD of all ventricular cell subtype; however, it does not prolong the M-cell APD. Thus, amiodarone may reduce the transmural dispersion of repolarization (7,8). This may, in part, explain why co-treatment with amiodarone + ibutilide is safer than treatment with ibutilide alone in the risk of ventricular arrhythmia.

In conclusion co-treatment with amiodarone and ibutilide for AF therapy was evaluated in detail during the present study. A significantly increased efficacy and safety of combination therapy was observed when compared with treatment of ibutilide alone. Therefore, combination pharmacological therapy with amiodarone + ibutilide may present as a useful adjunct to current cardioversion protocols for AF, particularly in cases of persistent AF.

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