

Ibutilide is efficacy but not safe in cardioversion of atrial fibrillation for patients aged over 75 years

Chunxia Huang (✉ qiqigelibo@163.com)

Southern Medical University <https://orcid.org/0000-0003-4822-1358>

ZhiMin Zhang

Shanxi Medical University

Bin Li

Shanxi Medical University

YunTian Li

Southern Medical University

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Abstract

Background: Atrial fibrillation (AF) is the common arrhythmia resulting in high morbidity and mortality. Ibutilide is used to convert AF to sinus rhythm pharmacologically. We aimed to evaluate the clinical efficacy and safety of ibutilide for patients over 75 years old with recent onset AF.

Methods: 81 patients over 75 years old with recent onset AF less than 72 hours, range from 75 to 85 years, were analyzed retrospectively from January 2015 to January 2019. 40 patients received ibutilide, and another 41 patients received propafenone as the control group. In ibutilide group, patients weighing over 60 kg were received 1 mg of ibutilide, and ibutilide at 0.01 mg / kg were administered when the patient's body weight was less than 60 kg. If cardioversion failed, 1 mg or 0.01 mg/kg of ibutilide would be given after 10 minutes. In control group, patients were received propafenone at 75mg. If there was no effect on cardioversion, 35 mg of propafenone would be given after 10 minutes.

Results: In control group 26 patients (63.4%) converted to sinus rhythm, and in ibutilide group, 35(87.5%) converted to sinus rhythm ($p < 0.05$, vs control group). The converting time of ibutilide group was shorter than control group ($13.5 \pm 9.27s$ vs $43.72 \pm 10.27s$, $P < 0.05$). The corrected QT (QTc) intervals was significantly prolonged in patients after the administration of ibutilide ($P < 0.05$). In ibutilide group, five patients (12.5%) appeared torsades de pointes (TdP) and converted to sinus rhythm via electrical cardioversion. Six patients (14.6%) developed severe bradycardia in control group, and the bradycardia alleviated after discontinuation of propafenone. Nine patients (21.9%) who failed in cardioversion with 24 hours by propafenone converted to sinus rhythm via electrical cardioversion.

Conclusion: Ibutilide could effectively convert recent onset (<72 hours) AF in patients aged over 75 years. However, it was worth noting that the high rate of TdP emerged in these elderly patients after the treatment of ibutilide.

Background

Atrial fibrillation (AF) is the common arrhythmia in elderly patients resulting in high cardiovascular morbidity and mortality. Patients with AF at advanced age over 75 years have high adverse events rates and a poor prognosis compared with those aged from 65 to 74 years [1]. The mortality of patients aged over 75 years with AF reached 18.2% [2]. Therefore, sinus rhythm is essential for these elderly patients with AF.

Ibutilide, a class III intravenous antiarrhythmic drug, is used to convert recent onset AF. However, ibutilide increases the high risk of TdP via prolonging of the QTc interval especially for the elderly patients. Due to aging, these patients present significant cardiac structural and electrical remodeling which causes different reaction to drug therapy [3]. In China, the low cost of ibutilide resulted in increasing use in cardioversion of AF in elderly patients, and the security and efficacy is still challenging in these cases [4]. Herein, data from January 2015 to January 2019, we reviewed the pharmacological cardioversion

treatments of 81 patients with new onset AF over the age of 75 and provided clinical proof for drug cardioconversion in elderly patients.

2. Methods

81 patients over 75 years old with recent onset AF less than 72 hours, range from 75 to 85 years, were analyzed retrospectively from January 2015 to January 2019 (table 1). The attending physician made the choice of therapy for each patient.

Drug dosing

40 patients received ibutilide, and another 41 patients received propafenone as the control group. In ibutilide group, patients weighing over 60 kg were received 1 mg of ibutilide, and ibutilide at 0.01 mg / kg were administrated when the patient's body weight was less than 60 kg. If cardioversion failed, 1 mg or 0.01 mg/kg of ibutilide would be given after 10 minutes. In control group, patients were received propafenone at 75mg. If there was no effect on cardioversion, 35 mg of propafenone would be given after 10 minutes. All patients were injected low molecular weight heparin subcutaneously at the same time to prevent left atrial thrombosis.

Contraindications of ibutilide treatment

The contraindications of ibutilide therapy were as follows: severe hypertension (systolic blood pressure \geq 180mmHg or diastolic blood pressure \geq 110mmHg); unstable angina pectoris; acute myocardial infarction; sick sinus node syndrome without pacemaker implantation; atrial ventricle block; TdP history; heart failure; thromboembolism.

Statistical analysis

Data are presented as the mean \pm standard deviation. Data analyses were performed by SPSS 23.0 (IBM Inc., Armonk, NY, U.S.A.). The Student *t* test was used to evaluating differences between two groups. The χ^2 test was used to compare categorical data. The value $P < 0.05$ was statistically significant.

Results

Ibutilide group

In ibutilide group, 35(87.5%) converted to sinus rhythm. The converting time of ibutilide group was 13.5 ± 9.27 s. The QTc interval was 352 ± 34 ms before administration of ibutilide. The average QTc intervals of 30min, 1h, 2h, and 4h after conversion were 453 ± 44 ms, 468 ± 34 ms, 471 ± 27 ms, and 473 ± 34 ms, and significantly prolonged ($P < 0.05$, table2). 5 patients (12.5%) appeared TdP and converted to sinus rhythm via electrical cardioversion. (table 3).

Control group

In control group 26 patients (63.4%) converted to sinus rhythm. 9 patients (21.9%) who failed in cardioversion with 24 hours converted to sinus rhythm via electrical cardioversion. The converting time of propafenone group was 43.72 ± 10.27 s. The QTc interval was 367 ± 14 ms before administration of propafenone. The average QTc intervals of 30min, 1h, 2h, and 4h after conversion were 387 ± 30 ms, 390 ± 18 ms, 390 ± 29 ms, and 405 ± 12 ms and didn't prolonged significantly ($P > 0.05$, table2). Six patients (14.6%) developed severe bradycardia(heart rate < 45 beats/min), and the bradycardia alleviated after discontinuation of propafenone(table3).

Discussion

There were 1.8% and 4.9 per 1,000 person-years prevalent and incident in AF for the elderly in China and the awareness of AF was low, management with poor, under-use of proven therapy [5]. The major causes of cardiovascular mortality was AF relevant with embolic stroke [6, 7]. Sinus rhythm is essential for AF patients at advanced age over 75 years in reducing cardiovascular morbidity and mortality. Paroxysmal and new onset AF can be converted to sinus rhythm pharmaceutically. AF patients with onset less than 48 hours are candidates for cardioversion without preceding anticoagulation, and pharmacological cardioversion is important and feasible[8].

Ibutilide, a class III antiarrhythmic drug, has minimal effects on hemodynamic and conduction in normal cardiac tissue. As an cardioconversion drug, ibutilide were used to convert recent-onset (< 48 hours) AF to sinus rhythm. Ibutilide is equivalent to procainamide in the cardioversion of new onset AF at 90 minutes (40% vs 46%) and better than intravenous amiodarone (40% vs 18%)[9]. In our study ibutilide was also effective in cardioversion of new AF lasting for 72 hours, and was superior to propafenone treatment. The converting time of ibutilide group was shorter than propafenone group.

Ibutilide causes the effective refractory period lengthened in the atrium and the ventricle[10, 11]. Ibutilide could prolong the QTc interval in patients with AF or Atrial flutter(AFL) due to high plasma concentrations[12]. The duration of the repolarized ventricles is reflected by QTc interval, and the activity of class III antiarrhythmic is indicated by QTc prolongation[13, 14]. However, administration of ibutilide causes prolongation of the (QTc) interval and high risk for ventricular tachycardia TdP [15]. Advancing age is a common risk factors for drug-induced TdP[16]. In this study, the average QTc intervals prolonged since 30 min and duration till 4 hours after the treatment of ibutilide. Prolonged QTc increased risk in the occurrence of TdP in these advanced age patients. Five patients appeared TdP, and electrical cardioversion is essential to terminated TdP.

Conclusions

As for patients over 75 years of age, the prevalence in AF continues to rise which presents challenge to clinicians' treatment and society economic burden. Pharmacological cardioversion is more economical than catheter radiofrequency ablation and is more feasible for low-income populations in China. Our results demonstrated that 87.7% recent onset (within 72 hours) AF elderly patients could convert to

normal heart rhythm after administration of ibutilide in cardioversion. However, in some of these patients, ibutilide prolonged QTc significantly which resulted in the emergence of TdP arrhythmia. Ibutilide appeared not safe as a cardioversion drug for AF patients over 75 years.

Although this study was a retrospective research, we provide a clinical evidence of pharmacological cardioversion in patients over 75 year- old.

Abbreviations

AF: Atrial fibrillation; QTc: Corrected QT; TdP: Torsades de pointes; AFL: Atrial flutter. LAD: Left atrial maximal diameter; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; NA: not applicable.

Declarations

Ethics approval and consent to participate

This study was performed in compliance with the Declaration of Helsinki, and was approved by the institutional ethical review board of Linfen hospital, Shanxi Medical University (No. 20150930002). Written informed consents were obtained from all patients before the procedure.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors contribution

Chunxia Huang and YunTian Li conceived the study; ZhiminZhang and BinLi collected and analyzed the data. All authors have reviewed the article and made substantial revisions to improve the scientific credibility of the content. All authors approved the final version to be published.

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Author details

¹The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, 510515, China. ²Linfen Peoples' Hospital, Shanxi Medical University, Linfen, Shanxi, 041000, China. ³Department of Cardiology, 305 Hospital of People's Liberation Army, Beijing, 100017, China.

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Tables

Table 1 Clinical features of two groups

Clinical characteristics	Ibutilide n=40	Propafenone n=41	P value
Mean age, yr	72.4±11.3	75.6±8.1	0.54
Range	(72-85)	(75-85)	
Height, cm	167.1±5.9	169.7±7.3	0.15
Range	(162-174)	(160-175)	
Weight, kg	64.2±10.5	66.2±11.2	0.38
Range	(60-83)	(61-76)	
Male patients	19	23	0.43
Female patients	21	18	0.30
Last episode duration (h)	38.7 ±16.3	35.2 ±19.0	0.31
Episodes/year (n)	1.5 ±2.4	1.7 ±1.6	0.39
LAD (mm)	37 ±4.7	39 ±1.2	0.39
LVEF (%)	55.9 ±5.1	56.3 ±3.8	0.78
LVEDD (mm)	52.6 ±2.9	54 ±1.1	0.45

Abbreviations: LAD = left atrial maximal diameter, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter.

Table 2 Parameters in electrocardiographic of two groups

Ibutilide (n=40)	Propafenone (n=41)	P value
Heart rate	135.2 ± 13.6	127.9 ± 12.5 0.06
QRS duration (ms)	87.2 ± 16.9	89.5 ± 13.7 0.73
QTc before administration(ms)	352 ± 34	367 ± 14 0.54
QTc at 30min after administration(ms)	453 ± 44*	387 ± 30 0.03
QTc at 1h after administration(ms)	468 ± 34*	390 ± 18* 0.03
QTc at 2h after administration(ms)	471 ± 27*	390 ± 29* 0.04

Abbreviations: NA not applicable. *P value <0.05 vs QTc before administration(ms)

Table3 Cardioversion outcomes of two groups

Ibutilide (n=40)	Propafenone (n=41)	P value	
converting time(second)	13.5±9.27	43.72±10.27	0.03
Conversion rate to sinus rhythm(n, %)	35(87.5%)	26 (63.4%)	0.04
TdP occurrence (n, %)	5(12.5%)	NA	NA
Bradycardia (n, %)	NA	6(14.6%)	NA
Electrical cardioversion(n, %)	5(12.5%)	9(21.9%)	NA

Abbreviations: NA not applicable.