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Conversion efficacy of intravenous ibutilide compared with intravenous amiodarone in patients with recent-onset atrial fibrillation and atrial flutter

Nikolaos V. Kafkas *, Sotirios P. Patsilinakos, George A. Mertzanos, Kostas I. Papageorgiou, John I. Chaveles, Ourania K. Dagadaki, Kostas M. Kelesidis

Cardiology Department of General Hospital Att. KAT, Greece

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Abstract

Aim: The aim of our study was to compare the efficacy and safety of ibutilide and amiodarone (intravenously) in converting recent-onset atrial fibrillation (AF) and atrial flutter (Af) to sinus rhythm (SR).
Methods: The study was prospective, randomized and included 152 (103 men and 49 women) consecutive patients with AF or Af of 3–48 h duration. Ibutilide is a selective class III antiarrhythmic agent which when administered intravenously can terminate AF and Af. Amiodarone is also a class III antiarrhythmic agent that when given intravenously or orally has proved to be more effective than other agents in terminating AF and Af [B.N. Singh, F.V. Mody, B. Lopez, J.S. Sarma. Antiarrhythmic agents for atrial fibrillation: focus on prolonging atrial repolarization. Am J Cardiol 1999 Nov 4; 84: 161R–173R.]. Seventy-nine patients (56 with AF and 23 with Af) that consisted group A were treated with ibutilide. Seventy-three (52 with AF and 21 with Af) consisted group B and were treated with intravenous infusion of amiodarone.
Results: The conversion rate of group A (ibutilide) was significantly higher than the conversion rate of group B (amiodarone) (80% vs. 57%, $p=0.0054$). As regards the kind of arrhythmia separately, for AF there wasn't significant difference (77% vs. 69%, $p=$ns) whereas for Af ibutilide was superior to amiodarone (87% vs. 29%, $p=0.003$). The conversion rates of ibutilide didn't differ for AF and Af (77% vs. 87%, $p=$ns).
Conclusions: Ibutilide is more effective than amiodarone in converting recent-onset Af to SR whereas both drugs are equally effective in converting recent-onset AF to SR.

Keywords: Atrial fibrillation-flutter; Conversion; Ibutilide; Amiodarone

1. Introduction

Atrial fibrillation (AF) and atrial flutter (Af) are the most common arrhythmias. Their prevalence is about 0.4% for AF and 0.1% for Af and can reach the value of 4% for patients who are older than 60 years [1,2].

The basic electrophysiological mechanism of these arrhythmias is reentry. AF is generally caused by multiple wavelets of reentry [3] and Af by a long reentrant circuit confined in the right atrium [4]. Main cardiac factors for the induction and maintenance of AF are the short and irregularly dispersed atrial refractory period (AFP) and the prolongation of the inta-atrial conduction. According to Allesie's theory [5], the main factor for the induction of AF is the shortening of the wavelength, which is the product of the intra-atrial conduction velocity with the refractory period. Following this rule class III antiarrhytmic agents, that prolong the duration of action potential and of the refractory period without influencing the conduction velocity, can restore sinus rhythm (SR) in patients with AF and Af. Ibutilide is a selective class III antiarrhythmic agent which when administered intravenously can terminate AF and Af. Several clinical trials have

* Corresponding author. 18, Mar. Antipa, Iraklio Att., Athens, 141 21, Greece. Tel.: +30 6944371090.
E-mail address: kafkasncard@yahoo.gr (N.V. Kafkas).

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shown that ibutilide terminates atrial arrhythmias by prolonging the duration of the action potential and the effective refractory period of atrial and ventricular myocardium [6,7]. Ibutilide is available only for intravenous use, since its bioavailability if orally administered is low due to the extensive hepatic metabolism. Previous studies have already proved that this agent is significantly more effective than placebo in converting AF and Af to SR [8–10]. Amiodarone is also a class III antiarrhythmic agent which when given intravenously or orally has proved to be more effective than other agents in terminating AF and Af [11].

The aim of this study was to compare the efficacy and safety of ibutilide and amiodarone in converting AF and Af to SR.

2. Methods

2.1. Patient's population

The study was prospective, randomized and included 152 consecutive patients with AF or Af of 3–48 h duration. The randomization was single-blinded. In each consecutive patient either ibutilide or amiodarone was administered according to a previously determined random sequence.

For detecting the time of onset of AF or Af, the testimony of the patients (if it was judged to be reliable) about their symptoms (palpitation, dyspnea or chest discomfort) was used. Subsects who were not able to determine the time of onset of the arrhythmia or did not feel any symptom were not included in the study. Seventeen of the 152 patients were already hospitalized in the cardiology department for other than AF or Af cause and were monitored by telemetry when the arrhythmia started.

The exclusion criteria were age <18 years old, systolic blood pressure <90 mm Hg, diastolic blood pressure >105 mm Hg, serum K^+ <4 mEg/L, ventricular rate <60 beats/min and QTc >450 ms. Patients with thyroid or liver dysfunction, lung fibrosis, unstable angina, recent myocardial infarction, history of torsades des pointes or patients that were already in drugs that could potentially prolong QT were excluded from the study.

Our hospital's ethical committee has approved the protocol of the study. The study was performed in accordance with Helsinki declaration and all patients have signed an informed consent.

2.2. Antiarrhythmic drugs

Seventy-nine patients (56 with AF and 23 with Af) that consisted group A, were treated with ibutilide. Ibutilide was administered intravenously at a dose of 1 mg in 10 min, which was repeated after an interval of another 10 min if termination of the arrhythmia hadn't been achieved with the first dose.

The other 73 patients (52 with AF and 21 with Af) consisted group B and were treated with intravenous infusion of amiodarone. The dosage was 5 mg/kg of body weight for the first 30 min followed by 1200 mg in the next 24 h.

Some patients were already taking other antiarrythmic drugs before randomization, such as digitalis (5 in group A and 3 in group B), propafenone (5 in group A and 6 in group B), diltiazem (8 in group A and 13 in group B) and verapamil (11 in group A and 8 in group B). There was no statistic difference between the two groups concerning these drugs.

2.3. Follow up

The drugs were considered effective if conversion to SR was achieved during the administration and up to 4 h after the cessation of the drug. The patients were under rhythm monitoring throughout the whole procedure and for 4 more hours after conversion to SR. Twelve −lead ECG was performed before, immediately after conversion to SR and every hour for the next 4 h. Blood pressure was recorded every 10 min for the first hour and every 1 h for the next 4 h. All the adverse effects of the drugs were recorded. Cessation of the drugs was done when conversion to SR was achieved, systolic blood pressure was <90 mm Hg, and when serious ventricular arrhythmia (couplets, ventricular tachycardia or torsades des pointes) prolongation of QRS duration more than 50%, bundle branch block or serious adverse effects were present. All patients remained hospitalized for at least 24 h and underwent a 24 h Holter recording. If termination of the arrhythmia was not achieved any other effort for conversion to SR was done at least 4 h after the cessation of ibutilide or amiodarone. In all these patients electrical conversion with a biphasic defibrillator was attempted.

3. Statistics

The conversion rates of the two drugs were compared with Yates corrected chi-square (χ^2) test. The times in which successful conversions were achieved for each group were compared with the use of Mann Whitney-*U* test. The mean values and the demographic data of the two groups were compared with the use of the Student's *t*-test.

4. Results

4.1. Clinical characteristics of population

One hundred fifty-two patients (103 men and 49 women) that fulfilled the inclusion criteria entered the study. One

Table 1
Clinical and instrumental characteristics of the study population

	Group A (ibutilide)	Group B (amiodarone)	*p*
Age (years)	62±16	64±18	ns
Weight (kg)	45–112	50–105	ns
Gender (men/women)	50/24	53/25	ns
History of heart disease	36(46%)	38(52%)	ns
Ejection fraction (%)	53±6	52±8	ns
Left atrium (mm)	43±5	45±6	ns

hundred eight patients had AF and 44 patients had Af of less than 48 h duration.

The two groups (A and B) didn't differ statistically as regards their age, the sex, the heart disease, the duration of the arrhythmia and the size of the left atrium and the ejection fraction of left ventricle (as they were estimated with the echocardiogram) (Table 1).

4.2. Conversion rates

In total, the conversion rate of group A (ibutilide) was significantly higher than the conversion rate of group B (amiodarone) (80% vs. 57%, $p=0.0054$, Table 2).

Nevertheless, the conversion rates of the two groups, didn't differ significantly when the arrhythmia was AF (77% vs. 69%, $p>0.05$, Table 2). The difference that was found in the total population was mainly due to the very significant difference that was observed when the responsible arrhythmia was Af (87% vs. 29%, $p=0.003$, Table 2).

The conversion rates of ibutilide didn't differ significantly for AF and Af (77% vs. 87%, $p=$ns), whereas amiodarone was significantly more effective when the arrhythmia was AF (69% vs. 29%, $p=0.000$).

Each drug lengthened significantly QTc (ibutilide 410±16 ms to 457±14 ms, $p=0.000$ and amiodarone 412±13 ms to 453±16 ms, $p=0.000$) but the average lengthening of the QTc interval didn't differ significantly between the two groups (46±5 vs. 44±11 ms, $p=$ns).There was no difference between patients with and without successful arrhythmia termination in both groups.

4.3. Arrhythmia termination time

The arrhythmia termination time was counted for each drug from the initiation time of the drug administration. The mean time to arrhythmia termination was significantly shorter with ibutilide than with amiodarone for AF (53.4±25.8 vs. 492±186 min, $p=0.000$) and for Af (28.4±16.3 vs. 762±318 min, $p=0.000$).

The termination time that was achieved by ibutilide was significantly shorter for Af than for AF (28.4±16.3 vs. 53.4±25.8 min, $p=0.000$). On the contrary the corresponding times of amiodarone showed that Af was terminated significantly later than AF (762±318 vs. 492±186 min, $p=0.000$).

The 24 h Holter recording after the conversion showed that there was no significant difference between the two groups as regards the in hospital recurrence of arrhythmia (Table 3).

Table 2
Conversion rates of ibutilide and amiodarone

Arrhytmia	Group A (ibutilide)	Group B (amiodarone)	Total
Atrial fibrillation	43/56 (77%)	36/52 (69%)	ns
Atrial flutter	20/23 (87%)	6/21 (29%)	0.003
Total	63/79 (80%)	42/73 (57%)	0.0054

Table 3
Recurrence of arrhythmia

	Group A (ibutilide)	Group B (amiodarone)	p
Recurrence of arrhythmia	7.9%	7.1%	ns

4.4. Adverse events

Polymorphic ventricular tachycardia (torsades des pointes) developed in 3 patients (3.8%) of the ibutilide group (group A). One of them occurred 30 min after conversion and was nonsustained (i.e. didn't require electrical termination) while the other two occurred, the first, 90 min after conversion and, the second, 15 min after the initiation of ibutilide infusion, both requiring electrical termination. QTc or the lengthening of QTc (compared with the baseline value) after the infusion of ibutilide didn't differ significantly in those three patients that suffered torsades des pointes.

Monomorhic, polymorphic, couples and triplets of premature ventricular beats were present in 9% in group A patients and in 3% in group B patients ($p=$ns). Monomorphic non-sustained ventricular tachycardia occurred in 10 patients who received ibutilide and in 2 patients who received amiodarone ($p=0.033$).

Three patients of the amiodarone group, exhibited hypotension (systolic blood pressure <90 mm Hg) and five patients of the same group presented local hypersensitivity at the site of the iv amiodarone infusion. Two of the ibutilide patients presented great prolongation of QTc (>600 ms) but without any arrhythmic events. Two more patients from the same group presented transient junctional rhythm that started about five minutes after the infusion of ibutilide.

5. Discussion

Ibutilide is a class III antiarrhythmic drug. It acts by inhibiting the outward repolarizing potassium current and by increasing the slow inward plateau sodium current, resulting to the prolongation of the monophasic action potential duration and as consequence of the atrial effective refractory period [12]. Previous studies have proven the effectiveness of ibutilide in converting AF and Af [13,14].

Amiodarone is a complicated molecule with peculiar pharmacokinetic profile that has the following properties: (a) blockade of a and b-adrenergic receptors, (b) inhibition of Na^+, K^+ and Ca^{2+} currents, (c) blockade of the thyroid hormones receptors, (d) inhibition of the enzyme Na^+–K^+ adenosine triphosphate (Na^+–K^+, ATP). When given intravenously, amiodarone and its metabolite (desethylomiodarone), prolongs the action potential duration of the ventricular muscle but shortens the action potential duration of Purkinje fibers. It also reduces conduction velocity.

The choice of the most appropriate drug for conversion of AF and Af should be based on the efficacy, the safety and the arrhythmia termination time. Ibutilide was chosen as a rapidly acting agent with probably remarkable conversion

rates. Its big disadvantage is the serious ventricular arrhythmias that it could cause. On the other hand, amiodarone is the most commonly used agent for converting AF and Af, is known to be quite safe when given intravenously, has variable conversion rates (from 4% up to almost 100%) and probably has a long termination time [11,15].

Ellenbogen et al. [8] reported in a study with 200 patients with AF and Af the total conversion rate for ibutilide of 47.5% while for placebo the conversion rate was 24%. Conversion rate was higher for Af that with AF (58% vs. 40%). The mean time to arrhythmia termination was 10–23 min. In other studies, ibutilide was superior to propafenone for treating Af (90% vs. 30%, $p<0.01$) [16] and AF (70.73% vs. 48.78%) [17]. In a comparison study, ibutilide was found superior than Sotalol in terminating Af (70% vs. 56%) and AF (44% vs. 11%) [18]. On the contrary, in another study [19] it was found that ibutilide had no significant advantage over amiodarone (45% vs. 50% ns) for the conversion of AF to sinus rhythm in patients after cardiac surgery with new onset AF.

In our study ibutilide was found to be more effective than amiodarone in converting Af to sinus rhythm. The higher success rate of ibutilide could be explained by the theory of the wavelength. Af is caused by a circus movement commencing at the inferior vena cava, traveling up the crista terminalis superiorly, and then turning inferiorly around the orifice of the superior vena cava [4]. Af is due to a stable single leading circle reentry with an excitable gap in its classic type (type I), whereas the less usual type II is may be caused by a "leading-circle" type reentry. Experimental studies have shown that the wavelength (refractory period × conduction velocity) is a crucial factor for the action of the antiarrhythmic drugs in reentry tachycardias [20]. Theoretically, in a reentry circuit with constant anatomic circuit length, the wavelength is proportional to the refractory period divided by the cycle length (CL). Thus, the effect of an antiarrhythmic drug on a reentry circuit, i.e. on the refractory period and on the conduction velocity, can be estimated by the change of the ratio: duration of the action potential/cycle length of the tachycardia.

Ibutilide prolongs the monophasic action potential duration (MAPD) and consequently the refractory period of the atrium. CL is also increased but in a lesser degree so that the ratio MAPD/CL is increased by 13%. The prolongation of the MAPD seems to be inadequate to close the total excitable gap and to extinguish the reentry circuit. Since ibutilide doesn't slow the conduction velocity, the reason for the increase of the CL in Af could be the conversion from a fully to a partially excitable gap [21,22], making the CL depending on the duration of the action potential. On the contrary, the drugs that directly cause slowing of the conduction velocity maintain the fully excitable gap.

So Af that has a steady reentry circuit with a large excitable gap, can be more easily terminated by drugs that prolong the action potential and the refractory period and can also influence the conduction velocity through closing the total excitable gap.

Ibutilide increases the wavelength and decreases (up to a critical number) the number of the arrhythmia wavelets, by prolonging CL and MAPD, increasing the statistical possibility that all wavelets might extinguish simultaneously and the arrhythmia could be terminated.

According to our findings ibutilide acts faster than amiodarone in conversion AF or Af to SR. On the other hand, amiodarone certainly appeared to be safer, yet ibutilide induced ventricular arrhythmias caused no deaths, meaning that the administration of this drug needs hospital environment and close monitoring.

In conclusion, these data may prone that ibutilide having acceptable safety is more effective than amiodarone in converting Af, while no difference in efficacy was shown for AF.

5.1. Limitations

The study was not double-blinded. The time of onset of the arrhythmia for the out patients could not be determined with absolute accuracy since our data for this information was based on the patients testimony. About 39% of the included patients were already receiving antiarrhythmic drugs and although there was no statistic difference between the two groups concerning these drugs, the evaluation of the proarrhythmic effects of ibutilide or amiodarone could be affected as regards these patients.

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