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RESEARCH ARTICLE

Vernakalant versus ibutilide for immediate conversion of recent-onset atrial fibrillation

Vogiatzis I, Papavasiliou E, Dapcevitch I, Pittas S, Koulouris E

Department of Cardiology, General Hospital of Veroia, Veroia, Greece

Abstract

Background: The pharmacological cardioversion of recent-onset atrial fibrillation (AF) is a challenge for the clinician. The aim of the study was to compare the efficacy, the safety, and the overall cost of intravenous (iv) administration of vernakalant, which is a relatively new atrial-selective antiarrhythmic agent, versus ibutilide, in cardioversion of recent-onset AF.

Methods: We enrolled in this study 78 patients (56 men, 22 women; mean age 63.72 ± 6.67 years) who presented with recent-onset AF. Cardioversion was attempted in 36 patients (group A: 24 men, 12 women; mean age 62.44 ± 7.24 years) by iv administration of vernakalant (3 mg/kg over 10 min and if needed after 15 min, a second dose 2 mg/kg over 10 min) while in 42 patients (group B: 32 men, 10 women; mean age 64.81 ± 6 years) iv ibutilide was administered (1 mg over 10 min and if needed after 10 min, a second dose 1 mg over 10 min).

Results: AF was successfully converted in 52.78 % of (n =19) patients of group A vs 52.38 % of (n =22) patients of group B (p =0.58), with an average time of conversion 11.8 ± 4.3 min for group A patients vs 33.9 ± 20.25 min for group B patients (p <0.0001). The average length of hospital stay for patients of group A was 17.64 ± 15.96 hours vs 41.09 ± 17.6 hours for patients of Group B (p <0.0001). In one patient of group A, the administration of vernakalant was discontinued due to hypotension while two other patients reported dysgeusia during their hospitalization. In three patients of group B, the administration of ibutilide was discontinued due to development of nonsustained ventricular tachycardia, which resolved with discontinuation of the drug. The cost of administered drugs was estimated at 488.22 ± 170.34 € for patients of group A vs 142.43 ± 54.45 € for patients of group B (p <0.0001), however, hospitalization costs were significantly lower in patients of group A (258.5 8± 124.73 € over 414.43 ± 100.32; p =0.002).

Conclusion: There was no significant difference in the efficiency of converting recent-onset AF between vernakalant and ibutilide. Although vernakalant is an expensive drug, we recorded fewer side effects and more rapid restoration, which reduced the overall cost of hospitalization of these patients. HIPPOKRATIA 2017, 21(2): 67-73.

Keywords: Atrial fibrillation, vernakalant, ibutilide, cardioversion, efficiency, cost, safety

Corresponding author: Dr Ioannis Vogiatzis, 3a Stougiannaki str, Panorama, 55236 Thessaloniki, Greece, tel: +302310345709, +306944276230, e-mail: ivogia@hotmail.gr

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia encountered in clinical practice (suffers about 1 % of the adult population)[1,2] and people who suffer from it, especially those aged more than 55 years, will constantly be increasing[3].

Early pharmaceutical or electrical cardioversion is necessary to improve symptoms, prevent the side effects of the prolonged crisis of arrhythmia and avoid hospitalization, which among others, provokes increased economic expenses[4,5]. In epidemiological studies and surveys all over the world[6,7], it appears to be associated with a lower frequency of transition of the arrhythmia to permanent AF[8].

Electrical cardioversion requires certain circumstances and presents various untoward issues (sedation, the presence of an anesthesiologist, and fasted patients for at least 6 hours)[9], while monitoring is needed for at least 6 hours, and the patients are not allowed to drive for 24 hours[10].

Medications currently used for cardioversion of AF are restricted by their delayed onset of action, slow metabolism, and proarrhythmic effects, thus, prolonging the hospitalization[4,11]. There is, therefore, a need for a pharmaceutical treatment and cardioversion of AF with fast-acting, effective, safe drugs, well tolerated by patients.

Vernakalant is a new antiarrhythmic drug, with fast action, effective, and well tolerated. It acts selectively in the atrial myocardium, with limited activity in the ventricles[12]. It is an inhibitor of the atrial potassium (K^+) and also sodium (Na+) channels, with a half-life of two to three hours[13]. Intravenous (iv) drug administration confronted the recent-onset AF (duration from three hours up to seven days) effectively in many clinical studies[14,15]. Its action was fast with a short half-life, which allowed the early discharge of patients from hospital[16].

Another effective and widely used drug in cardioversion of AF is ibutilide. It is an antiarrhythmic Class III agent, administered only iv, and is effective in recent-onset AF and atrial flutter. It prolongs the QT interval on the electrocardiography (ECG), like other Class III drugs, and predisposes to Torsades des pointes (TdP) abnormal heart rhythm. The risk with the use of ibutilide is 7.8 % of which 2.3 % is persistent tachycardia (sustained)[17].

This study aimed to compare the efficacy and safety of iv administration of vernakalant vs ibutilide in cardioversion of recent onset atrial fibrillation. Moreover, the cost of hospitalization of patients with recent-onset AF who were treated with those medications was estimated (cost-effectiveness analysis).

Methods

The study was conducted at the Department of Cardiology, General Hospital of Veroia from October 2015 until April 2016, and we enrolled patients who presented with recent-onset AF (one to 48 hours), who were evaluated and decided their arrhythmia to be converted to sinus rhythm. During the six month enrolment period, 123 consecutive patients with recent-onset AF were evaluated, 45 patients were excluded and 78 patients (56 men, 22 women) with mean age 63.72 ± 6.67 years were enrolled in the study. All eligible patients were hemodynamically stable with systolic blood pressure (SBP) >100 mmHg and <160 mmHg, and were receiving anticoagulant treatment if it was considered necessary.

We set as exclusion criteria for this study: a QTc interval on the ECG >440 msec, history of recent TdP, symptomatic bradycardia, sinus node dysfunction, and QRS >140 msec. Also, patients who had recently failed cardioversion were excluded, while exclusion was also considered if there were electrolyte disturbances or digitalis toxicity, contraindications to ibutilide or recent administration of vernakalant. Finally, cases of congestive heart failure (CHF; stage >III, NYHA), acute coronary syndromes (ACS), pacemakers, cardiac surgery in the preceding 30 days, atrioventricular block and end-stage disease, were excluded. During the six month period, 45 patients were excluded from the study due to the presence of the above exclusion criteria.

The population of this study was randomly allocated into two groups (randomization by their registry number: odd numbers allocated to group A, and even to group B). Cardioversion was attempted in 36 patients (group A: 24 men, 12 women; mean age 62.44 ± 7.24 years) by iv administration of vernakalant (3 mg/kg over 10 min and if needed after 15 min, a second dose 2 mg/kg over 10 min) while in 42 patients (group B: 32 men, 10 women; mean age 64.81 ± 6 years) iv ibutilide was administered (1 mg over 10 min and if needed after 10 min, a second dose 1 mg over 10 min). Drug administration was discontinued if any of the following was observed: QTc >550 msec or QRS >180 msec, symptomatic bradycardia or heart rate <40 beat per min (bpm), symptomatic hypotension or SBP <85 mmHg, a new bundle branch block, asymptomatic non-sustained ventricular tachycardia (VT) with duration of ≥10 consecutive beats, symptomatic VT, TdP, ventricular fibrillation (VF), one or more sinus pauses lasting ≥5 sec, complete atrioventricular block or other adverse events, not well tolerated by patients.

Electrical cardioversion or administration of drugs (digoxin or b-blockers or combination) to achieve rate control was allowed two hours following the initiation of drug administration, should the patient was still in AF. Patients remained hospitalized for at least six to eight hours after the administration of drugs and were monitored by telephone daily for seven days after hospital discharge.

Effectiveness

We calculated the rate of patients who were successfully converted to sinus rhythm within 90 min from the commencement of each medication and recorded the time to cardioversion. We also estimated the proportion of patients in each group who could be discharged from the hospital within two hours from the initiation of drug administration, covering the criteria of effectiveness and safety.

Cost of hospitalization

The total cost was estimated by summing the prices of all medications utilized for cardioversion of AF and the amount of money corresponding to the respective treatment patients received, i.e., which is charged to the EOPPY (Hellenic National Health Care Organization Services), the private insurance or the patient him/herself, depending on the insurance cover of each patient. This cost corresponds to the proportional DRGs (Diagnosis Related Groups), namely the X24X (hospitalization for less than 24 hours) and K46X (hospitalization for more than 24 hours)[18]. The hospital price for vernakalant is 338 € per vial and for ibutilide is 74 € per vial. Details of the calculation of the cost are presented in Table 1.

The study protocol was approved by the Ethical Committee of the General Hospital of Veroia (decision No: 13, 10/2/2014), patients were informed about the study protocol and all but one, who was excluded from the study, accepted it.

Statistical Analysis

Collected data analysis was performed using the IBM SPSS Statistics for Windows, version 19.0 (IBM SPSS, IBM Corp., Armonk, NY, USA). Initially, calculation of the normality for the distribution of quantitative variables was made, using the Kolmogorov-Smirnoff test (population >50 individuals). For comparison of the quantitative variables t-test and non-parametric Mann-Whitney test were used, while the x^2 test and the Fischer test were used to assess differences in the distribution of qualitative variables.

All time variables until the event (conversion of AF) were analyzed by logistic regression model (log-rank test) and presented in Kaplan-Meier curves, calculating and comparing the rates of cardioversion. The corre-

Table 1: Prices of medications utilized for cardioversion of atrial fibrillation and hospitalization costs estimation corresponding to the proportional Diagnosis Related Groups.

Cost of the Drug	Vernakalant 338 €	Iboutilide 74 €
DRG	**X24X**	**K46X**
Hospitalization Cost	• Hospitalization <24 h: 177 € + Drug	• Hospitalization 24 h: 444 € + Drug • Hospitalization 48 h: 444 € + Drug • Hospitalization 72 h: 504 € + Drug • Hospitalization >72 h: 504 € + Drug + 60 € / per day

DRG: Diagnosis Related Groups, X24X: hospitalization for less than 24 hours, K46X: hospitalization for more

sponding estimates of the confidence intervals (CI) were made using the statistical model of Cox (Cox regression analysis). The probability p <0.05 (2-way) was considered statistically significant.

Results

The basic epidemiological and demographic characteristics of the patients at the time of admission are listed in Table 2, and there are no significant differences between the two groups of patients.

AF was successfully converted in 52.78 % of (n =19) patients of group A vs 52.38 % of (n =22) patients of group B (p =0.58), with an average time of conversion 11.8 ± 4.3 min for group A patients vs 33.9 ± 20.25 min for group B patients (p <0.0001). Details in Figure 1 record the path to the cardioversion of the two groups of patients. The average length of hospital stay for patients of group A was 17.64 ± 15.96 hours vs 41.09 ± 17.6 hours for patients of group B (p <0.0001).

Table 3 lists the adverse events that occurred during the hospitalization of these patients due to drug administration.

In one patient of group A, the administration of vernakalant was discontinued in the first five min due to

Table 2: The basic demographic and epidemiological characteristics of the 78 enrolled patients with recent-onset atrial fibrillation, randomly allocated into group A (cardioversion by intravenous administration of vernakalant) and group B (cardioversion by intravenous administration of ibutilide).

	group A n =36	**group B n =42**	**p**
Age (years)	62.44 ± 7.24	64.81 ± 6.10	0.1
Gender (male)	24 (66.67)	32 (76.19)	0.1
History of relapses of AF	17 (47.23)	16 (38.09)	0.2
First onset AF	12 (33.34)	11 (26.19)	0.1
Average duration of episode (hours)	14.7 ± 13.5	15.4 ± 14.8	0.5
Duration ≤24 hours	23 (63.89)	20 (47.62)	0.7
Hypertension	27 (75)	23 (54.76)	0.2
CAD	18 (50)	13 (30.95)	0.1
Valvular disease	5 (13.89)	6 (14.28)	0.1
Lone AF	7 (19.4)	7 (16.67)	0.2
Left Atrium (mm)	42.6 ± 7.34	41.8 ± 6.4	0.09
EF %	56.8 ± 8.6	58.7 ± 7.94	0.4
EF <50%	3 (8.34)	3 (7.14)	0.23

Values are given as numbers (percentage in brackets) or means ± standard deviation, AF: atrial fibrillation, CAD: coronary artery disease, EF: ejection fraction.

Table 3: Adverse events that occurred during the hospitalization of the 78 patients with recent-onset atrial fibrillation (group A: cardioversion by intravenous administration of vernakalant, group B: cardioversion by intravenous administration of ibutilide).

	group A n =36	**group B n =42**
Dysgeusia	2 (5.56)	-
Hypotension	2 (5.56)	2 (4.76)
Sustained VT	-	3 (7.14)
Overall	4 (11.11)	6 (14.28)
Discontinuation	1 (2.78)	3 (7.14)

Values are given as number of events occurred (percentage in brackets), VT: ventricular tachycardia.

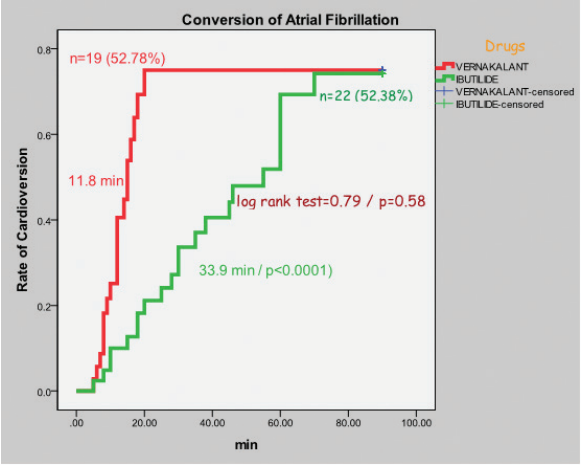

Figure 1: Comparison of time and rates of cardioversion of atrial fibrillation to sinus rhythm during the 90 min than 24 hours.

severe hypotension with sweating, dizziness, and nausea, which however subsided immediately after, while two other patients reported dysgeusia during their hospitalization. In one patient of group B, the administration of ibutilide was discontinued due to the occurrence of intense dizziness, gradually deteriorating, without any other ECG or hemodynamic complications and in three other patients due to development of nonsustained VT - TdP, which resolved with discontinuation of the drug. In one of these patients, multiple bursts of nonsustained VT at the end of the administration of the second dose of ibutilide was observed, while was still in AF. The patient had been submitted to mitral valve replacement with metallic valve ten years before, but he had a normal ejection fraction of the left ventricle (LVEF).

The QT interval on the ECG at two hours following the drug administration was prolonged in both patients' groups, more in group B, but without statistical significance, although marginally. In this group, the three episodes of TdP tachycardia were observed, and the administration of the drug was discontinued.

As recorded specifically by the researchers of this study, a greater number of patients in group A (n =14; 38.89 %) were fit and ready for discharge at two hours, compared to group B (n =5; 11.9 %) (Table 4).

Table 4 describes the cost vs the effectiveness and safety of the medications used. The vials of ibutilide cost significantly less compared to the respective of vernakalant, although in 29 patients (37.2 %) the administration of a second vial was required. However, in a considerably smaller proportion, patients of group B were capable to be discharged from the hospital within two hours due to the adverse events of ibutilide or for reasons of monitoring. Indeed, patients of group B had to remain hospitalized longer than patients of group A, so the cost of hospitalization rose significantly (Table 4).

Discussion

In clinical practice, an iv administered antiarrhythmic drug which can reliably and safely convert a recent-onset AF is highly desirable. Our study shows that vernakalant is a safer option than ibutilide. The percentage of patients who were converted was similar (52 %) but the cardioversion was faster (vernakalant: 12 min vs ibutilide: 33 min) and safer.

The recorded rapid conversion of arrhythmia with vernakalant agrees with the findings of the recent phase III studies, of drug administration in converting AF[16,19,20]. The benefits of such a rapid conversion are the decrease of risk of AF relapse, the reduced need for long-term antithrombotic therapy and electrical cardioversion, and of course, the reduction of the length of hospital stay for treatment and therefore cut down of the related health cost for the security funds[5,21]. According to our study findings, more patients treated with vernakalant, compared to ibutilide, could be discharged within the first two hours following the drug administration and safe return to their daily activities.

The use of currently available antiarrhythmic drugs for cardioversion of AF is limited by the delayed patients' presentation and increased risk of proarrhythmia. In recent-onset AF, iv propafenone is successful in 23-25 % of patients at 60 min, with an average time of conversion two hours[22], while iv flecainide converts 56 % of patients at 90 min[23]. Antiarrhythmic drugs with Class Ic agents, however, are contraindicated in patients with structural heart disease due to their proarrhythmic effects[24,25].

We chose ibutilide for comparison in the current study as it is one of the most effective antiarrhythmic drugs for cardioversion of AF, with rapid onset and success in 90 min which varies from 28 to 31% compared to placebo[26], and 55-61 % compared to other antiarrhythmic drugs[27-29]. The study's cardioversion success was 52.38 % probably due to inclusion of patients with AF onset longer than 24 hours, although studies[30] report the efficacy not to be affected by the time of AF onset. However, our reported

Table 4: Characteristics of the effectiveness and cost of administration of the two drugs (group A: cardioversion by intravenous administration of vernakalant, group B: cardioversion by intravenous administration of ibutilide).

	group A n =36	group B n =42	p
Time of hospitalization (hours)	17.64 ± 15.96	41.09 ± 17.6	<0.0001
QTc at 2 hours (msec)	420.86 ± 35.8	464.5 ± 29.6	0.055
Patient ready for discharge at 2 hours	14 (38.89)	5 (11.9)	0.03
Cost of medicines (€)	488.22 ± 170.34	142.43 ± 54.45	<0.0001
Cost of Care (€)	258.58 ± 124.73	414.43 ± 100.32	0.002

Values are given as numbers (percentage in brackets) or means ± standard deviation.

rate is in agreement with that of other relevant studies[26-29]. Ibutilide is approved by the FDA in the USA but the risk of occurrence of VT (TdP) is reported to be 3.6-8.3 %, so in general, there is skepticism regarding its use[21].

Although Class Ic agents, such as flecainide and propafenone, are used as first-line drugs for the conversion of AF in many European countries[24], we opt not to select them for comparison as their iv form is not officially released in our country, as in other European countries and their supply is possible only through government services.

Ibutilide was chosen to compare in the study because it is one of the most effective anti-arrhythmic drugs for cardioversion of AF, with rapid onset and success in 90 min which varies from 28 to 31 % compared to placebo[26] and 55-61 % compared to other antiarrhythmic drugs[27-29]. The study cardioversion success was 52.38 % probably because it included patients with AF onset time greater than 24 hours, although studies[30] report that the efficacy is not affected by the time of onset of the AF. However, this rate is in agreement with the results of other relevant studies[26-29]. The drug is approved in the USA (FDA), but at the risk of occurrence of ventricular tachycardia (TdP) 3.6-8.3 %, so in general, there is skepticism in the use of the drug[21].

Although the Group Ic drugs, such as flecainide and propafenone, are in some cases in the first-line for the conversion of AF in many European countries[24], were not selected because the iv form is not released officially in our country, as in other European countries and their supply is only through government services.

Amiodarone is widely used for iv cardioversion of AF all over the world[31], but it has a much slower onset of action and minor efficacy of its prolonged administration. Also, in a recent study[32] vernakalant demonstrated superior efficacy in comparison to amiodarone in the acute conversion of recent-onset AF, with the same safety and good tolerance.

Finally, procainamide has been approved in Canada but is rarely used for immediate cardioversion of AF in other countries, mainly in Europe, and is inferior compared to ibutilide and flecainide[27,33,34].

Vernakalant may be used in broader population groups with different characteristics, as it has no contraindications, neither the risks of other antiarrhythmic drugs.

Although the clinical efficacy of vernakalant and ibutilide appears to be similar, there are differences in the electrophysiological mechanisms of the two drugs that lead to this specific and important result. AF, is generally considered to be produced by multiple reentrant circuits[35]. The ability of ibutilide to prolong the refractory period of the atrial myocardium without altering the velocity[26,30] is the standard action of a Class III antiarrhythmic agent[36] and is achieved by the increased activity of slow, delayed Na^+ currents to the cell's interior, preventing the rapid-acting buffer flow of K^+ ion. This effect of ibutilide is not reduced, during a faster cycle length, keeping thereby its effect on the refractory period even at higher heart rates of the atrial myocardium[30]. This is confirmed by the findings of our study, namely a tendency to prolong the QTc interval at the initiation of the drug administration and a prolonged QTc interval after the cardioversion with ibutilide (compared with those not converted). Therefore, the refractory periods of the atrial and ventricular myocardium show a parallel behavior leading to beneficial effects on the level of the atrial myocardium (conversion) and the known risk of TdP on the ventricular myocardium.

On the other hand, vernakalant affects selectively the ion channels that are mainly present in the atrial myocardium and causes a rapid and effective treatment of the recent-onset AF[37]. In particular, it causes prolongation of the atrial refractory period in the myocardial cells, particularly in fast rates, such as AF, blocking ion channels of K^+. This ability is a thousand times lower than ibutilide and this may explain the potent non-extension of the QT interval and the low risk of TdP[37]. Finally, the expansion of the effective refractory period without change in action potential duration is an additional effect of the selective blocking of the Na^+ ions current on the atrial myocardium[38].

Generally, vernakalant administration was found to be safer than ibutilide. In patients of group A the most frequent adverse reactions were hypotension and dysgeusia, as observed in other studies[14,16]. Dysgeusia is associated with the drug excretion in saliva[20]. The drug is generally not considered to cause allergic reactions, and in fewer patients, its administration was discontinued due to side effects. The single patient who suffered hypotension and its administration was discontinued, before the commencement of treatment was fully hydrated and hemodynamically stable. However, the prevalence of hypotension following the drug administration was in our study lower compared with the findings of previous studies[14,16]. During the infusion of vernakalant, a transient increase of the QTc interval was observed, which was not associated with any proarrhythmic action of the drug. In an earlier study[19], an episode of death from ventricular tachycardia in a patient with co-existing valvular disease was observed. There is limited experience using vernakalant in patients with severe structural heart disease.

In patients of group B, a prolongation of the QTc interval was observed which remained throughout the infusion and four hours after its completion. Episodes of TdP occurred in three patients of Group B (7.14 % vs 2 % in other studies) necessitating discontinuation of the drug. Due to these complications and the prolongation of QTc interval, patients treated with ibutilide, were monitored closely for two to four hours after the drug administration and therefore only five (11.9 %) were ready to be discharged within two hours from infusion. For the same reasons they remained hospitalized for longer than patients of group A. However, during their follow-up no patient of either group reported any problem after the discharge.

Cardioversion of recent-onset AF with ibutilide was

estimated to be 30 times more expensive than with vernakalant. Although ibutilide costs less as a drug, the overall treatment is more costly due to more frequent adverse effects arising from its use, resulting to prolonged hospitalization of these patients, thus increasing the overall cost of treatment. Furthermore, a considerably smaller proportion of these patients was capable to be discharged within two hours from cardioversion, compared with those converted with vernakalant. Similar results were reported by a cost-effectiveness study comparing ibutilide with flecainide[23], and also previous studies[39,40], all concluding that ibutilide is a rather expensive drug. Our results support the same conclusion, after comparing ibutilide with vernakalant, which is 5-6 times more expensive.

Conclusion

There was no significant difference in the efficiency of converting recent onset AF between vernakalant and ibutilide. Vernakalant, although expensive drug, had fewer side effects and faster restoration, events that reduced the overall cost of hospitalization of patients.

Conflict of interest

Authors declare no conflict of interest.

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