Clinical Investigations

Cardioversion of Atrial Fibrillation with Ibutilide: When Is It Most Effective?

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Summary

Background: Atrial fibrillation (AF) is found in 1% of persons above the age of 60 years. More than 5% of the population older than 69 years and about 14% of octogenarians are at risk for this arrhythmia. It is estimated that 1.5 to 3 million persons in the United States alone suffer from AF. The public health implications and attendant morbidity are a significant drain on our health care system.

Hypothesis: The purpose of this study was to determine the clinical and echocardiographic predictors of success in converting AF of ≥ 24 h duration.

Methods: Demographic and clinical and echocardiographic parameters of 101 patients with recent onset AF (> 24 h) who received ibutilide were studied.

Results: Of 101 patients, 56 (55%) converted to sinus rhythm. Age, gender, hypertension, diabetes mellitus, left ventricular ejection fraction ($\leq 35\%$), congestive heart failure, and previous medication for rate control had no significant effect on the conversion rate. Conversion rate was only 30% (9/30 patients) in the presence of an enlarged left atrium (LA ≥ 5 cm) and 37.7% (23/61 patients) in the presence of mitral valve disease (MVD), whereas the conversion rate was 82.5% (33/40 patients) in the absence of MVD and 85% (29/34 patients) in the absence of both enlarged LA and MVD ($p < 0.001$). Patients with coronary artery disease (CAD) also exhibited a significantly greater response to ibutilide than patients without CAD (77 vs. 46%, p -value 0.005).

Conclusion: As a therapy for cardioversion of AF, ibutilide is most effective in a selected subgroup patients, such as in pa-

tients with CAD and in patients without MVD and/or markedly enlarged left atrium.

Key words: ibutilide, atrial fibrillation

Introduction

Atrial fibrillation (AF) is found in 1% of persons above the age of 60 years. More than 5% of the population older than 69 years and about 14% of octogenarians are at risk for this arrhythmia.^{1,2} It is estimated that 1.5 to 3 million persons in the United States alone suffer from AF. The public health implications and attendant morbidity are a significant drain on our health care system.³ The morbidity and mortality associated with AF include stroke, heart failure, syncope, and risk of sudden death.^{4,5} Whether maintaining sinus rhythm (SR) as opposed to achieving rate control will impact mortality is the primary focus of the ongoing Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.⁶ Sinus rhythm improves cardiac hemodynamics by restoring atrial contribution to the cardiac output and by controlling the heart rate, thereby improving exercise tolerance and functional capacity.⁷ It was shown in goat models that repeated induction of AF by rapid burst pacing reduced the atrial refractory period, which led to "electrical remodeling" and refractory AF ("atrial fibrillation begets atrial fibrillation").^{8,9}

Therefore, apart from preventing complications related to this arrhythmia, conversion to SR also prevents complications related to prolonged drug therapy including anticoagulation.^{10–12} In general attempts are made to convert new onset to sinus rhythm.¹³

Both pharmacologic and nonpharmacologic methods are available for cardioversion of AF.^{14,15} Among the pharmacologic methods available, ibutilide, a class III antiarrhythmic agent, has been shown to be effective in the acute treatment of AF.^{16–21} The spontaneous conversion rate in new onset AF within the first 24 h is as high as 50–70% with highest incidence in the first 8 h, and it drops to $< 8\%$ after 24 h. Therefore, only half of the patients with new onset AF will require cardioversion if monitored for > 24 h. It has also been shown to be cost effective when the patients are treated with direct current (DC) cardioversion.²²

We evaluated the response rate of ibutilide in AF of > 24 h duration to minimize the chance of spontaneous conversion.

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The clinical and echocardiographic determinants associated with successful ibutilide therapy were also characterized.

Methods

Study Population

In all, 150 patients (mean age: 68.7 ± 13.7 years; 52 male) with recent onset AF (> 24 h and ≤ 3 months), admitted between February 1997 and November 1999, were selected for study. Patients treated with atrioventricular (AV) nodal blocking agents, including long-term digoxin, beta blockers, or calcium-channel blockers, were included in the study. Patients were excluded if they had hemodynamic instability, recent myocardial infarction (< 48 h), unstable angina, class I or class III antiarrhythmic therapy, previous history of torsade de pointes, digoxin toxicity, hyperthyroidism, left atrial thrombus, overt liver disease, or pregnancy. After enrolling in the study, 44 patients were excluded because of spontaneous conversion to sinus rhythm, three patients required urgent DC cardioversion for hemodynamic instability, and two had hyperthyroidism; 101 patients (mean age: 69 ± 10 years; 52 male) underwent ibutilide therapy.

Protocol

All patients admitted with recent onset AF underwent a complete medical evaluation, which included assessment of risk factors, medication, and laboratory values including thyroid function. Ventricular rate control was achieved with AV nodal blocking drugs including, beta blockers, calcium-channel blockers, and digoxin. All patients underwent continuous electrocardiographic (ECG) monitoring. Transthoracic echocardiography was performed in patients with AF of < 48 h duration to assess for structural heart disease, while transesophageal echocardiography was performed for AF of > 48 h duration to exclude left atrial (LA) clot. Left ventricular ejection fraction (EF) was obtained by Simpson's method. Left atrial size was measured in the parasternal long axis in transthoracic echocardiography, and in the long axis on transesophageal echocardiography. Hypokalemia (K^+ level < 3.5 mEq/l) and hypomagnesemia ($Mg^{++} < 1.5$ mEq/l) were corrected prior to ibutilide infusion. All patients who were not on prior anticoagulation therapy received intravenous heparin.

A single dose of ibutilide, 0.01 mg/kg, in patients weighing ≤ 60 kg, and 1.0 mg in patients weighing > 60 kg, was diluted in 50 cc of normal saline and was infused over 10 min. If the arrhythmia failed to convert to SR within 10 min following the initial infusion, a second infusion of equal strength was given over a 10-min period.²³ The intravenous infusion was stopped if the patient converted to SR or developed significant proarrhythmia.

Continuous ECG monitoring was continued for a 12-h period following ibutilide therapy. Patients were closely observed for significant Q-T prolongation, proarrhythmia, occurrence of arrhythmias, hemodynamic compromise, or any other untoward effects of this therapy.

Statistical Analysis

Comparisons of clinical and echocardiographic parameter between responders and nonresponders to ibutilide were done by chi-square analysis. A p value of < 0.05 was considered statistically significant. Multivariate logistic regression modeling was performed to identify independent predictors of conversion to sinus rhythm. Adjusted odds ratio and 95% confidence interval from the logistic model were derived. The following parameters were evaluated: (1) response to ibutilide in the presence of hypertension, coronary artery disease, diabetes mellitus (DM), congestive heart failure (CHF), large LA size, valvular heart disease (mitral regurgitation, mitral stenosis or history of mitral valve replacement), left ventricular hypertrophy (LVH), and significant left ventricular systolic dysfunction ($EF \leq 35\%$); (2) drug therapies that include beta blockers, calcium-channel blockers, and digoxin; (3) the time of conversion to sinus rhythm; and (4) proarrhythmias.

Results

The overall conversion rate to sinus rhythm was 55.4% (56/101 patients). The mean conversion time was 44 min (range 8–210) with 87.5% of the patients responding within 1 h of initiation of ibutilide infusion (Fig. 1). The mean dose of ibutilide required for conversion was $1.8 \text{ mg} \pm 0.5$ (± 1 standard deviation [SD]) and 88% (89/101 patients) required a second dose of ibutilide.

Tables I and II summarize the demographics and impact of various parameters studied on the success rate of ibutilide. Clinically significant mitral valve disease (MVD) was present in 35 patients, 28 of whom had a previous history of mitral regurgitation (MR), 3 had both MR and aortic regurgitation (AR), 2 patients had mitral valve replacement (MVR) for rheumatic mitral stenosis, 1 had MR related to hypertrophic cardiomyopathy, and 2 had mitral valve prolapse. An additional 25 patients without clinical evidence of MR were found to have at least mild MR on echocardiography and were included in the subset. Mitral valve disease was present in 38 of 45 patients (84%) who did not respond to ibutilide; on the other hand, only 23 of 56 (37.7%) of the responders exhibited any evidence of MVD. The success rate of ibutilide was only 37.7% (23/61 patients) in the presence of MVD, but

FIG. 1 Conversion time from ibutilide infusion to sinus rhythm.

TABLE I Baseline characteristics: Responder versus nonresponder groups

Characteristics	Nonresponders (n=45)	Responders (n=56)	p Value
Age (years)	70 ± 11	67 ± 15	0.326
Male (%)	22 (48.9)	30 (54.4)	0.686
HTN (%)	20 (44.4)	30 (54.4)	0.422
CAD (%)	7 (15.5)	23 (41.0)	0.005
DM (%)	6 (13.3)	13 (23.2)	0.306
CHF (%)	10 (22.2)	16 (28.6)	0.501
Beta blockers (%)	11 (25)	17 (30.7)	0.654
Ca blockers (%)	16 (35.6)	26 (46.4)	0.313
Digoxin (%)	12 (26.7)	20 (35.7)	0.393
ACEI (%)	10 (22.2)	8 (14.3)	0.311
Low EF (%)	10 (22.2)	6 (10.9)	0.171
LVH (%)	11 (24.4)	12 (21.4)	0.813
MVD (%)	38 (84.4)	23 (41.1)	0.001
Enlarged LA (%)	21 (46.7)	9 (16.1)	0.001
Baseline QTc	418 ± 32	431 ± 38	0.174
Maximum QTc	495 ± 68	486 ± 85	0.686

Abbreviations: HTN = hypertension, CAD = coronary artery disease, DM = diabetes mellitus, CHF = congestive heart failure, ACEI = angiotensin-converting enzyme inhibitor, EF = ejection fraction, LVH = left ventricular hypertrophy, MVD = mitral valve disease, LA = left atrium.

82.5% (33/40 patients) in the absence of MVD (p value <0.0001; Fig. 2).

The mean (± 1 SD) LA size was 4.2 ± 0.7 cm among responder and 4.97 ± 0.7 cm in the nonresponder groups. A markedly enlarged LA (≥ 5 cm) was present in 46% (21/45 patients) of nonresponders, compared with 16% (9/56 patients) in the responder group ($p < 0.001$; Fig. 3).

Patients with MVD had a higher LA size than patients without MVD, and 24 patients exhibited both markedly enlarged LA (≥ 5 cm) and MVD. As expected, 19 of these 24 patients did not respond (response rate of 21%) to ibutilide therapy (Fig. 4).

The response rate in patients with CAD was higher than in patients without CAD (23/30, 77%, vs. 33/71, 46%; Fig. 5).

Age, gender, hypertension, DM, LVH, left ventricular dysfunction ($EF \leq 35$ vs. $EF \geq 35\%$), DM, and serum K^+ and serum Mg^{2+} levels did not influence the conversion rate (Table I). Treatment with calcium-channel blockers, beta blockers, or digoxin, and prolongation of Q-Tc duration (baseline Q-Tc of

FIG. 2 Response rate to ibutilide in the presence and absence of mitral valve disease (MVD) and enlarged left atrium (LA).

FIG. 3 Presence of a markedly enlarged left atrium (≥ 5 cm) in responders versus nonresponders to ibutilide ($n = 101$).

FIG. 4 Response rate to ibutilide in the presence and absence of mitral valve disease (MVD) with marked left atrium (LA) enlargement.

FIG. 5 Response rate to ibutilide in the presence and absence of coronary artery disease (CAD).

TABLE II Multivariate analysis: Predictors of response to ibutilide

Predicting factors	p Value	Odds ratio	95% CI
Failure to respond to ibutilide	Mitral valve disease (MVD)	0.0001	0.1284
	Enlarged left atrium (LA)	0.0001	0.2402
	MVD and enlarged LA	0.0003	0.1342
Response to ibutilide	Coronary artery disease	0.001	5.598

Abbreviation: CI = confidence interval.

433 ± 38 to a maximum QTc of 485 ± 85 ms in the responder group vs. baseline Q-Tc of 418 ± 32 to a maximum QTc of 495 ± 59 ms in the nonresponder group; $p = 0.686$) related to ibutilide therapy also did not significantly affect the efficacy of ibutilide.

Premature ventricular beats, both monomorphic and polymorphic, were frequently present both during and within 4 h after initiation of the therapy. The incidence of nonsustained ventricular tachycardia was 5.8% (all of them were < 5 beats), with no significant difference between responders and nonresponders. Two patients developed torsade de pointes. One patient responded to 2 gm of intravenous Mg^{+} and the other patients was cardioverted to sinus rhythm with DC shock. Torsade in both patients was encountered within 1 h of initiation of therapy. One patient developed sinus bradycardia, which resolved spontaneously within 12 h. Global T-wave inversion on ECG, that normalized within 24 h, was noted in one of our patients without coronary artery diseases.

Discussion

Ibutilide is a pure class III agent that prolongs the action potential duration by slowing the inward potassium rectifier current (I_{Kr}) and by enhancing the slow inward depolarizing sodium current.^{24–26} The resultant prolonging of the atrial refractory period (ARP) organizes the microreentries circuitry of AF resulting in SR. Prolongation of the action potential duration also prolongs Q-T interval, making patients vulnerable to torsade de pointes. After intravenous infusion, ibutilide is rapidly distributed in the body and metabolized to an inactive form. The first past clearance by the liver limits its oral use. The half-life is 2 to 12 h (mean 6 h).^{20–25}

Among the class III and class I antiarrhythmic agents, ibutilide is one of the most effective agents for cardioversion, and most of the patients convert to sinus rhythm within 1 h of initiation of therapy.^{27–30} All patients should be monitored closely for 4 h, as there is a 2 to 3% risk of torsade de pointes and occasional hypotension. Among the presently available modalities of cardioversion, electrical cardioversion has a much higher success rate of about 67–94%. Apart from a very low but definite risk related to anesthesia, patients can sustain local burns, and about 2 to 3% of patients may develop bradycardia and even cardiac arrest.^{31–33} Ibutilide and other class I and class III drugs are reasonable alternatives in those patients who refuse DC treatment. Furthermore, pretreatment with ibutilide has shown to increase the conversion rate of DC cardioversion to 100%.³⁴

In this study, a small LA size and absence of MVD predicted success with ibutilide as well as the presence of CAD. Nonresponders had significantly larger left atria than did the responders (5.0 ± 0.7 vs. 4.2 ± 0.7 cm, $p < 0.05$). The mean LA size of our study was comparable with previous studies (mean 4.5 ± 0.9) and varied from 3.2 ± 1.2 to 4.3 ± 1.1 cm and 4.5 ± 0.7 to 4.6 ± 0.9 cm, respectively.^{22, 24} Patients were considered to have MVD even though it was clinically insignificant and echocardiography revealed only mild MR. Change

in atrial geometry, even by a small MR jet, may to be responsible for atrial myopathy and a substrate for the reentrant circuits or chaotic rhythm. This may set up a milieu compatible for AF and resistance to ibutilide therapy.³⁵

The precise mechanism of AF in CAD is not known. Patient with and without CAD had comparable LA size; therefore, the response rate in the presence of CAD is not influenced by concomitant atrial enlargement. Furthermore, the drug has been shown to be effective in a canine model of coronary occlusion and left ventricular dysfunction.³⁶ We, therefore, speculate that atrial myopathy due to CAD represents a different substrate than valvular heart disease, and the exact mechanism needs to be evaluated with further studies.

As contrast to one of the previous studies, presence of CHF and digoxin use was not associated with adverse response in our group.³⁷ This is because the etiology of CHF is multifactorial and the response rate in the presence of CHF varies according to the prevalence of negative predictors such as MVD or positive predictor such as CAD in the population studied. It may possibly be due to a smaller number of patients with CAD (patients post coronary artery bypass graft [CABG]) in our study group.^{38, 39} Digoxin has been shown neither to be an effective therapy for cardioversion nor to have an additive effect on electrical or chemical cardioversion. Hence it is not expected to potentiate the response of ibutilide.

Prolongation of the Q-Tc duration has no effect on ibutilide efficacy because the Q-Tc prolongation is a global reflection of ventricular repolarization and affects responders and nonconverters to the same degree. It does not reflect the prolongation of action potential duration of the atrial myocardium. We also know from previous studies^{29, 40} that the degree of QT prolongation does not correlate with pharmacologic response and represents drug effect rather than its efficacy.

The design of our study differed from previous trials of ibutilide in that we continued to observe these patients for 24 h. It was intended to avoid the possible confounding phenomenon of spontaneous conversion in the first 24 h (can be as high as 50–70%) and therefore to reduce the cost of therapy.²²

Our study identifies the selective subgroups of the patients who are likely to respond to ibutilide. The clinical and echocardiographic parameters associated with a high response rate include presence of CAD (77%), absence of MVD (82%), absence of markedly enlarged LA (67%), and absence of enlarged LA as well as absence of MVD (85%). Therefore, fewer patients with these characteristics will require DC cardioversion (15–33%) if chemical cardioversion with ibutilide is selected as first-line therapy.

Limitations of the Study

This study has several limitations. It is not a randomized placebo-controlled study, and the two treatment strategies were not directly compared clinically. All patients had AF for > 24 h, but exact time of onset (between 24 h and 3 months) could not be ascertained in a few of these patients. We had very few patients post CABG compared with previous studies.

Nevertheless, the study population is what one would expect to see in a large general hospital.

Conclusion

Ibutilide is effective and safe in acute conversion of atrial fibrillation. Most patients convert to sinus rhythm within an hour of treatment. As a therapy for acute conversion of atrial fibrillation, ibutilide is most effective in patients with CAD or in patients without MVD and/or without markedly enlarged LA.

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