

Research Article

Ibutilide for the Cardioversion of Paroxysmal Atrial Fibrillation during Radiofrequency Ablation of Supraventricular Tachycardias

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Direct current electrical cardioversion (DC-ECV) is the preferred treatment for the termination of paroxysmal atrial fibrillation (AF) that occurs during radiofrequency ablation (RFA) of supraventricular tachycardias (SVT). Intravenous Ibutilide may be an alternative option in this setting. Thirty-four out of 386 patients who underwent SVT-RFA presented paroxysmal AF during the procedure and were randomized into receiving ibutilide or DC-ECV. Ibutilide infusion successfully cardioverted 16 out of 17 patients (94%) within 17.37 ± 7.87 min. DC-ECV was successful in all patients (100%) within 17.29 ± 3.04 min. Efficacy and total time to cardioversion did not differ between the study groups. No adverse events were observed. RFA was successfully performed in 16 patients (94%) in the ibutilide arm and in all patients (100%) in the DC-ECV arm, $p = \text{NS}$. In conclusion, ibutilide is a safe and effective alternative treatment for restoring sinus rhythm in cases of paroxysmal AF complicating SVT-RFA.

1. Introduction

Radiofrequency catheter ablation (RFA) has been established as an effective treatment for supraventricular tachycardias (SVT) [1, 2]. Paroxysmal atrial fibrillation (AF) may occasionally complicate SVT-RFA, resulting in repetitive electrical cardioversions and undesirable procedure delays.

Ibutilide is a newer class III antiarrhythmic agent for the cardioversion of AF and atrial flutter [3–5]. Unlike other class III agents which block the rapid component of the delayed rectifier outward potassium channels (I_{kr}), ibutilide activates the slow inward currents (mainly sodium current). These antiarrhythmic actions result in prolongation of action potential duration and refractoriness of normal myocardial tissue [3–5] and, therefore, the termination of re-entry arrhythmias such as atrial fibrillation and atrial flutter. However, ibutilide may also result in prolongation of the QT interval and increased risk for polymorphic ventricular tachycardias [4, 6, 7]. The safety of ibutilide in terminating paroxysmal atrial fibrillation has been previously shown in various populations [8]. The effect of ibutilide in the setting

of electrophysiological testing and ablation procedures has not been adequately studied. The aim of this study was to assess the safety and efficacy of ibutilide versus direct current electrical cardioversion (DC-ECV) for the termination of paroxysmal AF complicating RFA for supraventricular tachycardias.

2. Methods

2.1. Patient Population. Over a period of 47 months, 386 patients undergoing RFA for SVT in our laboratory were screened for eligibility in the study. Eligible was considered every patient who presented new onset AF during the RFA procedure that was not self-terminating after 15 minutes. Additional inclusion criteria were sinus rhythm at the beginning of the procedure, absence of structural heart disease, ventricular rate of at least 60 beats/min, $QTc \leq 440$ msec on 12-lead electrocardiogram, hemodynamic stability (systolic blood pressure >90 mmHg), normal hepatic and renal function, no history of torsades de pointes, and no symptoms or signs of congestive heart failure or unstable angina. New

TABLE 1: Population characteristics.

	Ibutilide N = 17	DC-ECV N = 17	P value
Gender (male/female)	8/9	10/7	NS
Age (years)	46 ± 23	47 ± 22	NS
QRS duration (msec)	79 ± 7	77 ± 7	NS
QTc duration (msec)	383 ± 34	381 ± 25	NS
Heart rate (beats per minute)	74 ± 12	74 ± 9	NS
Clinical tachycardia			
AFL (isthmus-dependent)	6	6	NS
AVNRT	7	6	NS
AVRT (concealed accessory pathway)	2	3	NS
AT	2	2	NS

DC-ECV: direct current external cardioversion; AFL: atrial flutter; AVNRT: atrioventricular nodal re-entry tachycardia; AVRT: atrioventricular re-entry tachycardia; AT: atrial tachycardia; NS: nonsignificant.

onset paroxysmal AF occurred in 66 out of 386 patients (14%) either spontaneously during catheter manipulation or during the stimulation protocol and was self-terminating in 32 patients within 15 minutes from onset. The remaining 34 patients, in whom AF persisted for more than 15 minutes, met the previous additional inclusion criteria and were enrolled in the study and randomized into two groups. Group A consisted of 17 patients who received ibutilide and group B of 17 patients who received DC-ECV. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of our Institution.

2.2. Drug Infusion. All patients were over 18 years old and weighted ≥ 60 Kg. One mg of ibutilide was infused undiluted intravenously over 10 minutes under continuous electrocardiographic and blood pressure monitoring until cardioversion occurred. If cardioversion was not achieved 10 minutes after the end of the first infusion, a second dose of 1 mg was administered, until sinus rhythm was restored or the maximum dose of 2 mg was reached.

2.3. DC Cardioversion. Sedation was performed by an anesthesiologist using intravenous administration of propofol. Initial dose of propofol was 0.5–1 mg/Kg with further uptitration until adequate sedation was achieved, under continuous electrocardiographic, oxygen saturation, and blood pressure monitoring. Adequate sedation was determined by loss of response to verbal stimulus or tactile stimulus. Sedation time was recorded as the time from first injection to the time of adequate sedation. DC cardioversion was performed using a monophasic defibrillator giving a first shock of 200 joules followed by a second shock of 360 joules in case of noncardioversion.

2.4. RFA Procedure. All antiarrhythmic drugs were discontinued for >5 half-lives before the procedure except for amiodarone, which was discontinued 2 weeks before the procedure. In cases of typical atrial flutter, the cava tricuspid isthmus was targeted using standard protocol as previously described [9]. Interruption was validated with differential

pacings. For atrial tachycardia (AT) cases the site of earliest activation during tachycardia was targeted. Slow pathway ablation using anatomic criteria was used for atrioventricular nodal reentrant tachycardia (AVNRT), and the site of the shortest ventriculoatrial interval during atrioventricular reentrant tachycardia (AVRT) was primarily used for concealed pathways. A 12-lead surface electrocardiogram and bipolar intracardiac electrograms were simultaneously recorded from the high right atrium, coronary sinus, His bundle region, right ventricular apex, and left atrium (where appropriate). Electrical stimulation was performed with both atrial and ventricular overdrive and programmed extrastimulus pacing. Success of the ablation was validated as noninducibility of tachycardia.

2.5. Statistical Analysis. Continuous variables were expressed as mean value and standard deviation (mean \pm SD), and categorical variables were expressed as absolute numbers and percentages. Shapiro-Wilk test was used to check for normal distribution of data. Comparisons between groups were done with independent student's *t*-test or Mann-Whitney test for nonnormally distributed variables. Similarly, comparison of mean values at baseline and after cardioversion was performed with paired *t*-test or Wilcoxon Signed Rank test for nonnormally distributed variables. Chi-square was used for exploring differences between categorical variables. All analyses were performed using SPSS versus 16.0 for Windows (Chicago, IL, USA). A *P*-value $< .05$ was considered statistically significant.

3. Results

Patient characteristics and time intervals for cardioversion are presented in Tables 1 and 2, respectively. Ibutilide infusion (mean dose 1.35 ± 0.49 mg) cardioverted successfully 16 out of 17 patients (94%) within 17.37 ± 7.87 min. This time included time for preparation and first infusion of ibutilide (9.75 ± 0.45 min) and time from the end of first infusion until cardioversion (5.31 ± 3.38 min), plus additional time (total waiting period of 10 minutes between infusions) required for a second dose administration in

TABLE 2: Time intervals (in minutes) for each step of ibutilide or DC-ECV cardioversion.

Patient number	Group A: ibutilide					Group B: DC-ECV					
	1st infusion N = 17	Time to CV N = 17	2nd infusion N = 4	Time to CV N = 3	Total time N = 16	Patient number	Call N = 17	Preparation/ sedation N = 17	Shock/ recovery N = 17	2nd shock N = 2	Total time N = 17
Pt #1	9	4	0	0	13	Pt #1	2	7	5	5	19
Pt #2	10	6	0	0	16	Pt #2	3	8	6	0	17
Pt #3	9	3	0	0	12	Pt #3	3	8	5	0	16
Pt #4	10	3	0	0	13	Pt #4	2	9	5	0	16
Pt #5	10	6	0	0	16	Pt #5	2	9	4	0	15
Pt #6	9	2	0	0	11	Pt #6	1	8	5	0	14
Pt #7	10	1	0	0	11	Pt #7	1	8	7	0	16
Pt #8	10	9	0	0	19	Pt #8	3	10	8	0	21
Pt #9	10	3	0	0	13	Pt #9	2	8	4	0	14
Pt #10	10	10	0	0	20	Pt #10	4	9	6	0	19
Pt #11	10	3	0	0	13	Pt #11	2	12	12	5	26
Pt #12	9	3	0	0	12	Pt #12	2	9	5	0	16
Pt #13	10	2	0	0	12	Pt #13	3	9	4	0	16
Pt #14	10	10	10	3	33	Pt #14	3	9	7	0	19
Pt #15	10	10	10	2	32	Pt #15	3	7	4	0	14
Pt #16	10	10	10	—	—	Pt #16	3	8	6	0	17
Pt #17	10	10	10	2	32	Pt #17	4	8	7	0	19
Mean ±SD*	9.75 ± 0.45	5.31 ± 3.38	10.00 ± 0.0	2.33 ± 0.58	17.37 ± 7.87	Mean±SD	2.53 ± 0.87	8.59 ± 1.18	5.88 ± 2.00	5.00 ± 0.00	17.29 ± 3.04

*Group A (ibutilide) patient no. 16 is excluded from the calculation of mean time intervals because of failure to restore sinus rhythm. Total mean time did not differ significantly between groups ($P = .118$).

DC-ECV: Direct current electrical cardioversion; CV: cardioversion.

3 patients, until sinus rhythm restoration (additional time to cardioversion 2.33 ± 0.58 min). One patient, in whom sinus rhythm was not restored despite the maximum dose of ibutilide, underwent successful DC-ECV. DC-ECV (200J in 15/17 patients whereas 2/17 patients received a second shock of 360 J) was successful in all patients (100%) within 17.29 ± 3.04 min. This time included time required for the call of the anesthetist (2.53 ± 0.87 min), patient preparation and sedation (8.59 ± 1.18 min), DC shock, and recovery (5.88 ± 2.00 min), plus 5 minutes for an additional shock in 2 patients. There were no significant differences in terms of efficacy and total time to cardioversion between the two study groups ($P > .05$).

No adverse events were observed. Ibutilide infusion was associated with a small increase in QT duration (from 383 ± 34 to 406 ± 36 , $P < .001$) but no patient presented torsades de pointes. AF relapsed in one of group B patients within 10 min of initial cardioversion, and an additional 360 J shock was applied successfully. No relapse was observed in Group A patients.

The RFA procedure was completed successfully in all but one patient (this patient had atrial tachycardia which was noninducible postibutilide infusion). RFA for atrial flutter (12 out of 34 patients) was performed using anatomic criteria during coronary sinus pacing and thus inducibility was not examined. In AVRT and AVNRT cases, the clinical

tachycardias were inducible, although ibutilide slightly prolonged the atrioventricular nodal effective refractory period (AVNERP) by 15 ± 6 ms. In 2 patients with atrial tachycardia, a prolongation of the atrial effective refractory period by 46 ms and 30 ms was observed after ibutilide infusion, and atrial tachycardia was not inducible in the first patient.

4. Discussion

In this study, we showed that ibutilide and DC-ECV are equally effective and safe methods for the cardioversion of paroxysmal AF that complicates the RFA of various types of supraventricular tachycardias.

Paroxysmal AF during RFA procedure that requires cardioversion may result in undesirable delays of the procedure. DC-ECV is an efficient and safe method for the restoration of sinus rhythm in patients with paroxysmal AF [10, 11], but it requires sedation, and the immediate presence of the anesthetist is not always feasible. In our department, we observed a rather quick response of the anesthetist that kept the total time for DC cardioversion low. Time can also be saved if the DC-ECV is performed without the presence of an anesthetist by cardiologists familiar with anesthetic drugs [12]. DC cardioversion during RFA causes further delays because sometimes interference with the sterile field cannot be avoided. Moreover, DC shocks may cause displacement of

the electrophysiology catheters, resulting in further delays of the ablation procedure.

Glatter et al. [13] demonstrated that intravenous ibutilide was very effective and safe in patients with pre-excited AF including children and concluded that ibutilide could be considered as a suitable alternative to intravenous procainamide in patients with pre-excited AF. Varriale et al. [14] showed that 1 mg of ibutilide successfully terminated AF in an 81-year-old woman with Wolf-Parkinson-White syndrome. Sorbera and Cohen [15] gave ibutilide during electrophysiological study to 3 patients with AF and atrioventricular nodal re-entry tachycardia (2 with concealed pathways) to successfully terminate AF.

In our study, ibutilide infusion was associated with 94% rate of cardioversion of paroxysmal AF to sinus rhythm. The rate of successful arrhythmia termination in our study is higher than previously reported with ibutilide [4–7]. DC-ECV was also highly effective (100%) in restoring sinus rhythm. Relapse was observed in one patient who was electrically cardioverted (6% within group B). Early relapse of paroxysmal AF after successful DC-ECV has been reported to occur in up to 30% of patients [16, 17]. Our high success and low relapse rates can be explained by the fact that the arrhythmia was treated very early (within 15–20 minutes of onset). It is known that the shorter the duration of the arrhythmia is, the higher the cardioversion rate is [4, 5].

We observed no complications in both arms of treatment. Adverse events that rarely complicate DC-ECV are sedation related (hypotension, oxygen desaturation) and shock related (ventricular fibrillation, sinus pause, myocardial damage). Gallagher et al. showed that high energy shocks of >200 J lower the risk of ventricular fibrillation and are not associated with other serious complications [18]. Ibutilide infusion is associated with an incidence of sustained polymorphic ventricular tachycardias which in previous studies varied from 1.7% to 8.3% [3–6, 19]. We did not observe any adverse effects of ibutilide in this study, even though a slight prolongation of the QTc interval was noted following ibutilide infusion. Our study population consisted of apparently healthy individuals, with structurally normal hearts and a QTc interval <440 msec at baseline. Therefore, this may explain the absence of ventricular arrhythmias and other complications in both arms of treatment.

Inducibility of the clinical arrhythmia during electrophysiological study may be potentially affected by any administered drug. A small series of 12 patients with Wolf-Parkinson-White syndrome has shown that propofol when administered for sedation during electrophysiological study had no effect on the effective refractory periods of the atrioventricular node, right ventricle, and accessory pathways and did not affect arrhythmia inducibility, but caused a slight prolongation of the right atrial refractory period [20]. Ibutilide prolongs atrial and ventricular refractory periods and, thus, may affect inducibility of the clinical arrhythmia. In this study, 12 out of 34 patients were treated for isthmus-dependent atrial flutter and arrhythmia inducibility was not examined. AVNRT and AVRT were inducible in all 18 patients in both groups. Only in 1 patient with atrial tachycardia who received ibutilide, the clinical

arrhythmia was not inducible. Ibutilide may have altered the electrophysiological properties of the atrium and may have caused noninducibility of the arrhythmia. However, the design of this study and the number of different types of SVT studied do not allow robust conclusions regarding the effect of ibutilide on arrhythmia inducibility.

There are several limitations in our study. None of the included patients had abnormal heart function; thus, our findings may not apply to patients with structural heart disease who present paroxysmal AF during SVT-RFA. Another limitation is the small number of patients included. The majority of our patients were treated for atrial flutter, and arrhythmia inducibility was not examined. Due to the underrepresentation of other types of SVT, we cannot extrapolate the observed neutral effect of ibutilide on tachycardia induction to all SVT categories, especially those involving accessory pathways.

In conclusion, ibutilide may be an effective and safe alternative to DC cardioversion for the termination of paroxysmal AF complicating electrophysiological testing and radiofrequency ablation of supraventricular tachycardias in patients without structural heart disease and normal baseline QTc duration.

References

- [1] W. M. Jackman, X. Z. Wang, K. J. Friday et al., "Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current," *The New England Journal of Medicine*, vol. 324, no. 23, pp. 1605–1611, 1991.
- [2] K. H. Kuck, M. Schluter, M. Geiger, J. Siebels, and W. Duckeck, "Radiofrequency current catheter ablation of accessory atrioventricular pathways," *The Lancet*, vol. 337, no. 8757, pp. 1557–1561, 1991.
- [3] D. M. Roden, "Ibutilide and the treatment of atrial arrhythmias. A new drug—almost unheralded—is now available to US physicians," *Circulation*, vol. 94, no. 7, pp. 1499–1502, 1996.
- [4] K. A. Ellenbogen, B. S. Stambler, M. A. Wood et al., "Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: a dose-response study," *Journal of the American College of Cardiology*, vol. 28, no. 1, pp. 130–136, 1996.
- [5] B. S. Stambler, M. A. Wood, K. A. Ellenbogen, K. T. Perry, L. K. Wakefield, and J. T. VanderLugt, "Efficacy and safety of repeated intravenous doses of ibutilide for rapid conversion of atrial flutter or fibrillation," *Circulation*, vol. 94, no. 7, pp. 1613–1621, 1996.
- [6] H. Oral, J. J. Souza, G. F. Michaud et al., "Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment," *The New England Journal of Medicine*, vol. 340, no. 24, pp. 1849–1854, 1999.
- [7] J. T. VanderLugt, T. Mattioni, S. Denker et al., "Efficacy and safety of ibutilide fumarate for the conversion of atrial arrhythmias after cardiac surgery," *Circulation*, vol. 100, no. 4, pp. 369–375, 1999.
- [8] M. Nair, L. K. George, and S. K. Koshy, "Safety and efficacy of ibutilide in cardioversion of atrial flutter and fibrillation," *The Journal of the American Board of Family Medicine*, vol. 24, no. 1, pp. 86–92, 2011.
- [9] C. T. Tai and S. A. Chen, "Cavotricuspid isthmus: anatomy, electrophysiology, and long-term outcome of radiofrequency

- ablation," *Pacing and Clinical Electrophysiology*, vol. 32, no. 12, pp. 1591–1595, 2009.
- [10] S. Levy, P. Lauribe, E. Dolla et al., "A randomized comparison of external and internal cardioversion of chronic atrial fibrillation," *Circulation*, vol. 86, no. 5, pp. 1415–1420, 1992.
- [11] S. Levy, P. Ricard, M. Gueunoun et al., "Low-energy cardioversion of spontaneous atrial fibrillation immediate and long-term results," *Circulation*, vol. 96, no. 1, pp. 253–259, 1997.
- [12] G. Morani, C. Bergamini, C. Angheben et al., "General anaesthesia for external electrical cardioversion of atrial fibrillation: experience of an exclusively cardiological procedural management," *Europace*, vol. 12, no. 11, pp. 1558–1563, 2010.
- [13] K. A. Glatter, P. C. Dorostkar, Y. Yang et al., "Electrophysiological effects of ibutilide in patients with accessory pathways," *Circulation*, vol. 104, no. 16, pp. 1933–1939, 2001.
- [14] P. Varriale, A. Sedighi, and M. Mirzaietehrane, "Ibutilide for termination of atrial fibrillation in the Wolff-Parkinson-White syndrome," *Pacing and Clinical Electrophysiology*, vol. 22, no. 8, pp. 1267–1269, 1999.
- [15] C. Sorbera and M. Cohen, "The effect of ibutilide on retrograde accessory pathway conduction," *Pacing and Clinical Electrophysiology*, vol. 23, no. 2, pp. 220–223, 2000.
- [16] I. C. Van Gelder, H. J. Crijns, W. H. Van Gilst, R. Verwer, and K. I. Lie, "Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter," *The American Journal of Cardiology*, vol. 68, no. 1, pp. 41–46, 1991.
- [17] W. C. Yu, Y. K. Lin, C. T. Tai et al., "Early recurrence of atrial fibrillation after external cardioversion," *Pacing and Clinical Electrophysiology*, vol. 22, no. 11, pp. 1614–1619, 1999.
- [18] M. M. Gallagher, Y. G. Yap, M. Padula, D. E. Ward, E. Rowland, and A. J. Camm, "Arrhythmic complications of electrical cardioversion: relationship to shock energy," *International Journal of Cardiology*, vol. 123, no. 3, pp. 307–312, 2008.
- [19] P. R. Kowey, J. T. VanderLugt, and J. R. Luderer, "Safety and risk/benefit analysis of ibutilide for acute conversion of atrial fibrillation/flutter," *The American Journal of Cardiology*, vol. 78, no. 8A, pp. 46–52, 1996.
- [20] M. D. Sharpe, W. B. Dobkowski, J. M. Murkin, G. Klein, and R. Yee, "Propofol has no direct effect on sinoatrial node function or on normal atrioventricular and accessory pathway conduction in Wolf-Parkinson-White syndrome during alfentanil/midazolam anesthesia," *Anesthesiology*, vol. 82, no. 4, pp. 888–895, 1995.