Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation

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Abstract

Objective—To compare the efficacy and safety of a single dose of ibutilide, a new class III antiarrhythmic drug, with that of DL-sotalol in terminating chronic atrial fibrillation or flutter in haemodynamically stable patients.

Design—Double blind, randomised study. **Setting**—43 European hospitals.

Patients—308 patients (mean age 60 years, 70% men, 48% with heart disease) with sustained atrial fibrillation (n = 251) or atrial flutter (n = 57) (duration three hours to 45 days) were randomised to three groups to receive a 10 minute infusion of 1 mg ibutilide (n = 99), 2 mg ibutilide (n = 106), or 1.5 mg/kg DL-sotalol (n = 103). Infusion was discontinued at termination of the arrhythmia.

Main outcome measure—Successful conversion of atrial fibrillation or flutter, defined as termination of arrhythmia within one hour of treatment.

Results—Both drugs were more effective against atrial flutter than against atrial fibrillation. Ibutilide was superior to DL-sotalol for treating atrial flutter (70% and 56% v 19%), while the high dose of ibutilide was more effective for treating atrial fibrillation than DL-sotalol (44% v 11%) and the lower dose of ibutilide (44% v 20%, p < 0.01). The mean (SD) time to arrhythmia termination was 13 (7) minutes with 2 mg ibutilide, 19 (15) minutes with 1 mg ibutilide, and 25 (17) minutes with DL-sotalol. In all patients, the duration of arrhythmia before treatment was a predictor of arrhythmia termination, although this was less obvious in the group that received 2 mg ibutilide. This dose converted almost 48% of atrial fibrillation that was present for more than 30 days. Concomitant use of digitalis or nifedipine and prolongation of the QTc interval were not predictive of arrhythmia termination. Bradycardia (6.5%) and hypotension (3.7%) were more common side effects with DL-sotalol. Of 211 patients given ibutilide, two (0.9%) who received the higher dose developed polymorphic ventricular tachycardia, one of whom required direct current cardioversion.

Conclusion—Ibutilide (given in 1 or 2 mg doses over 10 minutes) is highly effective for rapidly terminating persistent atrial fibrillation or atrial flutter. This new class

III drug, under monitored conditions, is a potential alternative to currently available cardioversion options.

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Keywords: atrial fibrillation; atrial flutter; antiarrhythmic agents; ibutilide; sotalol

Atrial fibrillation and atrial flutter are the most frequently occurring tachycardias in man: prevalence is estimated to be 0.4% for atrial fibrillation and 0.1% for atrial flutter,¹⁻³ and they may increase to 4% in people older than 60 years. Treatment for acute conversion of these arrhythmias consists of antiarrhythmic drugs or electrical cardioversion, or both.

The basic electrophysiological mechanism thought to be responsible for atrial flutter and fibrillation is that of re-entry, with atrial fibrillation being caused by multiple independent re-entry wavelets, and atrial flutter by one large circuit often located within the right atrium.¹⁻⁵ In both instances prolongation of the wavelength^{4,5} (the product of conduction velocity of the impulse and the refractory period) may cause conversion from atrial arrhythmia to sinus rhythm. On the basis of this principle class III antiarrhythmic agents, which increase duration of the action potential and the refractory period of atrial muscle without having much influence on conduction velocity, may help to restore sinus rhythm in patients with atrial flutter and fibrillation.⁶⁻¹² The precise electrophysiological mechanism by which class III agents exert their beneficial effect remains speculative.

Ibutilide fumarate (U-70226E) is a new class III agent for acute conversion of atrial flutter and fibrillation that has recently been introduced in the US.¹³⁻¹⁷ Introduction in Europe will take place throughout 1998. Preclinical animal studies have shown that ibutilide prolongs duration of the action potential and the effective refractory period of the atrium and ventricle, thereby preventing and suppressing (the induction of) atrial and ventricular arrhythmias.¹⁸⁻²¹ Ibutilide is available only as an intravenous preparation because of poor bio-availability caused by a large first pass effect during oral administration.

DL-sotalol combines class III antiarrhythmic activity with β adrenoceptor blocking action and is available in many countries as an intravenous formulation. Because it is widely

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Table 1 Number of evaluable patients

Arrhythmia	Ibutilide fumarate		DL-Sotalol	Total
	1 mg	2 mg		
Atrial flutter	16	20	21	57
Atrial fibrillation	83	86	82	251

used for the treatment of atrial arrhythmias in Europe,^{11 12} this drug was chosen as a comparator.

The European multicentre study reported here compares the safety and efficacy of intravenous ibutilide with that of intravenous DL-sotalol in the acute termination of sustained atrial flutter or fibrillation.

Methods

STUDY DESIGN

This multicentre trial was a prospective, double blind, randomised, parallel group comparison of two doses of ibutilide with a single dose of DL-sotalol in haemodynamically stable patients who had recent onset sustained atrial flutter or fibrillation. Recent onset was defined as continuous atrial flutter or fibrillation for longer than three hours but less than 45 days. All centres obtained ethics committee approval and all patients gave informed consent—319 patients were treated at 40 different sites.

The protocol intended to enrol 300 patients equally distributed between the two arrhythmia groups. This objective was not achieved, however, because of the slow recruitment of patients with flutter. A total of 300 patients with both arrhythmias was estimated to detect a difference of 17% between both doses of ibutilide combined and DL-sotalol, or 20% between one dose of ibutilide and DL-sotalol ($p < 0.05$, power 80%).

ELIGIBILITY CRITERIA

Patients older than 18 years with recent onset sustained atrial flutter or fibrillation were eligible when they: were haemodynamically stable (systolic blood pressure > 90 mm Hg and diastolic blood pressure < 105 mm Hg); had a normal serum potassium concentration (≥ 4 mEq/l); had a ventricular rate of > 60 beats/min; and had a rate corrected QT interval of no more than 440 ms in their 12 lead electrocardiogram (ECG). Patients with hyperthyroidism, or with a history or evidence of unstable angina pectoris, bronchospastic

disease, myocardial infarction or cardiac surgery within the previous 30 days, known sinus node dysfunction, second or third degree atrioventricular (AV) block, bundle branch block, Wolff-Parkinson-White syndrome and/or torsade de pointes were not included.

Concurrent treatment with verapamil, diltiazem, or drugs that prolong the QT interval was not allowed. Treatment with class I or III antiarrhythmic agents or with β adrenoceptor blocking agents was discontinued for more than five half lives before enrolment. Anticoagulation was the responsibility of the investigators.

The following information was collected to identify eligible patients: medical history (including earlier episodes of atrial fibrillation or atrial flutter and treatment, and time of onset of the current arrhythmic episode), physical examination (including blood pressure), 12 lead ECG, and laboratory evaluation (including digitalis concentrations).

STUDY MEDICATION

Patients were randomised to receive 1 mg ibutilide, 2 mg ibutilide, or 1.5 mg/kg DL-sotalol. Drugs were prepared in ampules of 25 ml of which 20 ml was given as a single 10 minute intravenous infusion using a similar infusion rate. Blinding was maintained by the drug being prepared by an individual not responsible for making assessments. Patients with atrial flutter and fibrillation were separately randomised to one of the treatment modes.

OBSERVATIONS AND EVALUATIONS

At least 15 minutes before administration of the drug, continuous ECG monitoring was started and continued until seven hours had passed after the start of drug infusion. A Holter recording was made during an additional 24 hours if conversion to sinus rhythm occurred. ECGs were recorded at 30 minutes, and one and seven hours (for patients who were successfully treated) after the start of infusion. The haemodynamic status of the patient was regularly checked by measuring heart rate and blood pressure every five minutes for 15 minutes before the end of infusion, and at 10 minute intervals for 50 minutes and then hourly for seven hours. Blood and urine were collected before drug infusion and seven hours later for routine safety laboratory evaluations of haematological and biochemical variables. This seven hour observation period was selected arbitrarily on the basis that side effects have been reported to occur within this period, and it was convenient in the daily logistics of the hospital.

Administration of the drug was stopped if: atrial flutter or fibrillation terminated; systolic blood pressure decreased to < 90 mm Hg; haemodynamic instability occurred because of rhythm changes; bundle branch block occurred; QRS duration was prolonged by more than 50%; the QTc interval exceeded 600 ms; new or repetitive forms of ventricular extrasystoles were noted; signs of bronchospasm occurred; if any other adverse effect was seen

Table 2 Demographic and baseline characteristics

	Ibutilide		Sotalol (n = 108)
	1 mg (n = 102)	2 mg (n = 109)	
Mean age (years)	61.9	59.5	59.2
Range	21–83	22–89	24–85
Mean weight (kg)	80.7	81.3	81.7
Range	45–119	55–120	49–120
Sex			
Female	31 (30.4%)	38 (34.9%)	27 (25%)
Male	71 (69.6%)	71 (65.1%)	81 (75%)
Median duration of arrhythmia (days)	16.0	5.4	7.2
Range	0.5–67.6	0.3–90.7	0.5–83.4
Concomitant digoxin	39 (38.2%)	43 (39.4%)	33 (30.6%)
Concomitant nifedipine	13 (12.7%)	4 (3.7%)	13 (12%)
History of heart disease	52 (51%)	46 (42.2%)	54 (50%)

Figure 1 Comparison of conversion rates induced by the two doses of ibutilide and sotalol in patients with atrial flutter and fibrillation. Numbers are total number of patients entered into each group. * $p < 0.05$ compared with sotalol; † $p < 0.05$ compared with 1 mg ibutilide.

and regarded by the investigator as detrimental to the patient's health.

Patients in whom the arrhythmia stopped and no new arrhythmias developed were discharged from hospital seven hours after the start of drug treatment with a Holter device. Patients in whom arrhythmias recurred or new ones developed after treatment were kept in hospital.

If the arrhythmia was not stopped within the one hour observation period the patient could be treated as desired by the investigator, with the suggestion that no other antiarrhythmic agents be given until at least four hours after infusion.

Medical events were recorded while patients were in hospital. They were contacted by telephone 72 hours after the start of infusion to record any additional medical events.

DATA ANALYSIS

The main end point was termination of the atrial arrhythmia for any period of time up to one hour after the start of infusion. This was assessed on the basis of the judgment of the investigator, while separate analysis from the ECG (Holter) was used for confirmation. To obtain an estimate of clinical usefulness, time to arrhythmia termination and time without atrial flutter or fibrillation were also recorded during the 31 hour observation period. QTc measurements were made from 12 lead ECGs.

During ECG monitoring (for seven hours after the start of infusion) the occurrence and

incidence of ventricular arrhythmias were determined and confirmed from the Holter tapes.

Medical events were listed in relation to individual patients and study medication.

STATISTICS

The statistical package used was release 6.08 of SAS (Statistical Analysis Software). All statistical tests were two sided, $p < 0.05$ was considered significant. Chi squared tests were applied for group comparisons of the main end point.

Relations among response (conversion *v* non-conversion), ibutilide dose, and selected predictor variables (duration of arrhythmia, use of digitalis or calcium channel blockers during the 24 hour period before infusion) were investigated separately for each predictor variable using a logistic regression analysis with a response variable of conversion (yes/no), explanatory variables of dose and each individual predictor variable, and an interaction term dose by predictor variable. The test for interaction was significant if it generated $p \leq 0.10$. If the test for interaction was non-significant ($p > 0.10$), the interaction term was eliminated from the model and a logistic regression analysis was used to analyse the relation between a response variable of conversion and explanatory variables dose and individual predictor variable.

Comparison between results obtained from reported conversions and those on Holter tapes was made by Pearson's contingency coefficient. Medical events were compared between treatment groups using a χ^2 test for homogeneity of proportions. Demographic and pretreatment characteristics were compared in each group by analysis of variance (ANOVA) for age, height, and weight, and χ^2 tests for race, sex, and variables from medical histories. QTc prolongation was compared in patients who converted and those who did not in the different treatment groups by one way ANOVA.

Results

Eleven of 319 patients who enrolled in the study were excluded: nine had arrhythmia for more than 45 days and two received incorrect dosage of the study medication because of a misinterpretation by an investigator. Holter tapes were obtained in 281 of the 319 patients. Therefore, 308 patients were evaluated for efficacy: 99 patients received 1 mg ibutilide, 106 patients 2 mg ibutilide, and 103 patients 1.5 mg/kg DL-sotalol (table 1).

The three treatment groups (considering all patients) were similar in age and weight. Thirty per cent of patients were women and 96% were white (table 2). They were similar with respect to medical history, physical examination variables, concomitant medication, duration of arrhythmia, and heart disease (table 2). There was no evidence for toxic concentrations of digitalis.

The screening ECG was taken on the same day as the infusion in 279 patients. A mixed fibrillation/flutter was diagnosed in 12 patients.

Table 3 Logistic regression analysis for duration of arrhythmias in evaluable patients ($n = 308$)

Variable	Coefficient	SE coefficient	p value
<i>With interaction term included</i>			
Medication	0.7382	0.2186	0.0007
Duration	-0.0612	0.0232	0.0082
Medication by duration	0.0233	0.0142	0.1017
<i>Without interaction term included</i>			
Medication	0.9765	0.1741	0.0001
Duration	-0.0281	0.0093	0.0024

SE, standard error.

Figure 2 Successful conversion rates of atrial flutter and fibrillation for the two doses of ibutilide and sotalol in relation to duration of the arrhythmia.

EFFICACY

Figure 1 shows overall success rates in evaluated patients. The higher dose of ibutilide (2 mg) was superior to DL-sotalol in both atrial flutter and fibrillation, and 2 mg ibutilide was statistically more effective than 1 mg ibutilide in atrial fibrillation ($p < 0.01$) but not in atrial flutter ($p < 0.4$). The lower dose of ibutilide was superior to DL-sotalol in terminating atrial flutter ($p < 0.05$) but not atrial fibrillation. Both doses of ibutilide were more effective against atrial flutter (56% for 1 mg ibutilide and 70% for 2 mg) than atrial fibrillation (20% and 44%, respectively).

Interpretation of overall efficacy rates as assessed by the investigators from 12 lead and monitoring ECGs versus Holter analysis showed good agreement (94%).

Logistic regression analysis indicated that there was a significant relation between duration of the arrhythmia and success of drug treatment (table 3). The mean duration of the arrhythmia was 11 days for patients who were successfully treated compared with 17 days for patients in whom treatment failed. The presence of marginally significant interaction effects, however, suggests the possible differential degrees of association between duration and conversion for the three treatment groups. There is also the suggestion that patients with longer lasting atrial flutter or fibrillation, or both (31–45 days), may require higher doses of ibutilide for conversion (fig 2). For such patients the 2 mg ibutilide dose becomes more

effective than 1 mg and reverses the trend that longer duration of atrial fibrillation decreases the success rate of drugs.

QTc prolongation occurred with all drugs 30 minutes, and one and seven hours after infusion. Comparison of the magnitude of QTc prolongation in patients in whom treatment was either successful or failed showed no significant differences between the groups. Successful conversion rates in the two ibutilide groups were not associated with the use of digoxin or nifedipine.

TIME TO TERMINATION AND DURATION OF THE ARRHYTHMIA FREE PERIOD

The mean time to termination of the arrhythmia was shortest after treatment with 2 mg ibutilide (table 4). This finding seemed to be independent of the type of arrhythmia, but reached significance only for the overall group. However, both doses of ibutilide achieved faster termination of the arrhythmia than DL-sotalol ($p < 0.05$) in the atrial fibrillation group.

The arrhythmia terminated within 20 minutes after the start of infusion in 83% (65/78) of patients who were successfully treated with ibutilide.

From the Holter recordings (about 31 hours) it was noted that most patients (66 of 76) remained free from their arrhythmia during follow up. There was no difference in success among the three treatment groups at the end of the 31 hour observation period.

PROARRHYTHMIC ACTIVITY

Ventricular extrasystoles were reported by investigators in 6% of patients who received 1 mg ibutilide, 9% in those given 2 mg ibutilide, and 2% in those given DL-sotalol (table 5). These findings did not reach significance in a group comparison ($p = 0.065$).

Drug related ventricular tachycardias (VTs) were reported during treatment in 19 of 319 patients. Table 5 shows the incidence of non-sustained or sustained, monomorphic or polymorphic VTs as indicated by the investigators. Four VTs are listed as a serious medical event. One patient with reported sustained polymorphic VT needed treatment with cardioversion. Figure 3 shows the onset of polymorphic VT in this patient, VT clearly occurred during atrial fibrillation and not after conversion to sinus rhythm. In the ibutilide group, all these proarrhythmic responses occurred within the one hour observation period. As shown in fig 3 the occurrence of arrhythmias was not restricted to patients who were successfully converted.

Eighteen of the 19 arrhythmias were confirmed on the Holter tapes but only three of the 16 reviewed were considered by four independent cardiologists to be true VTs after assessment of the tapes, the other episodes were interpreted as being very suggestive of aberrant conduction of a supraventricular rhythm. The magnitude of QTc changes was not predictive of torsade de pointes arrhythmias.

Table 4 Mean time (in minutes) to successful termination of atrial arrhythmia

Arrhythmia	Ibutilide		Sotalol	p value
	1 mg	2 mg		
Atrial flutter (n = 27)				
Mean (SD)	23 (11)	15 (8)	19 (4)	0.0833
Median	21	14	19	
Atrial fibrillation (n = 64)				
Mean (SD)	17 (17)†	12 (7)†	27 (20)	0.0049
Median	11	12	20	
All (n = 91)				
Mean (SD)	19 (15)	13 (7)*†	25 (17)	0.0017
Median	13	12	20	

*Significantly different from 1 mg ibutilide ($p \leq 0.05$); †significantly different from sotalol ($p \leq 0.05$); ANOVA.

Figure 3 Onset of the single sustained polymorphic ventricular tachycardia that required electrocardioversion from the Holter recording occurring 11 minutes after the start of 2 mg ibutilide infusion. Note that a longer RR interval and a prolonged QT interval precede the ventricular arrhythmia.

OTHER MEDICAL EVENTS AFTER TREATMENT

Reported medical events that were judged by investigators to be related to the study drug were primarily from the cardiovascular system. These were equally distributed across the treatment groups. Adverse effects of DL-sotalol specifically related to its β adrenergic blocking activities and included bradycardia (6.5% of patients) and hypotension (3.7%). Ibutilide had no adverse effects on heart rate or blood pressure, or on routine haematological or biochemical tests.

Serious medical events were listed in a total of 10 patients treated with ibutilide and in five treated with DL-sotalol. Four ibutilide events were proarrhythmic responses (see earlier).

Infusion of study medication was stopped prematurely in five patients: in three patients it was listed as a serious medical event because of complete AV block (sotalol), bundle branch block (1 mg ibutilide), or serious ECG abnormalities (heart rate > 200 beats/min caused by a more rapid AV nodal conduction) with severe hypotension (1 mg ibutilide); QTc in the other two patients who received 2 mg ibutilide exceeded 600 ms but no proarrhythmic events developed. Further serious medical events, all witnessed once, were seen in four patients who received 2 mg ibutilide, namely junctional bradycardia and a vasovagal reaction with severe hypotension, and in four who received DL-sotalol, namely bradycardia with hypotension.

The events judged not to be related to treatment were endocarditis and dyspnoea in patients given 2 mg ibutilide, and left heart failure and ventricular fibrillation in those given DL-sotalol.

Discussion

Ibutilide and DL-sotalol are methanesulphonides with class III electrophysiological and antiarrhythmic effects.^{12–21} Unlike DL-sotalol, ibutilide does not have β blocking activity at the doses used in this study. In canine studies, ibutilide was effective against atrial flutter (0.006 mg/kg),^{19–21} atrial fibrillation (0.150 mg/kg),²⁰ and the subacute phase of ventricular tachycardias (0.030 mg/kg) after myocardial infarction.¹⁸ The exact mode of action of ibutilide is a matter of discussion.¹⁶ Activation of a slow (Na^+) inward current,¹³ blockade of I_{Kr} ,^{14,15} and/or additional or combined effects¹⁵ may explain the class III effect. In contrast, activation of an outward potassium current at higher dosages may explain self limitation in prolongation of the cardiac action potential.¹³ Ibutilide has not been shown to produce important haemodynamic changes at doses of less than 3 mg/kg. Comparative studies in animals involving single cell preparations and models of ischaemia have shown that ibutilide is about 100 times more effective than DL-sotalol in prolonging action potential duration. Therefore dosages of the two compounds used in this study are considered comparable in terms of their electrophysiological activities. The dosage of DL-sotalol used here is commonly advised in Europe for the treatment of supraventricular arrhythmias,^{11,12} because it gives optimal success rates, while higher dosages are associated with adverse haemodynamic effects and increase the risk of proarrhythmic reactions.

In phase I studies, up to 0.030 mg/kg ibutilide was given by a 10 minute intravenous infusion. A dose dependent effect was seen, with a maximum near the end of the infusion time with a mean rate corrected QT interval prolongation of 18% (0.01 mg/kg) to 43% (0.03 mg/kg). QTc returned to baseline after a maximum of four hours, depending on the dose. Before the present study, 375 patients were treated with ibutilide for conversion of atrial flutter or fibrillation with a duration of up to a maximum of 90 days (placebo controlled studies and one comparative study with procainamide).^{22–25} Ellenbogen *et al*,²⁴ in a study

Table 5 Incidence and type of drug related ventricular arrhythmia in all patients

Ventricular arrhythmia	Ibutilide		Sotalol (n = 108)
	1 mg (n = 102)	2 mg (n = 109)	
Ventricular extrasystoles*	5.9%	9.2%	1.9%
Non-sustained monomorphic VT	4.9%	7.3%	3.7%
Non-sustained polymorphic VT	–	0.9%	–
Sustained polymorphic VT	–	0.9%	–

*Includes isolated ventricular extrasystoles, couplets, and triplets.
VT, ventricular tachycardia.

with 200 patients reported an overall success rate of 47.5% at a dose of 0.025 mg/kg, as compared with 2.4% in the placebo group. Success was higher in the atrial flutter group (58% *v* 40%). The median time to conversion was 10–23 minutes, while in 70% of successfully treated patients, termination occurred within 20 minutes. In a second study,²⁵ 266 patients were randomised to receive up to two 10 minute infusions of ibutilide (1 and 0.5 mg or 1 and 1 mg) or placebo. Ibutilide was superior to placebo in converting both atrial arrhythmias and more effective for atrial flutter (56% after two infusions) than for atrial fibrillation (31%). Two dosages of ibutilide were chosen in this study to evaluate further the optimal dose. Ibutilide was administered as a fixed dose rather than corrected for body weight to accommodate the physician in daily practice. Body weight was similar in the groups (> 80 kg, table 2) so that the dosages of ibutilide amounted to 0.0125 mg/kg for the 1 mg dose and to 0.025 mg/kg for the 2 mg dose.

The outcome of our study is in accordance with the findings that 2 mg ibutilide is more effective against atrial flutter (70%) than atrial fibrillation (44%), and when effective, ibutilide rapidly converts the arrhythmia (in 83% of patients within 20 minutes). Efficacy seems to be dose dependent, especially with regard to atrial fibrillation. Interestingly, the reported decreased efficacy of antiarrhythmic drugs to convert long standing atrial arrhythmias was not seen in patients given 2 mg ibutilide. Almost 48% of the total number of arrhythmias present for 31–45 days were converted with 2 mg ibutilide. This important finding needs to be confirmed by additional studies.

In addition, the present study provides evidence that ibutilide is more effective than DL-sotalol in converting these atrial arrhythmias. In other clinical studies, DL-sotalol (0.4–1.5 mg/kg) converted 47 of 106 (46%) episodes of supraventricular tachycardias or paroxysmal atrial fibrillation in seven open trials.^{11–12} The exact values from these studies were between 25% and 60% and seemed to depend on the dose of sotalol (higher doses producing greater effects with a maximum at approximately 1.5 mg/kg) and perhaps infusion time.^{11–12} It was decided therefore that the recommended dose of 1.5 mg/kg sotalol should be used in the present study (approximating to a unit dose of 100 mg), while infusion should be preferred to a single bolus dose. In contrast to the treatment of atrial fibrillation, DL-sotalol seems to be rather ineffective against atrial flutter.^{6–11–12} In our study, the efficacy of DL-sotalol to convert atrial fibrillation was low (11%) compared with that reported in the literature, however a study by Sung *et al* reported similar values.²⁶

As a placebo group was not used here we are unable to account for spontaneous termination of atrial fibrillation or flutter. This has been reported to be as high as 40% in patients with atrial fibrillation of less than 48 hours duration.²⁷

For future applications, we suggest that a first dose of 1 mg ibutilide should be adminis-

tered over a 10 minute period. If this dose fails to convert the arrhythmia within 10 minutes after the end of infusion, then a second 10 minute infusion of equal strength may be administered.²⁵

Another new class III agent (dofetilide) showed an overall efficacy rate of 53% for converting atrial fibrillation to sinus rhythm, whereas the conversion rate for atrial flutter was 80%.⁹ In more recent studies similar results have been reported for atrial flutter (75% and 54%, respectively) but much less efficacy was shown for atrial fibrillation (22% and 15%) using 0.008 mg/kg dofetilide.^{28–29}

The higher conversion rates of the newer class III drugs (ibutilide and dofetilide) in the treatment of atrial flutter compared with those in the treatment of atrial fibrillation can be explained by the wavelength theory. Atrial flutter is a stable re-entrant process in which lengthening of the refractory period leads to prolongation of the wavelength. Whether the wavelength concept is also useful to explain drug efficacy in atrial fibrillation has recently been questioned. In a goat study by Wijffels and coworkers³⁰ termination of atrial fibrillation by drugs could not be predicted by their effect on the wavelength. Rather, they showed that all drugs (classes I and III) progressively widen the excitable gap during atrial fibrillation. A different effect on this variable may explain the higher efficacy of ibutilide over DL-sotalol in terminating this arrhythmia.

Class I drugs are also used intravenously to treat atrial fibrillation or flutter. In a series of studies (patient numbers ranging from 10 to 52), the overall efficacy of flecainide (up to 2 mg/kg/10 min) for restoring sinus rhythm was between 65% and 90% in patients with paroxysmal atrial fibrillation.^{6–8–10} The overall conversion rate in patients with atrial flutter varies between 0% and 40%.^{6–10} In a study similar to the present one Stambler *et al* recently showed that ibutilide is superior to procainamide.²²

Duration of the arrhythmia seems to be a major determinant for successful termination. When paroxysmal atrial fibrillation was present for more than 24 hours then success rates with administration of flecainide dropped dramatically from 86% to 40%.⁶ Recent animal and human data may explain this finding and our observations on the basis of altered electrophysiological behaviour caused by chronic atrial fibrillation.^{30–32} These observations have changed the treatment of atrial fibrillation. Many electrophysiologists no longer consider this condition to be a relatively benign disease and now elect to treat this arrhythmia more aggressively.

Several proarrhythmic events have been reported in previous studies using class III antiarrhythmic drugs,^{12–33–34} ranging from conduction disturbances and extrasystoles to the most important one the occurrence of torsade de pointes. Several comparative studies in a rabbit model of torsade de pointes have been performed to assess the proarrhythmic potential of this class of drugs.^{35–36} Different results have been reported, but the important message

is that each drug tested can have proarrhythmic effects. The incidence of these events with DL-sotalol is 1–5%.¹² Of a total of 586 patients treated with ibutilide (including this study), the incidence of sustained polymorphic VT requiring electrical cardioversion was 1.7% and of non-sustained polymorphic VT 2.7% (a combined total of 4.3%). These episodes occurred within 30 minutes after the start of infusion. In addition, non-sustained monomorphic VT was seen in 4.9% of patients. Most proarrhythmic events in this study occurred when the atrial arrhythmia was still present and not directly after successful pharmacological cardioversion to sinus rhythm (as shown in fig 3).

It can be concluded that ibutilide is more effective than DL-sotalol in rapidly terminating atrial fibrillation and atrial flutter with a similar safety profile. Our observation that long standing atrial fibrillation can be converted by ibutilide merits further study.

Appendix

Participants in the Ibutilide/Sotalol Comparator Group—P L M Bernink (Martini Ziekenhuis Lokatie van Ketwich, Groningen, Netherlands); P Blomström (University Hospital, Uppsala, Sweden); P Bloomfield and H Oxenham (Royal Infirmary, Edinburgh, United Kingdom); J Brachmann (Medical University-Klinik Innere, Heidelberg, Germany); Brembilla-Perrot (Cardiologie A Hôpital d'adultes, Vandoeuvre les Nancy, France); C Brohet (Hôpital Saint-Luc Bruxelles, Bruxelles, Belgium); Brugada Terradellas (José, Hospital Clínico I Provincial de Barcelona, Barcelona, Spain); Chauvin (Centre Médico Chirurgical et Obstétrical, Strasbourg, France); H J G M Crijns (University Hospital, Groningen, Netherlands); H J Dargie (Western Infirmary, Glasgow, United Kingdom); F Dateling (Johannesburg Hospital, Parktown, South Africa); N Edvardsson (Sahlgrens Hospital, Gothenburg, Sweden); Fauchier (Hôpital Trousseau, Tours Cedex, France); S P Golitsyn (Cardiology Research Centre, Moscow, Russia); R Gomes (Seabra, Hospital de Santa Cruz, Linda-a-Velha, Portugal); A K Gruzdev (Central Clinical Hospital of the Medical Centre of the Russian Federation Government, Moscow, Russia); R Haberl (Klinikum Groschadern der University of Munich, Munich, Germany); R Henßge (Medical Academy Carl Gustav Carus, Dresden, Germany); G Jackson, Guy's Hospital, London, United Kingdom; P Jordaen (University O F S, Bloemfontein, South Africa); L Jordaens (University Hospital, Ghent, Belgium); V Kühlkamp (Med-Uni-Klinik u polikl, Tübingen, Germany); H Kulbertus (Universitaire CIIR Surt Tilman, Liege, Belgium); Mehmel Staedt (Klinikum Karlsruhe, Karlsruhe, Germany); A Moya Mitjan (Hospital Vall Hebron, Barcelona, Spain); M J Nagelsmit (Scheperziekenhuis, Emmen, Netherlands); H Queißer (Städt Krankenhaus Neustadt, Dresden-Neustadt, Germany); Reichenmiller (Marienhospital, Stuttgart, Germany); Richter (Klinikum Nord, Nürnberg, Germany); M Y Ruda (Cardiology Research Centre, Moscow, Russia); M J Schali (University Hospital Leiden, Leiden, Netherlands); A Schmidt (Karl Olga Krankenhaus, Stuttgart, Germany); P Smith (Dr Are Normann Medicinsk Avd Baerum SjukhusBaerum, Norway); C Sonnhag (University Hospital, Linköping, Sweden); K Stangl (Humboldt-Uni, Berlin, Germany); J Stephens (Oldchurch Hospital, Romford, United Kingdom); M R van der Linde (Protestant Ziekenhuis, Drachten, Netherlands); J S van Os (Ziekenhuis de Tjongerschans, Heerenveen, Netherlands); L M van Wijk (St Chr Ziekenhuis Refaja, Stadskanaal, Netherlands); J H J Weich (R S Blake, Tygerberg Hospital University Stellenbosh, South Africa); H J J Wellens (Academic Hospital, Maastricht, Netherlands); E Wunderlich (Städt Klinikum, Dresden Freidrichstadt, Germany); and S Yuan and B Olsson (University Hospital, Lund, Sweden).

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