Clinical research

Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset

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Aims This study compared the efficacy and safety of intravenous flecainide and ibutilide for immediate cardioversion of atrial fibrillation (AF).

Methods and results We conducted a prospective, randomised trial, including 207 patients with AF of recent onset (≤ 48 h). Flecainide was given over 20 min at a dose of 2 mg/kg body weight (maximum 200 mg), ibutilide was infused at a dose of 1 mg (or 0.01 mg/kg if less than 60 kg) over 10 min, followed by a 10 min observation period and an identical second dose if AF did not convert to sinus rhythm (SR). Treatment was considered successful if SR occurred within 90 min of starting medication. The conversion rates were 56.4% in patients given flecainide and 50.0% in patients given ibutilide (P = 0.34). Multivariate analysis revealed that a lower age for women independently increased the probability of conversion. None of the other variables, including left atrial size, left ventricular systolic function, presence of left ventricular hypertrophy, plasma levels of potassium or magnesium at baseline, or concomitant use of digoxin, beta-blocker, diltiazem or verapamil were predictors of conversion. The frequency of adverse events was comparable in the two treatment groups.

Conclusions There was no significant difference in the cardioversion efficacy or in the risk of adverse events between flecainide and ibutilide in patients with AF of recent onset. In patients without contraindications to both medications, the physician’s choice has to be governed by other factors.

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Introduction

Pharmacological cardioversion of atrial fibrillation (AF) is an attractive option if the arrhythmia is of recent onset.
Both flecainide \(^1\) and ibutilide \(^9\) have a suitable performance profile due to their relatively high efficacy and good tolerability in this setting. However, no direct comparison between a class I-C drug like flecainide and a pure class III drug like ibutilide has yet been performed. Thus, the purpose of this prospective, randomised, single-blind, multi-centre trial was to compare the efficacy and safety of flecainide and ibutilide for immediate conversion of AF.

### Methods

#### Study patients
Patients were considered potential candidates for entry into the study if there was sustained AF with a ventricular rate \(\geq 60\) beats/min at rest, lasting \(\geq 1\) h to \(\leq 48\) h. Patients with atrial flutter were not eligible. Exclusion criteria were clinical signs of congestive heart failure (New York Heart Association functional class \(>II\)), severely reduced left ventricular systolic function (mean left ventricular fractional shortening \(<20\%\)), unstable angina pectoris, acute myocardial infarction within the preceding 6 weeks, hypotension (systolic blood pressure \(<100\) mmHg), recent anti-arrhythmic therapy (treatment with anti-arrhythmic agents of class I or III within the previous 48 h or amiodarone within the previous 6 months), any previously documented atrio-ventricular or intraventricular conduction disturbances of more than first degree atrio-ventricular block or of more than unifascicular block, sick sinus syndrome (unless protected by a permanent pacemaker), prolongation of the QTc (corrected QT interval; Fridericia’s correction) \(>450\) ms, compromised renal function (i.e., serum creatinine \(>2.5\) mg/dl), hepatic insufficiency, uncorrected hypokalaemia or hypomagnesaemia, flecainide or ibutilide hypersensitivity, pregnancy and lactation, age \(<19\) or \(>90\) years, and inability or unwillingness to give written informed consent. Concurrent control of the ventricular rate with digoxin, beta-blockers, or calcium-channel blockers (verapamil, diltiazem) was permitted. The study protocol complies with the Declaration of Helsinki and was approved by the institutional committees on human research of the 10 participating hospitals.

#### Data collection
Complete medical history, physical examination, routine laboratory results (including thyroid function tests), 12-lead electrocardiogram, and an echocardiogram were obtained at baseline evaluation. Cardiac rhythm was monitored continuously for 4 h after starting medication. A 12-lead electrocardiogram was recorded at the time of conversion to sinus rhythm (SR) or on the appearance of a significant rhythm change and at 90 min after starting medication.

#### Enrolment and drug administration
At each enrolment centre patients were prospectively stratified according to the duration of AF (stratum A: \(\geq 1\) h to \(\leq 24\) h; stratum B: \(>24\) h to \(\leq 48\) h). In each stratum patients were randomly allocated to receive either flecainide (Aristocor \(^6\), F. Joh. Kwizda, Vienna, Austria) or ibutilide (Corvert \(^9\), Pharmacia-Austria, Vienna, Austria) which are both approved drugs in Austria. Stratification (with blocking) \(^16,17\) according to duration of AF was performed to ensure that the two treatment groups were balanced with respect to this known predictor of pharmacological cardioversion.\(^{12,9}\) Flecainide was given by infusion over 20 min at a dose of 2 mg/kg body weight (maximum 200 mg), ibutilide was infused at a dose of 1 mg (or 0.01 mg/kg body weight if less than 60 kg) over 10 min, followed by a 10-min observation period and an identical second dose if AF did not convert to SR. The infusion was discontinued if AF stopped or if a safety problem occurred, such as a fall in systolic blood pressure \(<90\) mmHg, an increase in QRS duration >50%, an increase in QTc to \(\geq 600\) ms, or the development of malignant ventricular arrhythmia. Electrical cardioversion was allowed after 90 min in treatment failures.

#### Study end-points
The primary end-point was conversion of AF to SR within 90 min after start of the medication. The secondary end-points were differences in the frequency of adverse events and differences between the two drugs in slowing of the ventricular rate in non-converters. Additionally, a post hoc cost analysis was performed.

#### Statistical analysis
The sample size was determined in advance based on the following assumptions: with a type I error of 0.05 (two-sided), a type II error of 0.20, a difference in conversion rates between the two drugs of 20%, and an estimated mean conversion rate of 60%, the calculated total study population was 200. Data with normal or asymmetric distribution are described by mean values \(\pm\) SD (standard deviation) or median and interquartile range, respectively, and compared between groups by \(t\)-tests or Mann–Whitney \(U\) tests, respectively. Conversion rates and the occurrence of adverse events were compared between treatment groups by using the Cochran–Mantel–Haenszel test \(^{18}\) stratified for duration of AF. The method of Kaplan and Meier was used to construct estimates of the cumulative proportion of patients converting to SR in each treatment group over time which were then compared by the log-rank test.

Multiple logistic regressions using the Statistical Analysis System Software Version 8.2 (SAS Institute Inc., Cary, NC, USA) were performed in the following way to detect effects of various variables on conversion rate. Firstly, a model including the factors treatment group, duration of AF (\(<24\) h, \(\geq24\) h), enrolment centre, sex, and their interaction was estimated. The interaction of sex and age was included according to the results of a previous study on similar patients.\(^8\) Secondly, forward selection was used to evaluate possible effects of the continuous variables of left atrial size, left ventricular systolic function, plasma levels of potassium and of magnesium at baseline, and of the dichotomous factors of left ventricular hypertrophy and concomitant use of digoxin, beta-blocker, diltiazem or verapamil. A score \(P\)-value <0.05 was used as the criterion for entry into the model. Effects of variables in the model were tested using Wald tests. Only linear effects of the continuous candidate variables were taken into account. Results from logistic regression are presented as OR (odds ratios) and 95% CI (confidence intervals). A two-sided \(P\)-value <0.05 was considered statistically significant.

#### Results

##### Patient characteristics
Altogether 207 hospitalised patients meeting the inclusion and exclusion criteria were enrolled into the trial...
Regarding underlying disease, 91 patients had arterial hypertension (58 with, and 33 without, left ventricular hypertrophy on echocardiogram), 30 had coronary artery disease (18 with prior myocardial infarction), 12 patients valvular heart disease, 1 hypertrophic cardiomyopathy, 1 acute pulmonary embolism, 3 chronic pulmonary hypertension, 4 previously undiagnosed hyperthyroidism, and 2 patients previously undiagnosed sick sinus syndrome. In 6 patients AF was triggered by alcohol, in 4 patients AF occurred 6–24 h after non-cardiac surgery, and in 11 patients a wide spectrum of other diagnoses was present (e.g., atrial septal aneurysm, pneumonia, sepsis, chest trauma). In 42 patients no discernible cause of AF could be found (idiopathic AF).

Response to randomised therapy

Overall, 57 of 101 patients (56.4%; 95% CI 46.2–66.3%) given flecainide and 53 of 106 patients (50.0%; 95% CI 40.1–59.9%) given ibutilide converted to SR within the first 90 min after start of the infusion ($P = 0.34$; OR 1.31; 95% CI 0.75–2.26). There was no statistically significant difference in the distributions of the time intervals to conversion between patients treated with flecainide and those treated with ibutilide ($P = 0.30$) (Fig. 1). Conversion rates varied depending on duration of the arrhythmia. In patients with AF present for $\leq 24$ h, conversion to SR was achieved in 48 of 79 patients (60.8%) in the flecainide group and in 43 of 84 patients (51.2%) in the ibutilide group ($P = 0.22$). In patients where AF was previously present for $> 24$ h to $< 48$ h, the conversion rates were 9 of 22 (40.9%) and 10 of 22 (45.5%), respectively ($P = 0.76$).

Multivariate analysis

Multiple logistic regression (Table 2) revealed that the effect of sex on conversion depends on the age of the patient.
patient such that female sex significantly increases the probability of conversion for patients aged up to 61 years independently of treatment allocation and the stratification factors duration of AF and centre. None of the other variables (including left atrial size, left ventricular systolic function, presence of left ventricular hypertrophy, plasma levels of potassium or magnesium at baseline, or concomitant use of digoxin, beta-blocker, diltiazem or verapamil) were predictors of conversion.

Prolongation of QTc

In the ibutilide group mean QTc at baseline was 380 ± 29 ms (385 ± 29 ms in patients who converted to SR compared to 375 ± 28 ms in non-converters; P = 0.091). Mean QTc prolongation after 90 min was 46 ± 39 ms (53 ± 41 ms in converters compared to 40 ± 34 ms in non-converters; P = 0.098). Women aged ≤ 61 years who converted to SR showed the most pronounced QTc prolongation after ibutilide (86 ± 41 ms).

In the flecainide group, the mean QTc at baseline was 379 ± 32 ms. Mean QTc prolongation after 90 min was 13 ± 30 ms (P < 0.0001 versus ibutilide) and almost completely due to the flecainide-induced prolongation of the QRS complex.

Transformation of AF into atrial flutter

This event occurred in 8 patients (7.9%) of the flecainide group and in 2 patients (1.9%) of the ibutilide group (P = 0.05). Except for 1 patient in the ibutilide group, none of these patients converted to SR within 90 min.

Changes in ventricular rate

Among converters, there was a borderline significant difference regarding ventricular rate after 90 min between the two treatment groups (76 ± 13 beats/min with flecainide versus 71 ± 12 with ibutilide; P = 0.03). Among non-converters, there was no significant difference regarding ventricular rate after 90 min (99 ± 22 beats/min with flecainide versus 102 ± 20 with ibutilide, P = 0.17).

Adverse events

These were reported in 12 (11.9%) of the 101 flecainide-treated patients and in 7 (6.6%) of the 106 patients receiving ibutilide (P = 0.19). Adverse events included chest pain (2 episodes with flecainide and 1 with ibutilide), dizziness (1 episode with flecainide), hypotension (3 episodes with flecainide), acute congestive heart failure (1 episode with flecainide), atrial flutter with 1:1 atrio-ventricular conduction at a rate of 210 beats/min (1 episode with flecainide), bradycardia with pauses up to 5 s after conversion (2 episodes with flecainide and 3 with ibutilide), bifascicular block (2 episodes with flecainide) and nonsustained monomorphic ventricular tachycardia (2 episodes with ibutilide). Several bouts of non-sustained torsade de pointes occurred at the end of the second 1.0 mg infusion of ibutilide in a male patient with normal left ventricular function while still having AF.

Cost analysis

Based on the actual prices in Austria, the mean drug cost per patient would have been 7.30 Euro in the flecainide group compared to 208.44 Euro in the ibutilide group. Of note, 71.7% of the patients randomised to ibutilide needed a second 1.0 mg infusion of ibutilide, bradycardia with pauses up to 5 s after conversion (2 episodes with flecainide and 3 with ibutilide), bifascicular block (2 episodes with flecainide) and nonsustained monomorphic ventricular tachycardia (2 episodes with ibutilide). Several bouts of non-sustained torsade de pointes occurred at the end of the second 1.0 mg infusion of ibutilide in a male patient with normal left ventricular function while still having AF.

Discussion

To our knowledge, this is the first direct comparison between a class I-C anti-arrhythmic drug like flecainide and a pure class III drug like ibutilide for immediate conversion of AF. Both drugs showed a moderately high efficacy in their ability to convert AF of recent onset (≤ 48 h) and no significant difference between the conversion rates of flecainide and ibutilide within 90 min of starting intravenous medication could be demonstrated.
Comparison with previous studies

Flecainide has been studied in a large number of randomised trials for acute termination of AF of recent onset. It was found to be more effective than placebo.4,7 Verapamil,2 digoxin,3 procainamide,5 propafenone,6 amiodarone7 and sotalol,8 and equally effective, but acting more rapidly than quinidine.1 Of note, there was a trend toward a greater efficacy of flecainide in trials using a shorter infusion time for the same total dose than our study.2,6 Randomised trials found ibutilide more effective for conversion than placebo,9,10 procainamide11 and sotalol.12 The observed conversion rate with ibutilide in our study is in accordance with these trials.

Possible mechanisms underlying efficacy of therapy

Whereas the clinical efficacy of flecainide and ibutilide regarding termination of AF of recent onset seems not to be significantly different, important discrepancies in the electrophysiological mechanisms leading to this benefit have to be noted. AF is widely believed to result from multiple re-entrant circuits.19,20 The minimum size of a circuit is related to the electrical wavelength (= conduction velocity \times effective refractory period) and the stability of AF is determined by the average number of these circuits or wavelets. Two different models which try to explain the anti-fibrillatory actions of class I-C drugs like flecainide currently exist. In the classical model, the anti-arrhythmic effect of drugs on AF is attributed to prolongation of the electrical wavelength,21,22 thereby reducing the possible number of simultaneous wavelets within the finite area of the atria until conduction failure leads to arrhythmia termination. The class I-C drug flecainide slows atrial conduction velocity with use-dependence and increases the atrial refractory period23 by its blocking effects on the fast inward sodium current and possibly additional potassium channel blocking properties.24 The effects on refractoriness predominate as indicated by drug-induced increases in the wavelength which are substantial even at short atrial cycle lengths as in AF.23 However, an alternative model was recently proposed to explain the action of class I-C drugs,25,26 which may be more related to their effect on the conduction velocity than on the refractory period. Preferential depression of wavelet conduction with a high curvature leads to an increase in the average AF cycle length and a widening of the temporal excitable gap (= difference between AF cycle length and atrial refractoriness during AF). This will lower the chance that wavelets encounter areas of partially refractory tissue. As a result, slowing of conduction and fractionation of wavelets will occur less frequently. Because widening of the excitable gap will also promote the fusion of wavelets, the balance between generation and extinction is expected to change toward a lower number of fibrillation waves which increases the chance of termination of AF.25 This critical effect of class I-C drugs on the conduction velocity may be more pronounced with a shorter infusion time, possibly explaining the trend for a greater clinical efficacy of flecainide in those trials.2,6

Ibutilide's ability to markedly increase the atrial effective refractory period without changing the conduction velocity27,28 is typical for its class III action, and is mediated by the enhancement of the slow inward sodium current and blockade of the rapidly activating, delayed rectifier potassium current.29 In contrast to older class III drugs like sotalol which show reverse use-dependence,30 the resultant effects of ibutilide on wavelength are not reduced as cycle length decreases, thereby maintaining its effects on refractoriness even at high atrial rates.27 In our study, we found a trend for a longer QTc at baseline and a trend for a more pronounced QTc prolongation in the patients converting after ibutilide (compared with those who did not), suggesting that the atrial and ventricular repolarisation times may show an essentially parallel behaviour leading to the beneficial effects at the atrial level and the known risk for torsade de pointes at the ventricular level.

Duration of AF and efficacy of acute therapy

There was a trend toward increased efficacy of flecainide in patients with shorter duration of AF (conversion rate 60.8% if duration of AF was ≤ 24 h versus 40.9% if duration of AF was > 24 h). In contrast, the efficacy of ibutilide appeared to be independent of the duration of AF. Obviously, no conclusions can be drawn from our data concerning the efficacy of both drugs beyond 48 h duration of AF. Our results are in accordance with findings of previous studies showing that the ability of class I-C agents to terminate AF decreases considerably with increasing duration of the arrhythmia,1,2,8 underpinning the concept of our stratified randomisation procedure. In contrast, a more sustained efficacy of ibutilide with longer duration of AF (albeit at a rather lower level) is consistently reported.9,12 Even during the first days of AF marked electrophysiological changes take place in the atria that clearly favour the perpetuation of AF.31,32 The reduced conduction velocity and the shortening of refractoriness occurring with long-standing AF, decreases the electrical wavelength and increases the number of fibrillatory wavelets, making the arrhythmia intrinsically more resistant to pharmacological cardioversion, irrespective of the proposed mechanisms for arrhythmia termination by drugs.

Predictors of cardioversion

Multivariate analysis confirmed the presence of a significant interaction between age and sex already observed in our previous study comparing flecainide and sotalol for AF.8 This interaction may be related to gender-specific differences in repolarisation time which is known to be greater at the ventricular level in pre-menopausal women than in men and to equalise after the menopause,33 as well as to gender-specific differences in drug-induced
prolongation of the repolarisation time as shown recently for pre-menopausal women after administration of ibutilide. These findings may also be valid at the atrial level thereby promoting the efficacy of anti-arrhythmic drugs which prolong the atrial refractory period in women of lower age with AF.

Cost effectiveness

Flecainide proved to be about 30 times more cost-effective than ibutilide, a finding which stands in line with recently published studies confirming ibutilide as a rather expensive treatment option from a hospital perspective.

Study limitations

Our trial did not include a placebo group due to our concerns of leaving symptomatic patients untreated. Moreover, placebo controlled trials already exist for both drugs. The trial was only single-blind, but the primary end-point of the study was not prone to subjective assessment. This study was not powered as an equivalence trial, therefore minor differences in efficacy between flecainide and ibutilide may still exist. It should be emphasised that the preserved left ventricular systolic function in our patient population may account for the low incidence of torsade de pointes in this study.

Conclusions

In patients with AF of recent onset, there was no significant difference in the conversion efficacy or in the risk of adverse events between flecainide and ibutilide. Hence, in this population with short-lasting AF, the marked differences in the electrophysiological actions of the drugs (class I-C versus class III) appeared to play only a minor role from a clinical viewpoint. At present, in patients without contraindications to both medications, the physician’s choice has to be governed by other factors. However, given the different electrophysiological profiles of the two drugs, we suggest a subsequent trial with a sequential design of drug administration to test the hypothesis that patients who fail to convert on one drug, could possibly benefit from the complementary action of the other drug.

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