Efficacy and safety of ibutilide vs. transoesophageal atrial pacing for the termination of type I atrial flutter

Andrea Mazza, Maria Stella Fera, Irma Bisceglia, Francesca Bettiol, Giovanni Pulignano, Pietro Tanzi, Carlo Gaudio, Ezio Giovannini

Division of Cardiology, S. Camillo Hospital, Via G. Livraghi, 00152 Rome, Italy
Central Service of Cardiology, S. Camillo Hospital, Rome, Italy
Cardiology Department, University "La Sapienza", Rome, Italy

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Abstract

Aims Comparing efficacy and safety of ibutilide vs. transoesophageal atrial pacing (ATP) for the termination of type I atrial flutter (AFL).

Methods and results Eighty-seven patients affected by AFL lasting between 2 h and 30 days were randomized in two groups: Group 1—i.v. ibutilide treatment, up to 2 mg, and Group 2—ATP, with "burst" and "ramp" pacing protocols. Sinus rhythm was restored in 36/45 (80%) patients in Group 1 vs. 18/42 (43%) in Group 2 (P < 0.0005). In Group 1, mean AFL duration was 11.4 ± 7.7 days in responders vs. 12.1 ± 7.6 days in non-responders (P = ns), while in Group 2 it was 2.7 ± 1.4 vs. 14.2 ± 5.4 days (responders vs. non-responders, respectively, P < 0.0001); 30/36 (83%) responders in Group 1 had AFL > 48 h vs. 10/18 (56%) responders in Group 2 (P < 0.05). Non-sustained polymorphic ventricular tachycardia occurred in 2 patients in Group 1 vs. none in Group 2 (P = ns). It did not require any specific treatment except the interruption of ibutilide infusion.

Conclusion Both ibutilide and ATP proved to be safe and effective for recent onset type I AFL termination, but ibutilide was more effective when the arrhythmia had lasted longer than 48 h.

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Introduction

Overdrive atrial pacing by transoesophageal approach (ATP) is a safe and effective treatment for restoring sinus rhythm in patients with type I atrial flutter (AFL), with a success rate of 55% reported in the literature, especially in the case of arrhythmias of recent onset [1-5]. However, the efficacy of ATP progressively decreases as time goes by, up to the point of becoming insignificant for AFL the duration of which is over 48 h [6].

Ibutilide, a new antiarrhythmic class III drug [7-9], proved to be effective in 53%-76% of cases [10-12] when administered at full dose, also in patients with a non-recent onset, despite its use being burdened by an incidence of polymorphic ventricular tachycardia, requiring electrical defibrillation in 17% of cases [11].

The purpose of our study was to compare the efficacy and safety of ibutilide vs. ATP in a group of patients consecutively presenting with AFL, up to 30 days after the onset.

Methods

The study included all the patients we saw between January 2000 and March 2002, suffering from "typical" or "reverse typical" AFL (sawtooth pattern of F waves in inferior leads or mainly positive and symmetrical F waves in the same leads, respectively, and an absence of an isoelectric line in both), of 2 h to 30 days duration, and no exclusion criteria. Exclusion criteria were: atypical AFL morphology in a 12-lead ECG, hemodynamic instability, systolic blood pressure <90 mmHg, NYHA class III-IV, age <18 years, pregnancy, hyperthyroidism, ventricular tachycardia suggested by the clinical interview or QTc interval >440 ms in a 12-lead ECG, acute myocardial infarction or heart surgery <30 days, treatment in progress with class I or class III drugs, average ventricular rate (AVR) <60/ min, left ventricular ejection fraction <40%, body weight <60 kg.

After performing a transthoracic M-mode and bidimensional echocardiograms with echo-Doppler, and a full haematochemical assessment, the patients admitted to the study with AFL >48 h, duly treated with anticoagulants, either by intravenous heparin according to the accelerated procedure, or already under treatment with oral warfarin, underwent transoesophageal echocardiography (Hewlett-Packard mod. SONOS 5500), in order to exclude the presence of thrombi in the left atrial appendage and/or left atrium, before being randomized.

Patients were randomized in two groups: Group 1—treatment by intravenous ibutilide and GR 2—treatment by ATP.

In Group 1, ibutilide was given by intravenous infusion of 1 mg in 10 min, followed by a further administration of 1 mg, after an interval of 10 min if the first dose had not been successful. The patients were monitored by means of a single ECG lead, from the beginning of the ibutilide administration until 4 h later, with periodic assessments of the QT and QTc intervals by 12-lead ECG (Hewlett-Packard, mod. M1700A), at a paper speed of 50 mm/s, at time 0, 10, 20, 30, 60, 90, 120 min and at 4 h from the beginning of the treatment. AFL cycle lengths and QT intervals were measured to the nearest 10 ms. The criteria for suspending the ibutilide administration were: termination of the patient’s atrial flutter, systolic blood pressure <90 mmHg, advanced AV block (AVR < 60/min), QRS duration ≥50% compared with the baseline ECG, QTc > 600 ms, premature ventricular beats in triplets. The effectiveness of the treatment was assessed 90 min after the initiation of the first dose of ibutilide.

In Group 2, ATP (MEDTRONIC, Minneapolis, MN, USA, stimulator mod. 5328) was performed setting the output of the stimulator slightly above the pacing threshold. Atrial capture during atrial pacing was considered to have been achieved when the morphology of the atrial waves changed on the surface ECG or when ventricular response during pacing changed. The stimulation protocol consisted of "burst" pacing, 8 s duration, starting with a rate of 130% of the AFL rate, then decreased in steps of 10 ms until termination of the AFL was achieved, or until a 100 ms pacing cycle length was reached. If AFL persisted, we proceeded to perform "ramp" pacing, with cycles from 250 to 80 ms for 10 s duration, up to five times, either obtaining termination of AFL (sinus rhythm or atrial fibrillation), or ending the procedure.

The non-responder patients of both groups underwent transthoracic electrical cardioversion by biphasic synchronous DC shock, with a defibrillation procedure of up to three shocks at 70, 120 and 150 J.

Statistical analysis

The results are expressed as means ± the standard deviations. In Group 1, two-tailed Student’s t test was used to compare continuous variables, derived from 12-lead ECG tracings recorded at baseline,
and from those which showed the maximum lengthening of the AFL cycle or of the QTc interval, independent of the recording time. The chi-square test was used to compare categorical variables. Fisher’s exact test was used when appropriate. $P$ values $<$ 0.05 were considered significant.

**Results**

Eighty-seven patients (45 male, 42 female, mean age 56 ± 10 years) entered the study. They were all symptomatic with palpitations and sometimes with exertional dyspnea, so that the onset of the arrhythmia could be quite well defined in all cases. A "typical" morphology of AFL in the 12-lead ECG, with the characteristic sawtooth pattern of flutter waves in inferior leads and absence of an isoelectric line were present in 65 (75%) patients, while a "reverse typical" morphology with mainly positive and symmetrical flutter waves in the same leads was observed in 22 (25%) patients. The atrio-ventricular conduction ratio varied from 2:1 to 4:1. Organic heart disease was present in 69 (79%): hypertensive in 39 (45%), valvular in 15 (17%), ischaemic in 8 (9%), dilated cardiomyopathy in 4 (5%), congenital in 3 (3%), while AFL was isolated in 18 (21%). Forty-five patients were randomized in Group 1, and 42 to Group 2. There were no significant statistical differences concerning the clinical and instrumental variables between the two groups (Table I). In Group 1 we found a lengthening of the AFL cycle length, from 227 ± 18 to 245 ± 21 ms ($P$ < 0.0001), and of the QTc interval, from 404 ± 19 to 450 ± 20 ms ($P$ < 0.0001) (Fig. 1). In Group 1 we obtained the restoration of sinus rhythm in 80% of cases (36/45)—71% (32/45) during or immediately after the first infusion of ibutilide in 9% (4/45) during or immediately after the second dose—vs. 43% (18/42) in Group 2 ($P$ < 0.0005) (Fig. 2). In this group, sinus rhythm restoration occurred directly in 12% (5/42) of cases, while in 31% (13/42) after a short phase of atrial fibrillation. In Group 2, atrial capture was obtained in all patients with a mean output of the stimulator of 20.5 ± 2.4 mA (range 16–24 mA) and a fixed duration of 10 ms. None of the patients in this group was symptomatic due to the pacing and no sedation was required. Mean time to conversion in responders of Group 1 was 15 ± 5 min (range 7–32 min). In Group 1, the average AFL duration among the responders was 11.4 ± 7.7 vs. 12.1 ± 7.6 days in non-responders ($P$ = ns), while in Group 2 it was 2.7 ± 1.4 for responders vs. 14.2 ± 5.4 for non-responders ($P$ = 0.0001) (Fig. 3).

When considering the whole study population (i.e., responders and non-responders), 8 patients had AFL < 48 h both in Group 1 and in Group 2; among them, sinus rhythm was restored in 6/8 (75%) in Group 1 vs. 8/8 (100%) in Group 2 ($P$ = ns). The remaining 37 patients in Group 1 and 34 in Group 2 had AFL > 48 h; among them, sinus rhythm restoration was achieved in 30/37 (81%) in Group 1 vs. 10/34 (29%) in Group 2 ($P$ < 0.006) (Fig. 4).

In Group 1 the average lengthening of the QTc interval was 46 ± 6 ms, without any statistically significant difference between responders and non-responders (respectively, 46 ± 7 vs. 47 ± 4 ms, $P$ = ns).

In two patients of Group 1, non-sustained polymorphic ventricular tachycardia occurred (at the beginning of the second infusion in one and during the second infusion in the other); in both cases, ibutilide failed to restore sinus rhythm, but the ventricular arrhythmias receded once the drug had been suspended, without requiring any specific treatment. When polymorphic ventricular tachycardia occurred QTc intervals were, respectively, 450 and 480 ms, with a prolongation of 50 ms with respect to baseline and with an atrio-ventricular conduction ratio varying from 2:1 to 4:1. Both of them had arterial hypertension and the brady-tachycardia syndrome was ruled out by 24-h Holter monitoring performed after the electrical cardioversion had restored the sinus rhythm. No adverse event occurred among Group 2 patients, nor among those of Group 1 during the 4-h monitoring ($P$ = ns). At the end of the study, the non-responders of both groups underwent external electrical

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and instrumental characteristics of the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>23/22</td>
</tr>
<tr>
<td>Left atrium (mm)</td>
<td>38 ± 7</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>Heart disease</td>
<td>35 (78%)</td>
</tr>
<tr>
<td>Atrial flutter cycle length (ms)</td>
<td>227 ± 18</td>
</tr>
<tr>
<td>Typical flutter morphology</td>
<td>33 (73%)</td>
</tr>
<tr>
<td>Reverse typical flutter morphology</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>Atrial flutter duration (days)</td>
<td>11.5 ± 7.7</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>404 ± 19</td>
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cardioversion, which proved effective in restoring
the sinus rhythm in all cases.

Discussion

The success in restoring sinus rhythm by ATP in pa-
tients suffering from AFL has been reported exten-
sively in the literature, reaching about 55% in
recent onset AFL [3,4], particularly if within 24 h.
However, the success percentage of this tech-
nique progressively declines with time, until it be-
comes insignificant in AFL of over 48 h duration [6].
This limit seems to be due to stabilization of the
reentrant circuit, which makes penetration of the
stimulated wavefront into the circuit more and
more difficult, so preventing pacing from extin-
guishing the excitable gap which characterizes
AFL. Therefore, this is consistent with our study’s
success in restoring, by means of ATP, sinus rhythm
in 43% of cases among a group of patients whose
AFL had an average duration of 9 days. Fur-
thermore, the average duration of the arrhythmia
among the responders of that group was 2.7 days,
significantly shorter than that recorded among
non-responders. We, notably, excluded from the
study patients with atypical morphologies of AFL,
just because they are less likely to be interrupted
by ATP, irrespective of AFL duration.

Conversely, ibutilide, a new class III antiarrhyth-
mic drug, whose electrophysiological effect is that
of increasing the depolarizing slow sodium current,
and of blocking the repolarizing outward potassium
current during phase 3, thus prolonging the
duration of the monophasic action potential and
of the refractory period [13], proved to be very ef-
ective in terminating AFL of longer duration, when
given in full dose, obtaining positive results from
53% to 76% cases [10–12]; the prolongation of the
refractory period due to the drug’s administration
can cause the whole excitable gap of the reentrant

![Atrial flutter cycle length and QTc interval at baseline and after ibutilide in Group 1 patients (mean values ± SD).](image1)

![Atrial flutter duration (mean ± SD) in patients responders vs. non-responders in both groups.](image2)
circuit to be affected by refractoriness, thus terminating the AFL due to the reentrant wavefront’s inability to proceed [14]. Furthermore, the effectiveness of ibutilide in terminating AFL appeared to be definitely greater than the results yielded by other class I and class III antiarrhythmic drugs, as proven by a number of direct comparisons [12,15]. This may be due to the lack of a reverse use-dependent effect on refractory periods, which is an effect that limits the efficacy of other antiarrhythmic drugs [16,17].

In our study, the termination of AFL with the restoration of sinus rhythm was achieved in 80% patients treated with ibutilide, a percentage significantly greater than the positive results obtained by ATP. In agreement with what has been previously mentioned, this difference may be due to the AFL’s time of onset, which in our study reached up to one month. While the effectiveness of ibutilide remained high for any duration of AFL up to 30 days, with 83% responders in Group 1 suffering from AFL > 48 h, the average duration of AFL in ATP responders was 2.7 days, with 44% responders suffering from AFL < 48 h, and the remaining cases of AFL whose duration was only slightly longer.

The success percentage obtained in our population exceeds the one reported by Stambler and colleagues [11], who showed an efficacy of 63% in a group of patients with AFL the duration of which ranged between 3 h and 45 days: in this case, it is possible that the study’s different inclusion criteria, and the population’s different clinical features, such as the percentage of patients suffering from valvular heart disease, with left atrial dilatation or reduced ejection fraction, may explain our population’s achievement of a better success percentage. Besides this, Vos and colleagues [15] reported an efficacy of ibutilide of 70% in terminating AFL whose onset occurred within 45 days, a percentage that rises to 76% in the study by Volgman and colleagues [12], which concerned 17 patients suffering from AFL with an average duration of 22 days, treated with ibutilide up to 2 mg.

In concordance with the electrophysiological properties of this drug, in our study, ibutilide showed a slight effect on conduction velocity: in fact, among the treated patients, the AFL’s cycle was lengthened by an average of 18 ms, considerably less than the average increase showed by the QTc interval. This testifies the drug’s stronger electrophysiological effect on refractory periods than on conduction velocity, as already fully proven by previous studies, both experimental and performed on man [18–20].

In our study, the average lengthening of the QTc interval in patients treated with ibutilide was 46 ms, without any significant difference between responder and non-responder patients. It is known from the literature that the extent of the QTc interval lengthening after ibutilide does not anticipate the drug’s effectiveness on AFL nor on atrial fibrillation [10,11]. Despite the lengthening of the QTc interval reflecting the drug’s effect on the ventricular refractory period, Buchanan and colleagues showed in experimental models that the increase of the atrial refractoriness represents an important aspect of the antiarrhythmic effectiveness of ibutilide [21,22]. We suggest that the width of the excitable gap, variable from case to case, is able to explain the lack of relation between the extent of the QTc interval increase and the termination of AFL: slight gaps may be filled by rather modest QTc increases, while excitable gaps of considerable width may not be extinguished even by a more marked lengthening of the atrial refractory period.

In our study, ibutilide failed to restore sinus rhythm in 9 patients; since our study was focused on the direct comparison between two treatment modalities of AFL, we did not plan a cross-over design, so that none of the non-responder patients in Group 1 underwent ATP. In this respect, the usefulness of ibutilide for enhancing pacing termination of AFL has already been demonstrated by Stambler and colleagues [20], who showed that ibutilide and procainamide facilitate pacing induced termination of AFL compared with placebo (88% vs. 18%), and has been recently described by Cheng and colleagues [23], though in a small number of patients; therefore, this strategy might represent an efficacious step-up protocol for sinus rhythm restoration in patients affected by AFL, consisting of ibutilide as a first-line treatment, followed by ATP if ineffective. It is conceivable that this protocol would
leave only a small proportion of patients as candidates for electrical cardioversion.

We did not encounter any case of polymorphic ventricular tachycardia that required electrical defibrillation, but the administration of ibutilide was suspended in two cases due to the onset of non-sustained polymorphic ventricular tachycardia. However, it should be underlined that the proarhythmic events reported in the literature have always occurred immediately or a few minutes after the treatment had begun, in patients with a base QTc interval > 440 ms, or with a compromised haemodynamic condition (advanced functional class, reduced ejection fraction) [10], which in our study represented an exclusion criterion. Therefore, an accurate selection of patients chosen for ibutilide treatment can minimize the drug’s risk of eliciting this arrhythmia.

In conclusion, both ibutilide and ATP proved to be effective and safe in terminating AFL with a very recent onset, but the use of ibutilide appears to be the best choice in AFL of over 48 h duration.

References