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*Heart* 2010 96:546-549
doi: 10.1136/hrt.2009.187963

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Intravenous administration of flecainide or propafenone in patients with recent-onset atrial fibrillation does not predict adverse effects during ‘pill-in-the-pocket’ treatment

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ABSTRACT

Background Pill-in-the-pocket treatment should be prescribed only if the administration of a loading oral dose of flecainide or propafenone has been proved safe in hospital, since major adverse effects have been reported in 5% of patients during in-hospital treatment. However, in emergency rooms, the oral administration of these drugs for the conversion of atrial fibrillation (AF) is very rarely used because it is time consuming.

Objective To investigate whether tolerance to intravenous administration of flecainide or propafenone might predict the safety of pill-in-the-pocket treatment—the out-of-hospital self-administration of these drugs after the onset of palpitations—in patients with AF of recent onset.

Methods One hundred and twenty-two patients with AF of recent onset who were successfully treated (conversion of AF within 2 h without major adverse effects) in hospital with intravenous flecainide or propafenone were discharged on pill-in-the-pocket treatment.

Results During a mean follow-up of 11±4 months, 79 patients self-treated 213 arrhythmic episodes; treatment was successful in 201 episodes (94%). Major adverse events occurred in five patients (6%) and in four (5%) of these during the first oral treatment (one syncpe, two presyncope, one sinus arrest). No patient reported symptoms attributable to bradyarrhythmia or hypotension during the self-treatment of arrhythmic recurrences when the first oral treatment was not accompanied by any major adverse effects. The study was prematurely terminated because of the high incidence of major adverse effects during the first out-of-hospital treatment.

Conclusion The patient’s tolerance of intravenous administration of flecainide or propafenone does not seem to predict adverse effects during out-of-hospital self-administration of these drugs.

A loading oral dose of flecainide or propafenone is effective in converting recent-onset atrial fibrillation (AF) to sinus rhythm (SR). These two drugs display similar efficacy, are better than placebo and act more rapidly than other antiarrhythmic drugs.1–4 In one Italian multicentre study,4 the out-of-hospital self-administration of flecainide or propafenone—the pill-in-the-pocket approach—was investigated in 210 patients with AF of recent onset and with mild or no heart disease. Treatment was successful in 94% of the arrhythmic episodes, with a mean time to resolution of symptoms of about 2 h. Major adverse effects were observed in only one patient (0.7%) (atrial flutter at rapid ventricular rate). This treatment markedly reduced emergency room (ER) visits and hospitalisations. However, after in-hospital oral treatment, 5% of the patients were not enrolled, owing to major adverse effects, such as symptomatic bradycardia or hypotension or transient atrial flutter; these results suggest that the first treatment with a loading oral dose of flecainide or propafenone should be carried out in hospital. The recent ACC/AHA/ESC guidelines for the management of patients with recurrent AF also recommend pill-in-the-pocket treatment for selected patients only if oral treatment has been proved safe in hospital.5 Oral flecainide and propafenone are very rarely used for the conversion of AF in the ER, since doctors prefer intravenous administration, which has a more rapid action than the time-consuming oral administration. Consequently, pill-in-the-pocket treatment is largely underused, because of the lack of an in-hospital ‘screening treatment’.

The aim of this study was to investigate whether tolerance to intravenous administration of flecainide or propafenone could predict the safety of the pill-in-the-pocket approach. For this purpose, a loading oral dose of flecainide or propafenone was prescribed for selected patients with recent-onset AF that had been successfully treated in hospital by intravenous administration of these drugs.

METHODS

Study population

Inclusion criteria were as follows: patients aged >18 years requiring ER intervention for recent-onset (<48 h) electrocardiographically documented episode of AF with a mean heart rate >70 beats/min and a systolic blood pressure ≥100 mm Hg; history of palpitations with abrupt onset, haemodynamically well tolerated (absence of symptoms such as dyspnoea, presyncope or syncope); number of episodes in the past year ≥1 and <12 (excluding the target episode); no cardiacological symptoms apart from the arrhythmic episodes.

Patients were excluded if they had one or more of the following findings: electrocardiographic evidence of ventricular pre-excitation, left bundle branch or bifascicular block (QRS >120 ms);
a previous episode of AF lasting ≥10 days; ischaemic heart disease; dilated or hypertrophic cardiomyopathy; history of heart failure; severe valvular heart disease; chronic cor pulmonale; left ventricular dysfunction (ejection fraction <50%); a long QT or Brugada syndrome; bradycardia—tachycardia syndrome (resting heart rate ≤50 beats/min or repetitive sino-atrial blocks during waking hours); documentation of previous episodes of second- or third-degree atrioventricular block; previous thromboembolic episodes; acute disease; very severe general diseases (muscular dystrophies, systemic collagen diseases, etc); renal or hepatic insufficiency; hypokalaemia (potassium level <3 mEq/l); suspected or known pregnancy; known intolerance of flecainide or propafenone; prophylactic antiarrhythmic treatment or cognitive skills inadequate for self-treatment (evaluated by the cardiologist).

We recorded the medical history of all patients and performed a physical examination, electrocardiography, routine biochemical laboratory tests (including thyroid hormone assay) and two-dimensional echocardiography. Other investigations, such as exercise stress testing, were performed when clinically indicated. Recruitment began on 1 October 2007.

The study was approved by the local ethics committee and written informed consent was obtained from all participants. To ensure the safety of the study, informed interim analyses of the efficacy and adverse effects of out-of-hospital treatment were performed every 6 months by an independent data- and safety-monitoring committee. This committee was established in order to recommend early termination of the study if inefficacy of the treatment or major side effects were seen. No formal rules for interrupting the study were adopted before the initiation of enrolment.

In-hospital antiarrhythmic treatment
Patients were treated with intravenous flecainide or propafenone either in the ER or in the cardiology ward. Each hospital applied its own admission criteria, which were the same during the study period as in the year preceding enrolment. The researchers of each centre used the drug (either flecainide or propafenone) with which they were more familiar.

For AF conversion, intravenous propafenone and flecainide were administered in a single dose of 2 mg/kg. After drug administration, heart rhythm was monitored for at least 3 h, blood pressure was measured every 30 min and a 12-lead ECG was recorded every 30 min. The treatment was considered ‘successful’ if the interval between administration of the drug and conversion to SR was ≤2 h and there were no observable adverse effects, such as symptomatic hypotension (systolic blood pressure ≤80 mm Hg), symptomatic bradycardia after SR restoration, dyspnoea, presyncope, syncope, conversion to atrial flutter or atrial tachycardia, or episodes of sustained or unsustained ventricular tachycardia.

Out-of-hospital episodic treatment
Patients were recruited for in-hospital treatment if all the inclusion criteria were fulfilled and no exclusion criteria were documented after medical history, physical examination and electrocardiographic recording. Patients were selected for out-of-hospital treatment from among those who were treated successfully in hospital and were not excluded during subsequent examinations. A loading oral dose of flecainide was prescribed for the patients treated successfully with intravenous flecainide: 300 mg if the patient weighed ≥70 kg or 200 mg otherwise. A loading oral dose of propafenone was prescribed for the patients treated successfully with intravenous propafenone: 600 mg if the patient weighed ≥70 kg or 450 mg otherwise.

Before discharge, all patients were instructed to take the drug 5–10 min after any subsequent onset of palpitations. Patients were instructed to remain in a resting state (sitting or supine position) after ingestion of the drug, until the palpitations had stopped or at least 4 h had passed. They were also given a form and asked to record the number of arrhythmic episodes they experienced, the exact times of onset of palpitations, drug ingestion, termination of symptoms and any adverse effects.

Patients were advised to contact the ER if their palpitations did not cease within 6–8 h after drug ingestion, if they had symptoms that had not occurred during previous arrhythmic episodes (eg, dyspnoea, presyncope, syncope), or if they felt a marked increase in heart rate after drug ingestion. Finally, patients were advised not to take more than one oral dose in any 24 h period. After discharge, patients were seen in the outpatient clinic every 4 months.

Statistical analysis
Data are expressed as mean±SD. Continuous variables were compared by using Student t test for independent samples. A two-tailed χ² test was used to determine the statistical significance of associations in two-by-two tables. The efficacy of the oral drug was provided as a crude estimate. A p value of <0.05 on two-sided testing was considered to indicate statistical significance.

RESULTS
In May 2009, the study was interrupted on the recommendation of the data- and safety-monitoring committee because the results suggested that the intravenous administration of flecainide or propafenone does not predict the occurrence of adverse effects after a loading oral dose of these drugs. A 5% incidence of major side effects during the first out-of-hospital treatment was regarded as high, considering that such patients have haemodynamically well-tolerated episodes of AF.

In-hospital treatment
A total of 122 patients with AF of recent onset were enrolled following successful in-hospital treatment with intravenous flecainide (23 patients) or propafenone (99 patients)—that is, the tachyarrhythmia was interrupted within 2 h and the above-mentioned adverse effects and/or exclusion criteria did not emerge. In these patients, the mean duration of AF before in-hospital treatment was 336±259 min and the mean time to conversion to SR was 63±52 min. These patients were discharged on pill-in-the-pocket treatment: 23 were given flecainide (16: 300 mg; 7: 200 mg) and 99 propafenone (76: 600 mg; 23: 450 mg).

Clinical characteristics
The clinical characteristics of the 122 patients are reported in table 1. Seventy-one patients had no signs of organic heart disease, while the remaining 51 (42%) had mild heart disease (hypertension in 41, valvular heart disease without ventricular hypertrophy or dilatation in eight, other conditions in two).

Out-of-hospital treatment
The mean follow-up period was 11±4 months. Of the 122 patients, 36 (50%) did not have any arrhythmic recurrences during the follow-up period, while 86 (70%) reported a total of 262 episodes of palpitations with abrupt onset, 215 of which (81%) were treated by 79 patients with either flecainide (in 20 patients) or propafenone (in 59 patients). The mean time from the onset of symptoms to the ingestion of the drug was 55±98 min. The drug was effective (ie, palpitations were
Table 1 Clinical characteristics of the patients enrolled for out-of-hospital treatment of recurrent atrial fibrillation

<table>
<thead>
<tr>
<th>No of patients</th>
<th>122</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60±11</td>
</tr>
<tr>
<td>Sex male, n (%)</td>
<td>67 (55)</td>
</tr>
<tr>
<td>Patients with mild heart disease, n (%)</td>
<td>51 (42)</td>
</tr>
<tr>
<td>AF history (years)</td>
<td>4±4</td>
</tr>
<tr>
<td>No of symptomatic AF episodes in the past year* (per patient)</td>
<td>2.9±2.7</td>
</tr>
<tr>
<td>ER contacts in the past year* (per patient)</td>
<td>1.4±1.3</td>
</tr>
<tr>
<td>Hospitalisations in the past year* (per patient)</td>
<td>0.5±0.6</td>
</tr>
<tr>
<td>Duration of AF target episodes before in-hospital treatment (min)</td>
<td>336±259</td>
</tr>
<tr>
<td>Patients who have undergone previous prophylactic treatment, n (%)</td>
<td>77 (63)</td>
</tr>
<tr>
<td>Left ventricular EF (%)</td>
<td>59±6</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>40±5</td>
</tr>
</tbody>
</table>

*Excluding the target episode.

AF, atrial fibrillation; EF, ejection fraction; ER, emergency room.

Comparison with the year before enrolment

The mean number of symptomatic episodes per month recorded in the group of 122 patients enrolled was 28.8 in the year before enrolment (excluding the target episode) and 25.3 during the follow-up period; this difference was not significant. During follow-up, the number of calls for ER intervention was 0.8 per month, which was significantly lower than the number per month in the year before the target episode (14.6, p<0.001). The number of hospitalisations per month during the follow-up period was also significantly lower (0.4 vs 4.7, p<0.001).

Adverse effects

Major adverse effects after self-administration of the drug during one arrhythmic episode were reported by five (6%) of the 79 patients who used the drug during follow-up. In four (5%) of these patients the adverse effects occurred during the first out-of-hospital self-administration of the drug (one syncope, two presyncopal, one sinus arrest) and in one (1%) during the third treatment (atrial flutter at a rate of 120 beats/min). Of the patients who had a major adverse effect during the first treatment (table 2), one had syncope; the ECG recorded in hospital showed periods of complete atioventricular block, which disappeared in the following hours. Two patients had presyncope. One of these measured his blood pressure with an electronic device just after the presyncopal episode; systolic blood pressure was 88 mm Hg and mean heart rate was 95 beats/min. One patient asked for ER intervention because of anxiety and was treated, according to the prescription, with a loading oral dose of propafenone; this patient had a sinus arrest lasting 7 s, which was interrupted by cardiac massage by a doctor. These four patients were receiving treatment with propafenone.

Thirteen of the 122 patients (10%) dropped out of the study; five of the previously described major adverse effects, four because the drug was ineffective and four because of multiple episodes requiring antiarrhythmic prophylactic treatment.

Adverse effects after the first oral out-of-hospital treatment

Of the 79 patients who self-administered the drug during follow-up, four dropped out of the study after the first oral administration because of major adverse effects. Of the remaining 75, 65 had a total of 135 arrhythmic recurrences treated out-of-hospital. No symptom attributable to bradyarrhythmia or hypotension occurred during any treated episode. One patient, as previously mentioned, felt acceleration of heart rate after drug ingestion because of conversion of AF to atrial flutter.

DISCUSSION

The main finding of this study was the high incidence of major adverse effects (5% of patients) during the first out-of-hospital treatment with a loading oral dose of flecainide or propafenone, unpredicted by the tolerance to the intravenous administration of these drugs.

The patient population of this study was similar to that of the previous pill-in-the-pocket study with regard to age (60±11 vs 59±11 years), sex distribution (men 55% vs 58%), presence of mild heart disease (42% vs 44%) and history of AF (4±4 vs 4±5 years). The efficacy of pill-in-the-pocket treatment was the same in the two studies, out-of-hospital treatment being successful in 94% of arrhythmic episodes in both studies. The time to resolution of symptoms was about 2 h in both studies and the reduction in ER visits and hospitalisations was similar. The incidence of major adverse effects during the first treatment with a loading oral dose of flecainide or propafenone was also the same (5%) in both studies. However, in the previous study, patients with major adverse effects during the first (in-hospital) oral treatment were excluded, and during out-of-hospital treatment only one patient (0.7%) had a major adverse effect: atrial flutter at a rapid ventricular rate. In this study, too, this was the only side effect observed in those patients in whom the first oral treatment was not associated with any major adverse effects. These results suggest that the patient’s tolerance to the intravenous administration of class IC drugs does not predict major adverse effects.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Mild heart disease</th>
<th>Drug</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 74</td>
<td>Female</td>
<td>70</td>
<td>Hypertension</td>
<td>Propafenone 600 mg</td>
<td>Syncope due to A-V block</td>
</tr>
<tr>
<td>2. 71</td>
<td>Male</td>
<td>80</td>
<td>No</td>
<td>Propafenone 600 mg</td>
<td>Presyncope due to hypotension</td>
</tr>
<tr>
<td>3. 72</td>
<td>Male</td>
<td>75</td>
<td>Hypertension</td>
<td>Propafenone 600 mg</td>
<td>Presyncope</td>
</tr>
<tr>
<td>4. 66</td>
<td>Female</td>
<td>78</td>
<td>Hypertension</td>
<td>Propafenone 600 mg</td>
<td>Sinus arrest</td>
</tr>
</tbody>
</table>
during a loading oral dose of these drugs. For this reason, it was considered reasonable to terminate the study.

The results for flecainide and propafenone are presented together because the study was not designed to detect individual differences between these two drugs. However, all the patients with major adverse effects were receiving treatment with propafenone. Further data on larger population samples should be collected in order to assess the predictive ability of an intravenous testing with flecainide.

It is well known that 5-hydroxy-propafenone, a metabolite of propafenone, exerts a strong electropharmacological activity; it may therefore contribute to the antiarrhythmic effect of propafenone. The antiarrhythmic potency of propafenone has been quantified in humans by monitoring the magnitude of electrocardiographic changes. While prolongations of PQ interval and QRS duration were detected after oral administration of propafenone, these effects were not significant after intravenous administration. These results show that propafenone induces more marked electrocardiographic changes when administered orally. The amount of 5-hydroxy-propafenone in the serum (propafenone/5-hydroxy-propafenone ratio) strongly depends on the route of administration. After an oral dose, the serum concentration of 5-hydroxy-propafenone rises markedly, while after intravenous administration no metabolites are detectable. Therefore, propafenone displays different antiarrhythmic properties according to whether it is administered intravenously or orally, the latter modality being more effective than the former. This evidence might explain why the patient’s response to intravenous administration of the drug could not predict the effects of an oral administration of the same drug.

The pharmacodynamic properties of flecainide do not exhibit this differential behaviour and the clinical effects of this drug are comparable whether it is administered intravenously or orally. In some studies, flecainide or propafenone has been continuously infused after the administration of the intravenous bolus, in order to maximise the antiarrhythmic effect. In this study we used only bolus administration, as it is effective in recent-onset AF and is a widely used, simple modality in patients with AF lasting <48 h. However, it is possible that further infusion of the drug after bolus injection might have improved the predictive ability of intravenous administration.

In conclusion, the intravenous administration of propafenone should not be used as a ‘screening treatment’ for the pill-in-the-pocket approach. The results of this study further confirm the safety of out-of-hospital treatment when the first treatment with a loading oral dose of flecainide or propafenone is not associated with major adverse effects.

Funding The study was sponsored by Associazione Italiana di Anitmorologia e Cardiostimolazione (AIAC).

Competing interests None.

Ethics approval The research protocol has been approved by the ethics committee of each centre and informed consent has been obtained by all the patients.

Patient consent Obtained.

Provenance and peer review Not commissioned; not externally peer reviewed.

REFERENCES


APPENDIX

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