Is there a synergic effect of propafenone associated with atrial overdrive pacing for atrial arrhythmia prevention? A randomised crossover study

S Garrigue, S S Barold, S Cazeau, M Hocini, P Jais, M Haissaguerre, J Clementy

Abstract

Objective—To assess the effect of adding propafenone to atrial overdrive for the prevention of atrial arrhythmia episodes in patients with DDD pacemakers.

Design—22 patients (8 female, 14 male, mean (SD) age 67 (9) years, range 48 to 77) with DDD pacemakers and frequent paroxysmal atrial arrhythmia episodes were evaluated in a randomised crossover study.

Setting—University hospital.

Methods—Atrial overdrive was defined as a paced rate of 10 paced beats/min above the mean ventricular rate stored for the last 24 hours in the pacemaker memory function. The protocol consisted of two phases of one month each. The first phase consisted of atrial overdrive alone, while in the second phase, propafenone (600 mg/day) was added to atrial overdrive (atrial overdrive + propafenone). All 22 patients underwent the two phases in random order.

Results—Mean ventricular rate was 72 (8) beats/min with atrial overdrive vs 73 (6) with atrial overdrive + propafenone (NS). With atrial overdrive, 14 patients (64.6%) had no recorded atrial arrhythmia vs 15 (68.2%) with atrial overdrive + propafenone (NS). There was no statistical difference between the atrial overdrive and atrial overdrive + propafenone phases with regard to the number of atrial arrhythmia episodes (14 (27) vs 13 (28)), their total duration (30 (78) vs 29 (63) h), and their maximum duration (41 (72) vs 31 (58) min). However, in the brady-tachy subgroup with persistent atrial arrhythmias, atrial overdrive + propafenone produced a shorter mean cumulative duration of atrial arrhythmia than atrial overdrive (104 (115) vs 178 (149) h, p = 0.04), with a significant decrease in the number of atrial arrhythmia episodes (134 (98) vs 102 (83), p = 0.05). The proportion of asymptomatic atrial arrhythmia episodes increased only in the AV block group during atrial overdrive + propafenone (p = 0.03). Three patients had atrial arrhythmias during atrial overdrive + propafenone but not with atrial overdrive alone.

Conclusions—In DDD paced patients, the overall effect of propafenone during atrial overdrive is variable. Propafenone may increase the proportion of asymptomatic atrial arrhythmia episodes. A proarrhythmic effect of propafenone was documented (aggravation of atrial arrhythmias). These results need to be confirmed by further larger randomised studies.

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Keywords: dual chamber pacing; atrial overdrive pacing; atrial arrhythmia; propafenone

Propafenone is a type IC antiarrhythmic drug commonly used for the treatment of atrial tachyarrhythmias. We recently documented the antiarrhythmic effect of atrial overdrive alone in the prevention of atrial arrhythmias during DDD pacing and postulated that the combination of atrial overdrive plus propafenone might be more effective than atrial overdrive alone. Consequently, we conducted a randomised prospective crossover study to evaluate the effect of propafenone in patients with DDD pacemakers undergoing atrial overdrive for atrial arrhythmia control.

Methods

PATIENTS

The study is an extension of our previously published protocol for the evaluation of overdrive suppression of atrial arrhythmias by atrial pacing and involved the same 22 patients (eight women, 14 men, mean (SD) age, 67 (9) years, range 48 to 77) with DDD pacemakers (Chorus 6234, ELA Medical, Montrouge, France) (table 1). Only the 11 patients with sick sinus syndrome (n = 5) and brady-tachy syndrome (n = 6) had received antiarrhythmic drugs before the study (range 5 to 13 months); five (45%) were asymptomatic (absence of palpitations, dyspnoea, shortness of breath, or other symptoms consistent with arrhythmia) and the last 24 hour Holter recording just before the study did not reveal any ventricular or atrial arrhythmia. Four patients with brady-tachy syndrome had been on amiodarone, and the washout was three months before inclusion in the study. The other seven patients on antiarrhythmic drugs underwent a washout period of at least five half lives. We then confirmed that all the patients had had atrial arrhythmias before atrial overdrive while not on antiarrhythmic drug treatment over a one month period. All were on warfarin. Atrial arrhythmia documentation, in terms of frequency and maximum and cumulative durations, was similar to our previous study. No patient developed chronic atrial fibrillation or
Fig 1. The previous study, depicted at the top, consisted of three phases of one month each. Clinical and pacemaker evaluations were performed at the beginning of each phase and at the end of phase III. The same 22 patients then underwent the present protocol consisting of a randomised crossover study with atrial overdrive alone versus atrial overdrive with propafenone during phase IVA and IVb. The pacemaker memory function was programmed for a one month period and results were assessed at the end of each phase.
The prP, postventricular atrial refractory period.

AV, atrioventricular; ppm, paced beats/min; PV, postventricular; PVAR, postventricular atrial refractory period.

*All 22 patients had the same value so the standard deviation equals 0.

The cox2(% and compared by the MacNemar’s test.

W test). Qualitative variables are expressed as n

paired non-parametric test (Wilcoxon paired

expression for one group of patients (with atrial

This study was considered as a paired statistical

DATA ACQUISITION

regardless of the prevailing heart rate or

programmed parameters. Consequently, an

atrial arrhythmia episode can be detected and

registered at the time of onset, independently

of the sinus rate. Two stages are involved for

this sequence: first, a temporary diagnostic

phase lasting 30 seconds during which the AV

synchrony is limited to 120 ppm or the

programmed upper rate if slower; second, a

fallback phase when the DDD mode is

converted to the VVI (strictly the VDI) mode

with a gradual reduction in the pacing rate to

70 ppm. The pacemaker memorises the total

number of fallback episodes a month and the

longest fallback duration. It also generates three

separate histograms of all the interatrial,

interventricular, and atrioventricular (AV) in-

tervals for a total of 30 days. The histogram

data allowed us to identify sustained atrial

arrhythmia episodes and to determine the total

duration of all arrhythmia episodes with a mar-

gin < 5%.

FREQUENCY OF ATRIAL ARRHYTHMIAS

In the 22 patients taken as a group, atrial over-
drive was associated with a total of 14 (27)

atrial arrhythmia episodes, v 13 (28) with atrial overdrive + propafenone (NS; table 3). During

atrial overdrive, eight of 22 patients (36.4%;

four with AV block and four with the

brady-tachy syndrome) had atrial arrhythmias,

while during atrial overdrive + propafenone,

seven of 22 patients (31.8%; three with AV

block, three with the brady-tachy syndrome,

and one with sick sinus syndrome) had atrial

arrhythmias (NS; fig 2).

In the 15 patients (seven with atrial overdrive + propafenone, eight with atrial overdrive alone) who presented with persistent atrial

arrhythmias, we observed a significant expo-

Table 2 Pacemaker data

<table>
<thead>
<tr>
<th></th>
<th>Phase IVa</th>
<th>Phase IVb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower rate (ppm)</td>
<td>72 (8)</td>
<td>73 (6)</td>
</tr>
<tr>
<td>Upper rate (ppm)</td>
<td>145 (10)</td>
<td>145 (10)</td>
</tr>
<tr>
<td>AV delay (ms)</td>
<td>141 (13)</td>
<td>141 (13)</td>
</tr>
<tr>
<td>AV delay (ms)</td>
<td>192 (9)</td>
<td>192 (9)</td>
</tr>
<tr>
<td>PVARP (ms)</td>
<td>234*</td>
<td>234*</td>
</tr>
<tr>
<td>PV atrial blanking (ms)</td>
<td>203*</td>
<td>203*</td>
</tr>
<tr>
<td>Atrial sensitivity (mV)</td>
<td>0.9 (0.2)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>Pulse duration (ms)</td>
<td>0.49*</td>
<td>0.49*</td>
</tr>
<tr>
<td>Bipolar atrial pacing threshold at the pulse width above (V)</td>
<td>1.1 (0.2)</td>
<td>1.3 (0.3)</td>
</tr>
</tbody>
</table>

*p < 0.05 between patients with atrial overdrive and patients with atrial overdrive associated with propafenone.

Table 3 Atrial arrhythmia episodes

<table>
<thead>
<tr>
<th></th>
<th>AV block (n = 8)</th>
<th>SS syndrome (n = 5)</th>
<th>BT syndrome (n = 6)</th>
<th>CS syndrome (n = 3)</th>
<th>Total (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>78 (5)*</td>
<td>74 (5)*</td>
<td>75 (6)</td>
<td>83 (7)</td>
<td>79 (7)</td>
</tr>
<tr>
<td>Patients without AA</td>
<td>68 (6)</td>
<td>4 (100%)</td>
<td>4 (66.7%)</td>
<td>0</td>
<td>8 (36.4%)</td>
</tr>
<tr>
<td>Number of AA episodes</td>
<td>5 (2)</td>
<td>68 (97)</td>
<td>0</td>
<td>14 (27)</td>
<td></td>
</tr>
<tr>
<td>Proportion of atrial pacing (%)</td>
<td>66 (4)</td>
<td>71 (8)</td>
<td>63 (9)</td>
<td>65 (3)</td>
<td>66 (3)</td>
</tr>
<tr>
<td>Total duration of AA episodes (hours)</td>
<td>4 (2)</td>
<td>104 (126)</td>
<td>30 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During of longest AA episode (min)</td>
<td>81 (71)</td>
<td>112 (81)</td>
<td>41 (72)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (SD) or percentage.

*p < 0.05 between patients with atrial overdrive and patients with atrial overdrive + propafenone.

†Number determined by the fallback count in the memory of the pacemaker.

‡Ventricular.

§Percentage of all atrial beats.

AA, atrial arrhythmia; AV, atrioventricular; BT, brady-tachy; CS, carotid sinus; SS, sick sinus.
nential correlation between the number of atrial arrhythmia episodes and the percentage of atrial pacing ($r = 0.95; p < 0.001$). The mean percentage of atrial pacing in patients with atrial arrhythmia episodes during atrial overdrive and/or atrial overdrive + propafenone was statistically similar to that of patients without atrial arrhythmia episodes (65 (12)% vs 56 (21)%, respectively; NS), showing that the presence of atrial arrhythmia episodes did not influence the percentage of atrial pacing from patient to patient.

CUMULATIVE DURATION OF ATRIAL ARRHYTHMIA EPISODES
Analysis of patient subgroups showed a similar mean cumulative duration of atrial arrhythmias in all eight patients in the AV block group (4 (2) hours in phase IV with atrial overdrive vs 2 (3) hours in phase IV with atrial overdrive + propafenone, NS). In contrast, the group of six patients with brady-tachy syndrome had a significantly shorter mean cumulative duration of atrial arrhythmias during atrial overdrive + propafenone than during atrial overdrive alone (57 (85) hours with atrial overdrive + propafenone vs 104 (126) hours with atrial overdrive; $p = 0.02$) (table 3). No patient with sick sinus syndrome or carotid sinus syndrome developed atrial arrhythmias with atrial overdrive, while one patient with sick sinus syndrome had one short atrial arrhythmia episode lasting 0.2 h during atrial overdrive + propafenone (table 3).

MAXIMUM DURATION OF ATRIAL ARRHYTHMIA EPISODES
For all the 22 patients, the maximum duration of atrial arrhythmia episodes was statistically similar in both phases (41 (72) min in phase IV with atrial overdrive vs 31 (58) min in phase IV with atrial overdrive + propafenone) (table 3). In the patient subgroups there was also no significant difference in the longest atrial arrhythmia episode duration for patients with AV block (81 (71) min in phase IV with atrial overdrive vs 69 (72) min in phase IV with atrial overdrive + propafenone), or for patients with brady-tachy syndrome (112 (81) min in phase IV with atrial overdrive vs 91 (102) min in phase IV with atrial overdrive + propafenone) (table 3).

SYMPTOMS
No patient complained of dizziness or syncope during the protocol (table 4). In eight patients propafenone was associated with minor side effects not requiring discontinuation (bitter taste in five, nausea in two, and weakness in three).

Table 4  Symptoms during atrial arrhythmia episodes

<table>
<thead>
<tr>
<th></th>
<th>AV block (n = 8)</th>
<th>SS syndrome (n = 5)</th>
<th>BT syndrome (n = 6)</th>
<th>CS syndrome (n = 3)</th>
<th>Total (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial overdrive, phase IVa or IVb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with AA</td>
<td>4 (50%)</td>
<td>0</td>
<td>4 (66%)</td>
<td>0</td>
<td>8 (36.4%)</td>
</tr>
<tr>
<td>Patients with symptoms</td>
<td>4 (100%)</td>
<td>4 (100%)</td>
<td>9 (7) (D)</td>
<td>7 (5) (D)</td>
<td>16 (72.7%)</td>
</tr>
<tr>
<td>Number of symptomatic events</td>
<td>1 (1) (D)</td>
<td>13 (0) (P)</td>
<td>11 (6) (P)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of asymptomatic AA episodes</td>
<td>0.5 (1.5); 23%</td>
<td>47 (21); 69%</td>
<td>16 (10); 46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial overdrive and propafenone, phase IVa or IVb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with AA</td>
<td>3 (37.5%)</td>
<td>1 (20%)</td>
<td>3 (50.0%)</td>
<td>0</td>
<td>7 (31.8%)</td>
</tr>
<tr>
<td>Patients with symptoms</td>
<td>3 (100%)</td>
<td>3 (100%)</td>
<td>1 (100%)</td>
<td>1†</td>
<td>8 (36.4%)</td>
</tr>
<tr>
<td>Number of symptomatic events</td>
<td>1 (2) (D)</td>
<td>1 (D)</td>
<td>1 (DT)</td>
<td>1 (DT)</td>
<td>5 (6) (D)</td>
</tr>
<tr>
<td>Number of asymptomatic AA episodes</td>
<td>1 (2); 71%*</td>
<td>0</td>
<td>49 (18); 72%</td>
<td>0</td>
<td>15 (8); 58%*</td>
</tr>
</tbody>
</table>

Data are mean (SD) or percentage.
* $p < 0.05$ between patients with atrial overdrive and patients with atrial overdrive and propafenone.
†Patient with no atrial arrhythmic episode recording in the memory function of the PM.
AA, atrial arrhythmia; AV, ativoventricular; BT, brady-tachy; CP, chest pain; CS, carotid sinus; D, dyspnoea; P, palpitations; SS, sick sinus.
in one). Analysis of the 22 patients showed that the frequency of asymptomatic atrial arrhythmia episodes was greater with atrial overdrive + propafenone than with atrial overdrive alone (58% v 46%, \( p = 0.048 \)). The brady-tachy syndrome group showed the highest percentage of asymptomatic atrial arrhythmia episodes in phase IV with atrial overdrive and in phase IV with atrial overdrive + propafenone (69% v 72%, respectively), but the difference was not statistically significant (table 4). In contrast, patients with AV block had a statistically significant increase in asymptomatic episodes with atrial overdrive + propafenone v atrial overdrive (71% v 23%, \( p = 0.02 \)) (table 4).

**EFFECT OF PROPAFENONE WITH ATRIAL OVERDRIVE**

A potential synergistic effect of propafenone with atrial overdrive was evaluated. Covariable analysis between atrial overdrive alone and atrial overdrive + propafenone showed no specific propafenone effect in reducing the number of atrial arrhythmia episodes in the whole population (n = 22). Fourteen patients had no atrial arrhythmia episodes with atrial overdrive v 15 patients with atrial overdrive + propafenone (NS). Only four patients had atrial arrhythmia episodes during both atrial overdrive and atrial overdrive + propafenone (fig 2).

**EFFECT OF PROPAFENONE IN PATIENTS WITH PERSISTENT ATRIAL ARRHYTHMIA DURING ATRIAL OVERDRIVE**

During atrial overdrive + propafenone, three patients with brady-tachy syndrome had persistent atrial arrhythmia episodes v four during atrial overdrive alone (NS; table 3). However, in this specific brady-tachy subgroup with persistent atrial arrhythmias, the atrial overdrive + propafenone phase showed a significantly shorter cumulative duration of all atrial arrhythmia episodes than the phase with atrial overdrive alone (104 (115) v 178 (149) hours, respectively; \( p = 0.04 \)) (fig 3). Moreover, in the same group, the mean number of atrial arrhythmias was significantly smaller during the atrial overdrive + propafenone phase compared with atrial overdrive alone (102 (83) v 134 (98), \( p = 0.05 \)) (fig 3).

In the AV block subgroup with persistent atrial arrhythmias (fig 3), the atrial overdrive + propafenone phase exhibited a significant reduction in terms of atrial arrhythmias cumulative duration (5 (3) v 8 (2) hours, \( p = 0.04 \)) but without significant difference in the mean number of atrial arrhythmia episodes (8 (4) during atrial overdrive v 10 (5) during atrial overdrive + propafenone, NS).

**EFFECT OF PROPAFENONE IN PATIENTS WITHOUT ATRIAL ARRHYTHMIAS DURING ATRIAL OVERDRIVE**

Three patients had no atrial arrhythmias during phase IV with atrial overdrive, while atrial arrhythmia episodes were observed during phase IV with atrial overdrive + propafenone. In these patients, one (AV block) developed three short atrial arrhythmia episodes (the longest being 32 minutes), only one of which was asymptomatic. Another patient (with brady-tachy syndrome) had eight atrial arrhythmia episodes with a cumulative duration of 16 hours: four were asymptomatic. The last patient (sick sinus syndrome) had one short symptomatic atrial arrhythmia episode of 28 minutes. All three had a comparable percentage of atrial pacing in phases IVA and IVB (respectively 66% v 64% for the patient with AV block, 72% v 69% for the patient with brady-tachy syndrome patient, and 74% v 76% for the patient with sick sinus syndrome).

**Discussion**

In our previous study, with a modest degree of atrial overdrive and no antiarrhythmic agents, atrial arrhythmias were prevented in 14 of our 22 patients and atrial arrhythmias were reduced in frequency and cumulative duration in the other eight patients (four with brady-tachy syndrome and four with AV block).1 This was the starting point of the present study in which the combination of atrial overdrive and propafenone produced a total of 15 patients without atrial arrhythmias. In the entire cohort of 22 patients, there was no statistically significant reduction in the number of atrial arrhythmias and in the longest and cumulative durations of atrial arrhythmia episodes with propafenone. However, in the brady-tachy group with persistent atrial arrhythmias despite atrial overdrive, propafenone caused a significant reduction in the number of atrial arrhythmia episodes (134 (98) v 102 (83), \( p = 0.05 \)) and in the cumulative atrial arrhythmia duration from 178 (149) to 104 (115) hours (\( p = 0.04 \)). Likewise, in the AV block subgroup with persistent atrial arrhythmias despite atrial overdrive,
propafenone reduced the cumulative atrial arrhythmia duration significantly (5 (3) v 8 (2) hours; p = 0.04).

ASYMPTOMATIC ATRIAL ARRHYTHmia EPISODES
When compared with the atrial overdrive phase, the atrial overdrive + propafenone phase showed a significant increase in the number of asymptomatic atrial arrhythmia episodes in the overall cohort, but mainly in patients with AV block (23% v 71%; p = 0.03) and not in the brady-tachy patient subgroup. This increase of asymptomatic atrial arrhythmias in the AV block group probably reflected a decrease in ventricular rate, as suggested by Pritchett et al. This suggests that if only symptomatic atrial arrhythmia episodes are identified, the true number of atrial arrhythmia episodes will be underestimated in patients treated with propafenone or other antiarrhythmic agents.

EFFECT OF PROPAFENONE
In this study, a fixed dose of propafenone (600 mg/day) was used without titration. Recently, Pritchett et al have shown in a large population that there was no significant difference between a propafenone dose of 900 mg/day and 600 mg/day in terms of plasma concentration over a one month period.

Three patients with atrial arrhythmias in the atrial overdrive + propafenone phase eventually became free of atrial arrhythmias during the atrial overdrive phase. We cannot explain why this paradoxical effect was not observed when the sequence was reversed, starting with the atrial overdrive phase in atrial arrhythmia-free patients. The difference may reflect the small number of patients in the study. Nevertheless, the worsening of atrial arrhythmia episodes appears to represent a proarrhythmic effect of propafenone, previously reported on a much smaller scale in patients treated for atrial arrhythmias without a pacemaker. Earlier studies probably underestimated the atrial proarrhythmic effect of propafenone because of their limited monitoring techniques (24 hour Holter surface ECG, compared with the long term pacemaker memory data in our study).

LIMITATIONS OF THE STUDY
This was a pilot study with a small number of patients. We are conscious of the weak statistical power in the study. However, our population of 22 patients had sufficient power to detect a difference of 25% or more between the proportion of patients free of atrial arrhythmias with atrial overdrive alone, versus those with atrial overdrive + propafenone. The level of significance (p < 0.05) was provided at a statistical power (1−β risk) of 60%. Patients were prospectively randomised so that, independently of time, three cases of potential proarhythmic effects of propafenone were observed, while with atrial overdrive + propafenone versus atrial overdrive alone a difference of only one patient free of atrial arrhythmias was shown. Our observations in a relatively small population obviously need to be confirmed in larger randomised studies.

CONCLUSIONS
Our study has shown the variable effect of propafenone in patients with DDD pacemakers treated with atrial overdrive for atrial arrhythmia prevention. Overall the antiarrhythmic effect of propafenone was disappointing, though it may be useful in increasing the proportion of asymptomatic atrial arrhythmias in symptomatic patients. Such results might lead to a re-evaluation of the antiarrhythmic agent efficacy in terms of atrial arrhythmia suppression. In view of the potential proarrhythmic effects of propafenone, patients with atrial arrhythmias refractory to propafenone should be treated with atrial overdrive only after propafenone has been discontinued. Similarly, patients with atrial arrhythmias refractory to both atrial overdrive and propafenone should be re-evaluated by atrial overdrive alone to rule out a possible propafenone proarrhythmic effect.

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