Short-term and long-term effects of propafenone.}

**Abstract**

**Symptoms of arrhythmogenesis, and side effects of propafenone.**

**Conclusion**

We conclude that propafenone is effective in the treatment of ventricular arrhythmias, but that it should be used with caution due to potential side effects, particularly during short-term administration. Further studies are needed to determine the optimal dosage and duration of treatment.

**Acknowledgments**

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**References**


predict persistence or loss of long-term efficacy and arrhythmogenic effects related to antiarrhythmic treatment in these patients.

**Patients and methods**

**Patient selection**

The ethics committee of the University of Freiburg approved the study, which was conducted from December 1987 to November 1989. We studied 100 patients (69 men, 31 women; median (SD) age 62 (6) range 28–78) with frequent ventricular extrasystoles (>30/h) and ventricular pairs or tachycardia who had given informed consent (table). We included only those patients with symptoms of arrhythmia.

Ninety-three patients had organic heart disease (for example, diagnosed by exercise testing or echocardiography). Thirty-two had had catheterisation of the right or left ventricle.

Exclusion criteria were myocardial infarction within the past six months, presence of myocardial ischaemia during an exercise test before the study (an exercise test was negative in all the patients), heart failure NYHA class IV, sustained ventricular tachycardia (>30 repetitive beats or tachycardia that was not haemodynamically tolerated by the patient), bradyarrhythmia (<50 beats/min) and conduction disturbances of the sinotubular and atrioventricular nodes, more than second degree bundle branch block, atrial fibrillation, sustained ventricular tachycardia, a baseline QT-interval of >500 ms (Romano-Ward and Jervell-Lange-Nielsen-syndrome), serum potassium <3.0 mmol/l, serum creatine >2 mg/dl, hepatic disease, concomitant medication with other antiarrhythmic agents and calcium channel blocking agents (except nifedipine), and previous treatment with propafenone. Patients taking digoxin were included only if treatment had been started before they entered the study.

**Study design**

Before entry into the study all patients underwent a 10 day placebo period with 24 hour Holter recordings on days 3 and day 10. The second Holter recording was used to assess the spontaneous variability of ventricular arrhythmias and to confirm the arrhythmia suppression obtained during active treatment.

All patients included in the active treatment study were treated with propafenone (150 mg three times a day) for one week. If arrhythmia suppression was not effective, the dose of propafenone was increased during the second week to 600 mg/day (300 mg twice a day). The first group of 50 patients was given propafenone (900 mg/day, 300 mg three times a day) in hospital if they did not respond to the lower doses. The criteria for response were those of Morganroth et al and Grabosky et al (a reduction in ventricular extrasystoles of >84%, of ventricular pairs by >90%, and of ventricular tachycardia by 100%).

Arrhythmogenic events were defined according to the criteria reported by Podrid et al. All patients had a weekly electrocardiogram, measurement of plasma drug concentrations, and assessment of side effects.

All patients who were considered to be suitable for long-term treatment with propafenone were studied after three, six, and 12 months of treatment by 24 hour Holter recording, electrocardiogram, plasma drug concentration, and side effects. Non-responders who did not have therapeutic plasma concentrations of propafenone plasma had repeat 24 hour Holter recording two weeks later.

All Holter recordings were analysed semiautomatically by a Cardiodata MK 4 system. The recording time was 24 hours; the Holter recording was repeated in patients who had fewer than 18 hours of registration time that was artefact free. All ventricular tachycardia episodes were displayed and documented. A visual 1:1 analysis for the incidence of arrhythmias was performed blindly in 5% of the tracings by a second investigator. Both the sensitivity and the specificity of the analysis were >98%.

**Statistical analysis**

All measurements are reported as median values or, when indicated, as mean +/– SD. Single and partial correlations were analysed by a χ2 test (including Yates’ correction coefficient). Student’s t test, and the U test for comparison of median values. Analysis of variance was done by the “repeat-measurement” model for pre and post dose changes. All
tests were performed at a two-sided significance level of 0.05. Multivariate regression analysis was used to determine the influence of different clinical variables on the short term efficacy of propafenone.

Results
Propafenone 450–600 mg/day was initially effective in 44/100 patients (44%) enrolled in the study. In 43/44 responders and 23/56 non-responders arrhythmia related symptoms were abolished. After one year 31/44 patients continued to respond to propafenone. None of the patients died suddenly during treatment with propafenone.

ARRHYTHMIA VARIABILITY DURING THE PLACEBO AND TREATMENT PERIODS
Figures 1–3 reveal spontaneous arrhythmia variability. Examination of Holter recordings during placebo treatment showed that about 50% of patients showed a decrease and 50% an increase in the frequency of single ventricular extrasystoles. In order to address the effect of the underlying heart disease on the spontaneous variability of arrhythmia we analysed the patients with coronary artery disease separately from those without. There was a clear difference in the spontaneous variability of repetitive arrhythmias. A reduction of 100% or an increase of >100% in the frequency of ventricular pairs or tachycardia after placebo was more common in patients with coronary heart disease (figs 2 and 3).

Spontaneous arrhythmia variability was important when propafenone efficacy was analysed. Figures 1–3 summarise the effects of a daily dose of 450 mg propafenone in all patients. In patients without coronary heart disease 35% had total suppression of ventricular tachycardia after propafenone; however, this was only 18% more than that seen during the placebo period (fig 3B). In patients with coronary artery disease total suppression of ventricular tachycardia was seen in 44% of patients during the placebo period.
During treatment with propafenone this was unexpectedly reduced to 12% (Fig 3).

The graphs used in figs 1–3 also allowed us to assess the efficacy of propafenone independently of the criteria used to define a responder. This can be of importance when arrhythmia related symptoms are significantly reduced in individuals who do not fulfil the response criteria. When we examined all the responses to treatment with 450 mg propafenone we found that propafenone had different effects on ventricular extrasystoles, ventricular pairs, and tachycardia (Fig 3). For example, in repetitive arrhythmias increased efficacy of propafenone (shown by a leftward shift of the response curve) was often associated with a lowering of the plateau level, indicating that an increasing proportion of patients show some evidence of proarrhythmia at the same time (figs 2 and 3).

Because the spontaneous variability of ventricular arrhythmias was high we used combined criteria (for example >84% reduction of ventricular extrasystoles, a 90% reduction in the frequency of bigeminy, and the complete suppression of ventricular tachycardia) as a measure of the antiarrhythmic efficacy of propafenone. We studied the reliability of these criteria by comparing the initial two placebo Holter recordings that were separated by a week. During the placebo period none of our patients met these criteria.

During treatment with propafenone, the resting heart rate decreased from 74 to 68 beats/min ($p < 0.05$), the PR interval increased from 0.15 to 0.22 s ($p < 0.05$), and the QRS and QT intervals remained unchanged.

**SHORT AND LONG-TERM EFFICACY OF ORAL PROPafenone**

During dose titration, 44/100 patients (44%) were responders to propafenone (450 mg/day, 30 patients; 600 mg/day, 14 patients). When the dose was increased to 900 mg/day in centre A another six patients (12%) were added to the responder group. The median incidence of ventricular extrasystoles in 24 hours was reduced from 8434 to 2125 in non-responders (median reduction 66%) and from 5642 to 207 in responders (median reduction 96%). Episodes of ventricular pairs were reduced from 65 to seven in non-responders (median reduction 88%) and from 104 to 0 episodes in responders (median reduction 100%). Episodes of ventricular tachycardia over 24 hours were reduced from 6 to one in non-responders and from 4 to 0 episodes in responders.

Of the patients responding to 450–600 mg/day propafenone, 43/44 responders and 23/56 non-responders lost their arrhythmia related symptoms after propafenone. In the non-responders loss of symptoms was associated with a significantly higher reduction in the rate of ventricular extrasystoles ($p < 0.01$) and a lower Lown class after treatment ($p < 0.01$).

Multivariate analysis showed a positive correlation between arrhythmia suppression during short-term propafenone therapy and a lower patient age ($p < 0.012$), while sex, underlying heart disease, NYHA class, Lown class (IVA, B), concomitant digitalis medication, occurrence of side effects, or presence of coronary heart disease were unrelated to propafenone efficacy.

Thirty-eight of the 44 patients (86%) completed a one year follow up while taking 450–600 mg/day; 31 remained as responders (that is, 31% of all patients considered for antiarrhythmic treatment and 74% of all the surviving patients treated long-term). However, 11 of these patients (25%) needed a change of dose after three or six months despite a therapeutic plasma concentration of propafenone. Three of the six patients who did not complete one year follow up required the 900 mg/day dose. The other three patients died from non-sudden and non-cardiac death or in an accident. One patient died from progressive heart failure, one stopped propafenone after carcinoma was diagnosed, and one because of side effects.

Figure 4 shows the response curve for all patients after three, six, and 12 months. In multivariate analysis of the possible predictors of long-term efficacy of the initial propafenone dose we examined all the variables tested for short-term efficacy. Except the titration dose itself, none of these variables was predictive of permanent arrhythmia suppression in the responder group. Though, a permanent response was significantly more likely in patients who initially responded to 450 mg/day (25/29 patients) than in those who responded to 600 mg/day (8/12, $p < 0.01$). At centre A where the dose titration included 900 mg only 4/9 responders continued to take propafenone after one year.

**SIDE EFFECTS AFTER SHORT AND LONG-TERM TREATMENT WITH PROPafenone**

During short term treatment six patients stopped propafenone because of side effects (450 mg/day, two with nausea; 600 mg/day, one with vomiting; 900 mg/day, three with

![Figure 4: Effect of propafenone on ventricular extrasystoles (VE) after three (closed line), six (solid line), and 12 months (dotted line) of therapy compared with the initial placebo Holter recording (−100% reduction to +100% increase). A total of 44 patients is included initially responded to propafenone 450–600 mg/day (ordinate = 100%).](http://heart.bmj.com)
Long-term treatment with propafenone

nausea) and two patients because of exacerba-
tion of ventricular extrasystoles (>400% increase). Side effects were reported in a total of
36/100 patients (36%).

During the follow up one patient stopped
treatment because of side effects. Ten of 44
patients reported transient side effects during
long-term treatment. None of the initial re-
sponders to propafenone had arrhythmogenic
events during Holter recording.

Discussion
Recent data from the CAST study24 have
fuelled the debate25-30 on the risk-benefit ratio
of the use of agents with class IC antiarrhythmic
activity. In the CAST study post-infarction
patients who initially responded to flecainide or
ecaainide had a worse outcome during the
follow up while taking these drugs than
patients taking placebo. This study, however,
also raised many unresolved questions about all
patients with arrhythmia. First, is the high risk
of agents with class IC activity in the CAST
study also found in patients without recent
myocardial infarction. Second, do patients
with more frequent and repetitive arrhythmias
(21% of patients in the CAST study) have a
better benefit/risk ratio? Third, is repeated
Holter monitoring mandatory to detect loss of
efficacy and arrhythmogenic effects during long-
term treatment in patients who initially
responded to treatment? Fourth, how should
we treat patients with potentially uncontrolla-
ble arrhythmias who required treatment for
symptoms after CAST. Fifth, should we expect similar results with other class IC
agents, such as propafenone?

Although propafenone shares some of the
electrophysiological features of flecainide and
ecaainide it differs from both. It has additional β
blocking6-10 and calcium-channel blocking
properties.6,9,10 The β blocking dose-related effect
was found even at low doses in the study
by Härte116 and others11-13 and may enhance the
class I properties of propafenone.21 Placebo
studies showed the clinical effectiveness of
propafenone,21 which was as effective as
disopyramide,21 quinidine,31 tocainide,21
flecainide22 or even amiodarone in suppressing
ventricular arrhythmias.37 It was no more
arrhythmogenic than other agents with class IC
activity.38 Unfortunately, there are few valid
long-term studies of propafenone in which
Holter monitoring obtained months after the
start of treatment could confirm that its anti-
arrhythmic efficacy persists and that arrhyth-
omogenesis does not increase.39

Efficacy of Propafenone During Dose
Titration and Long-Term Treatment
The present study aimed to assess long-term
efficacy and safety of propafenone in a group of
100 patients with symptomatic ventricular
arrhythmias. Patients with recent myocardial
infarction were excluded. Therefore our study
can not be compared with CAST. Addition-
ally, all our patients had >30 ventricular
premature beats, 89% of patients had repet-
titive ventricular arrhythmias, and all patients
clearly had symptoms caused by arrhythmias.
As in previous reports, the spontaneous
variability during placebo treatment was high
in our patients and increased with the complex-
ity of the clinical arrhythmia, especially in
patients with coronary artery disease. This
variability affected the efficacy of propafenone.
Propafenone at a dose of 450 mg/day totally
suppressed repetitive ventricular arrhythmias
in about 10% of patients; after placebo the
proportion of patients with total suppression
was three times higher. To eliminate the false
positive results established by the two 24 hour
Holter recordings after placebo we used com-
bined and restrictive criteria for drug induced
suppression of arrhythmia.

We chose to show data on arrhythmia vari-
bility, on propafenone efficacy, and on
arrhythmogenicity simultaneously and inde-
dependently of statistical criteria. We used data
from the two placebo Holter recordings to
assess the spontaneous arrhythmia variability
and to create the baseline curve. When we
added data on the efficacy of propafenone to this
data, we showed that the placebo and
propafenone curves showed a complete picture
of the arrhythmic and proarrhythmic
potency of the drug in a particular patient
group.

The major aim of the present study was to
assess data on the prediction of the long-term
efficacy of propafenone treatment. All our
patients were given a daily dose of 450–600 mg
propafenone which was effective in 44% of
patients during a short-term study. These
results resemble those reported by others4,14 and
and those we reported in 100 patients when
doses of 450 mg and 750 mg were used and the
response rate was 56%.5 We found that
arrhythmia related symptoms disappeared in
41% of patients not classified as responders.
However, those non-responders with symp-
toms and those without were clearly different in
terms of the effect on ventricular extrasystoles
and suppression of repetitive arrhythmias. It
remains uncertain whether these patients who
lost their symptoms during treatment but did
not meet the criteria for response should con-
tinue further treatment. The overall safety of
propafenone during this one year observation
period favours continuation of treatment at the
lowest dose of propafenone that prevents
symptoms.

Multivariate Analysis for the Prediction
and the Maintenance of the Efficacy and
Safety of Propafenone
Multivariate analysis showed that older
patients were less likely to respond to propaf-
enone. There were no correlations with other
clinical variables. Side effects or acute arrhyth-
omogenesis were not predicted by any of the
clinical variables. In the present study the dose
was increased to 900 mg/day only in hospital
for safety reasons and the increase added
another 12% of patients to the responder
group. Unfortunately, large studies of the long-
term effects of propafenone based on repeat
Holter recordings are rare, as are studies of the
predictors of long-term efficacy. In our study
at the end of one year 70% of patients given long-term treatment and 31% of patients with symptoms remained responders to propafenone. However, the likelihood that propafenone treatment would still be effective after one year decreased as the titration dose increased; thus, it was reduced by >50% when the titration dose was 900 mg/day. Multivariate analysis showed that the titration dose was the variable most predictive of long term propafenone efficacy. Because of the 25% loss of propafenone efficacy during the follow-up, repeat Holter monitoring is mandatory especially in patients with higher titration doses. This is also relevant to the CAST study because with higher doses of class I agents there was a likelihood of >50% that treatment would be ineffective after one year of therapy.

In the CAST study there was considerable interest in mortality and the occurrence of arrhythmogenic events during Holter monitoring in patients treated because they have symptoms. Though our patient group was too small for us to make any definite conclusions, none of our patients died from sudden cardiac death during the one year follow-up, nor did any of our patients require defibrillation devices during subsequent Holter monitoring. So in our study a placebo group was unlikely to provide more information on this point. In the CAST study, however, a significant number of patients died suddenly after antiarrhythmic therapy.

CLINICAL IMPLICATIONS

This study emphasises the importance of careful assessment of the spontaneous variability of ventricular arrhythmias inherent in a particular group of patients considered for antiarrhythmic treatment. We used a type of graphical analysis which provides an interesting overview of the spontaneous arrhythmia variability and of the antiarrhythmic and arrhythmogenic potency of any antiarrhythmic agent. When propafenone was used in a dose of up to 600 mg in patients with frequent symptomatic arrhythmias, about half of the patients were effectively treated and most of these patients remained responders during one year of follow up. Only the titration dose was a predictor of the persistence of the drug response. Therefore, patients treated by propafenone over longer periods should have repeat Holter monitoring.

35 Klempt HW, Nayebagha A, Febry E. Antiarrhythmische
The aortic root in bicuspid aortic values

It is well known that the aortic root at commissural and supra-aortic levels increases in bicuspid aortic stenosis; it is less well known that such root dilation may be instrumental in contributing to aortic regurgitation with bicuspid valves in the absence of any obstruction.

What is of interest is that the aortic root is also dilated with functionally normal bicuspid aortic valves. The aortic root abnormality is thus primary and not a mere secondary phenomenon.

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Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves

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To determine whether aortic root dilation associated with a bicuspid aortic valve occurs independently of valvulare hemodynamic abnormality, aortic root dimensions were measured by two-dimensional echocardiography in 83 adults with a functionally normal (n = 19), mildly regurgitant (n = 26), severely regurgitant (n = 27) or stenotic (n = 11) bicuspid aortic valve and compared with findings in normal subjects matched for age and gender. Aortic root measurements were made at four levels: annulus, sinuses of Valsalva, supraaortic ridge and proximal ascending aorta. Seventy-one percent of patients with a bicuspid aortic valve were men.

When compared with control subjects, all hemodynamic sub-groups showed a significantly larger aortic root size at three levels: sinuses of Valsalva, supraaortic ridge and proximal ascending aorta (p < 0.05 to p < 0.001). The prevalence of aortic root enlargement among all hemodynamic subgroups ranged from 9% to 59% at the level of the annulus, 36% to 78% at the sinuses, 47% to 79% at the supraaortic ridge and 50% to 64% in the ascending aorta.

Thus, there is a high prevalence of aortic root enlargement in patients with a bicuspid aortic valve that occurs irrespective of altered hemodynamics or age. These findings support the hypothesis that bicuspid aortic valve and aortic root dilation may reflect a common development defect.

(1 J Am Coll Cardiol 1992;19:283-8)