Short-term and long-term treatment with propafenone: determinants of arrhythmia suppression, persistence of efficacy, arrhythmogenesis, and side effects in patients with symptoms

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Abstract

Objective—To assess the clinical criteria predicting the short and long-term efficacy of propafenone, an agent with class IC antiarrhythmic activity and a broad pharmacological profile.

Designs—Prospective study of propafenone at doses of 450 to 900 mg/day during a six week dose titration period (including a placebo phase with two separate 24 Holter recordings). Responders to treatment were followed for one year.

Patients—One hundred patients with frequent ventricular arrhythmias (> 30 extrasystoles/h) of Lown class III and IVA/B and without evidence of myocardial infarction within the past six months.

Analysis—Multivariate regression analysis of spontaneous arrhythmia variability and of different clinical variables to determine the short and long-term efficacy and safety of propafenone.

Measurements and main results—Propafenone 450 mg/day was effective in 30/100 patients (30%), and at 600 mg/day another 14 responded. The efficacy of propafenone correlated with a low spontaneous arrhythmia variability and, as shown by multivariate analysis, with a lower patient age ($p < 0.05$). When the dose was increased to 900 mg/day a further six (12%) patients responded. However, with increasing doses of propafenone, the one year probability of effective treatment decreased from 86% (450 mg/day) to 67% (600 mg/day) and to 44% (900 mg/day). After restudying the patients at three, six, and 12 months and after dose adjustment in 11/44 patients (25%), 31 patients (70%) remained responders. Loss of permanent antiarrhythmic efficacy was best predicted by the initial dose that achieved a response. No patient died suddenly or had arrhythmogenic effects during Holter monitoring. Side effects occurred in 36% of patients but these rarely limited long-term treatment.

Conclusions—A younger age, low spontaneous arrhythmia variability, and particularly a low titration dose were the

best predictors of the short and long term efficacy of propafenone. All other responders should have repeated Holter recordings during the first year of treatment.

Propafenone is a potent antiarrhythmic drug and is widely used in Europe and the United States for the management of ventricular arrhythmias.¹⁻⁵ It has class IC activity and produces considerable sodium-channel blockade in heart muscles and Purkinje fibres⁶⁻¹⁰ with little effect on ventricular repolarisation.¹¹ Additionally, propafenone produces β adrenergic blockade in vitro^{6,9,10,11-13} and in vivo,^{14,15} and has weak calcium channel blocking properties.^{6,9,10} Short-term, placebo controlled, double blind studies (dose range from 450 to 1200 mg/day) showed suppression of frequent ventricular extrasystoles and of episodes of non-sustained ventricular tachycardia in 60-85% of patients treated with propafenone.^{2,5,16,17} Similar results were reported in uncontrolled studies.^{3,18-20} The combination of potent sodium channel and β blocking properties are characteristics known to stabilise the electrophysiological properties of myocardial cells.²¹ Propafenone is therefore viewed as being of particular interest.^{1,22,23}

However, evidence from the Multicenter Cardiac Arrhythmia Suppression Trial (CAST) of an excess mortality among post-infarction patients treated for ventricular arrhythmias with the class IC drugs encainide and flecainide has called into question the overall benefit of class IC drugs.²⁴ Because propafenone has similar electrophysiological effects to encainide and flecainide and because information on its long-term effects is incomplete,^{25,26} the use of propafenone has also been restricted. At present, it is uncertain whether propafenone can be safely and effectively used for long-term treatment of patients with symptomatic and frequent ventricular arrhythmias, but without recent myocardial infarction.¹

In a prospective, one year follow up trial, we studied 100 patients with symptoms of frequent ventricular arrhythmias to examine long-term efficacy and safety of propafenone treatment. We used multivariate analysis to

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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), bradycardia <50 beats/min and conduction disturbances of the sinoatrial 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 under-

went an initial wash-out period of one week and a qualifying 24 hour Holter monitoring period. The patient was only included in an active treatment group if the first 24 hour Holter examination showed >30 symptomatic ventricular extrasystoles per hour and repetitive ventricular arrhythmias (ventricular pairs or salvos). Baseline examinations (physical examination, electrocardiogram, chemical blood analysis, echocardiogram) were performed at this time. The ejection fraction was determined in all patients by invasive measurements or by echocardiography.

All patients underwent a 10 day placebo period with 24 hour Holter recordings on day 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 a 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 Graboys *et al* (a reduction in ventricular extrasystoles of >84%, of ventricular pairs by >90%, and of ventricular tachycardia by 100%).^{26–28} Arrhythmogenic events were defined according to the criteria reported by Podrid *et al*.²⁹ 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 χ^2 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

Data on 100 patients before antiarrhythmic treatment

Variable	Value
Sex (M:F)	69:31
Age (mean (SD)) (y)	62.7 (6.8)
Underlying heart disease (patients):	
Coronary artery disease	50
Previous MI	(14)
Cardiomyopathy	14
Valve disease	9
Pulmonary heart disease	7
Other heart disease	13
No heart disease	7
NYHA classification (patients):	
NYHA I	33
NYHA II	50
NYHA III	17
NYHA IV	0
Ejection fraction (%) (mean (SD))	41 (8)
Ventricular arrhythmias (patients):	
>30 symptomatic VE/h	100
Lown class III	11
Lown class IVA	35
Lown class IVB	54
VE/24h (mean (SD))	10.875 (6594)
VB/24h (mean (SD))	209 (278)
VT/24h (mean (SD))	26 (46)
Previous antiarrhythmic treatment	18/100

MI, myocardial infarction; NYHA, New York Heart Association; VE, ventricular extrasystole; VB, ventricular pairs; VT, ventricular tachycardia.

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

Figure 1 Changes (from a 100% decrease to a 400% increase) in the frequency of ventricular extrasystoles (VE) between the first and second placebo 24 h Holter recordings (+400% increase) and during a Holter recording when the patient was treated with propafenone (450 mg/day) (propafenone) in patients with coronary artery disease (A) and those without (B). The shaded area indicates a superior effect of propafenone.

Figure 2 Changes (from a 100% decrease to a 400% increase) in the frequency of ventricular pairs (VB) between the first and second placebo 24 h Holter recordings and during a Holter recording made when the patient was treated with propafenone (450 mg/day) in patients with coronary artery disease (A) and those without. The shaded area indicates a superior effect of propafenone and the hatched area indicates a superior effect of placebo.

Figure 3 Changes (from a 100% decrease to a 400% increase) in the frequency of ventricular tachycardia (VT) between the first and second Holter recordings and during a Holter recording when the patient was treated with propafenone (450 mg/day) in patients with coronary artery disease (A) and those without (B). The shaded area indicates a superior effect of propafenone and the hatched area indicates a superior effect of placebo.

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 assess 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/daily (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.

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%).

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

nausea) and two patients because of exacerbation 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 responders to propafenone had arrhythmogenic events during Holter recording.

Discussion

Recent data from the CAST study²⁴ have fuelled the debate³⁰⁻³⁵ 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 encainide 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 uncontrollable 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 encainide it differs from both. It has additional β blocking^{3 6 9-13} and calcium-channel blocking properties.^{6 9 10} The β blocking dose-related effect was found even at low doses in the study by Härtel³⁶ and others^{13 19} and may enhance the class I properties of propafenone.²¹ Placebo studies showed the clinical effectiveness of propafenone,¹⁶ which was as effective as disopyramide,^{31 32} quinidine,³³ tocainide,³⁴ flecainide³⁵ 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 antiarrhythmic efficacy persists and that arrhythmogenesis does not increase.²⁵

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. Additionally, all our patients had >30 ventricular premature beats, 89% of patients had repetitive 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 complexity 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 combined and restrictive criteria for drug induced suppression of arrhythmia.

We chose to show data on arrhythmia variability, on propafenone efficacy, and on arrhythmogenicity simultaneously and independently 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 graph, the area between the placebo and propafenone curves showed a complete picture of the antiarrhythmic 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 others^{1 4 16} 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 symptoms 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 continue 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 propafenone. There were no correlations with other clinical variables. Side effects or acute arrhythmogenesis 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 propafenone responder show arrhythmogenesis 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.

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ABSTRACTS IN CARDIOLOGY

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.

M J DAVIES

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 valvular 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: anulus, 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 anulus, 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.

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