Propafenone: A Promising New Antiarrhythmic Agent

Edward N. Shen, M.D., F.C.C.P.*

(Chest 1990; 98:434-41)

Propafenone is a new class IC antiarrhythmic agent that has just been released in the United States for use in treatment of malignant ventricular arrhythmias (Rythmol, Knoll Pharmaceuticals, Whippany, New Jersey). It was first marketed in Europe in 1977, and has gained wide acceptance there and in Canada for the treatment of various types of ventricular and supraventricular arrhythmias. It acts primarily by inhibiting the fast inward sodium current. Like flecaïnide and encainide, it has very prominent conduction slowing effects, with relatively little change in repolarization and corrected QT interval. In addition, it has mild beta blocking effects and very weak calcium entry blocking action. It is extensively metabolized, with two known active metabolites, the formation of one of which is genetically determined. Its metabolism is saturable, with bioavailability increasing with higher dosage. It exhibits very strong suppression of ventricular ectopy, with more variable efficacy in sustained ventricular tachycardia. It is also very effective in controlling all forms of supraventricular reentrant tachyarrhythmias including atrial fibrillation. This report reviews the pharmacology, electrophysiology, efficacy and safety of this agent.

Clinical Pharmacology

Propafenone is 2-[2-hydroxy-3-(propylamino)propoxy]-3-phenylpropriophenone hydrochloride (Fig 1). It is available in both the oral and intravenous forms in Europe, but is initially available in the United States as an oral formulation. Given orally, more than 95 percent of the drug is absorbed.1,2 Because of extensive presystemic (first-pass) hepatic metabolism that is saturable at low doses, propafenone exhibits a dose-dependent bioavailability, which increases non-linearly with increasing dose. At single doses of 150 mg or 300 mg, bioavailability is about 5 to 12 percent; with 450 mg, an increase of up to 40-50 percent is noted. This is consistent with saturability of a hepatic clearance mechanism. Correspondingly, a non-linear relationship exists between dosage and steady-state concentration, with a threefold increase in dosage from 300 to 900 mg per day causing a ten-fold increase in mean plasma concentration.3 Propafenone is well absorbed after oral administration, and peak concentration is achieved 2 to 3 h after each dose. It is almost entirely metabolized, with less than 1 percent appearing unchanged in the urine.

During long-term therapy, the mean serum half-life is about 6 h, with a range of 2 to 10 h for most patients.4 Great intersubject variability is observed, ranging from 2 to 32 h. Recent studies have shown that propafenone is metabolized by a hepatic oxidative pathway which utilizes a specific cytochrome P-450 known as P-450<sub>2D6</sub>. This enzyme is responsible for the 5-hydroxylation of propafenone as well as the disposition of some 30 other compounds (including encainide and metoprolol). The activity of this enzyme is characterized and more conveniently studied by the 4-hydroxylation reaction of debrisoquin, an antihypertensive agent.5,6 Two genetically determined patterns of propafenone metabolism exist. Of all patients, 90 percent are rapid metabolizers, with an elimination half-life ranging from 2 to 10 h. They metabolize propafenone into two metabolites: 5-hydroxypropafenone and N-depropylpropafenone.5,7 These two metabolites have antiarrhythmic activity comparable to propafenone, but both are present in concentrations less than 20 percent of the parent agent. The 5-hydroxylation reaction is saturable, accounting for the nonlinear rise in the parent propafenone concentration with higher dosage. Less than 10 percent of all patients are poor metabolizers, and in these patients the elimination half-life ranges from 10 to 32 h. In poor

*Associate Professor of Medicine, John A. Burns School of Medicine, University of Hawaii; Director, Clinical Electrophysiology, Straub Clinic, Honolulu.

Reprint requests: Dr. Shen, 888 South King Street, Honolulu 96813

Figure 1. Chemical structure of propafenone.
metabolizers, N-depropylpropafenone occurs in concentrations of about 10 percent of the parent compound, but cytochrome P-450\textsubscript{IA} is functionally absent and 5-hydroxylation does not occur, with 5-hydroxypropafenone consequently undetectable. The poor metabolizer phenotype is an autosomal recessive trait. Rapid metabolizers display saturable metabolism, whereas poor metabolizers do not. Despite these differences, steady-state is achieved after four to five days of oral dosing in all patients. It is probably not necessary to determine a patient's metabolic phenotype, as there does not appear to be any difference in antiarrhythmic action or serious side effects of the drug between rapid and poor metabolizers (with the exception perhaps of the latter having more central nervous system side effects). The therapeutic plasma level of propafenone has been suggested to be 0.5 to 2.0 \( \mu \text{g/mL} \). This concentration range has not been found to adequately predict either the antiarrhythmic activity or the adverse effects, largely because of the genetic polymorphism and the relative contribution of the two active metabolites. The one exception is that the central nervous system side effects are more common with levels of greater than 0.9 \( \mu \text{g/mL} \), regardless of phenotype. The dosage in clinical use should be guided by the achievement of desired therapeutic effect or adverse reactions rather than the plasma level. The drug is 97 percent protein bound, mainly to alpha,-acid glycoprotein. Considerable tissue binding of propafenone occurs as the steady-state volume of distribution is 3 L/kg of body weight. This tissue uptake is not surprising because propafenone is a highly lipophilic drug.

Propafenone has known interactions with digoxin, increasing the steady-state concentration of digoxin by 37 to 83 percent without affecting renal clearance. It also raises the plasma concentration of warfarin, with an increase in prothrombin time of approximately 25 percent. Metoprolol, which has been shown to exhibit the oxidative phenotype associated with debrisoquin, displays pronounced (two-to fivefold) elevations in plasma concentrations during coadministration with propafenone. Thus, its beta-blocking activities and side effects may be exaggerated. Propanolol, though not clearly linked to the debrisoquin phenotype, also exhibits a twofold rise in plasma concentration when given with propafenone. Cimetidine causes increases of about 20 percent in several of propafenone's pharmacokinetic parameters, including peak plasma concentration and mean steady-state concentration, without changing conduction intervals as measured by surface electrocardiogram. Propafenone has been safely administered to patients receiving quinidine or procainamide. Quinidine, a potent inhibitor of 5-hydroxylation in rapid metabolizers, increases propafenone plasma concentration more than twofold, without changing the electrocardiographic parameters or ventricular ectopy frequency.

**Electrophysiology**

Propafenone blocks the fast inward sodium current, and is categorized as a class I agent according to the Vaughan-Williams classification scheme. It slows the upstroke (phase 0) of the Purkinje fiber action potential. Unlike quinidine, the prototype of this class, propafenone has little effect on repolarization and action potential duration and falls into the subclass IC, to which agents such as flecainide and encainide also belong.

The sodium channels are blocked by the antiarrhythmic agent during the upstroke and plateau phases of the action potential with dissociation during diastole. The rate of dissociation is most rapid with IB agents (like lidocaine, mexiltiline) and least rapid with IC drugs. The IA agents (like quinidine, procainamide, disopyramide) act somewhere in between. With higher heart rates, more frequent action potentials and less time for diastole, binding increases and thus blockage increases (rate dependency). For a IC agent like propafenone, there is significant rate dependency. Furthermore, the drug dissociates so slowly that binding is prominent even at normal heart rates, accounting for the strong conduction slowing effect of this subclass of agents. This is characterized on the surface electrocardiogram by a prolonged QRS duration (a measure of the intraventricular conduction time), which is present even during sinus rhythm. The major metabolites, 5-hydroxylpropafenone and N-depropylpropafenone, have similar sodium channel blocking effects, with the latter being less potent.

In humans, propafenone has no significant effect on spontaneous sinus rate or sinus-node function. It causes small but significant prolongation in the atrioventricular (AV) nodal and His-Purkinje conduction times (as measured by the A-H and H-V intervals respectively), by an average of 10 to 15 percent. The conduction time through extranodal accessory pathways is also prolonged. On the surface electrocardiogram, the delay in AV nodal conduction is seen as a prolongation of the P-R interval. In addition to slowing conduction velocity, it prolongs the refractoriness in all cardiac tissues: atrial, AV nodal, and ventricular (as evidenced by increases in their respective effective refractory periods), affecting the atrium more than the ventricle. Propafenone has also been reported to increase the refractoriness in extranodal accessory pathways.

The combination of delaying conduction velocity and increasing tissue refractoriness (the determinants of reentry) probably accounts for the majority of its antiarrhythmic actions. In ischemic canine Purkinje fibers, it also suppresses delayed after-depolarizations.
and triggered activity.24

No significant change in the rate-corrected Q-T interval is noted, as consistent with a class IC antiarrhythmic agent. Of note, when combined with another agent which prolongs the Q-T interval (eg, amiodarone), potentiation may occur and torsades de pointes has been reported.25

In chemical structure, propafenone bears some resemblance to beta blockers. In vitro and in vivo, it does exhibit competitive beta-blocking action in various cardiac and non-cardiac tissues. In the isolated human left ventricular tissue, studies of competitive inhibition revealed that propafenone had 1/50 the activity of propranolol. McLeod and co-workers26 evaluated the chronotropic response in six healthy subjects during exercise and during isoproterenol administration, after either 300 mg of propafenone or 40 mg of propranolol was administered. They noted a modest reduction in both the isoproterenol and exercise-induced heart rate response and suggested that the relative affinity of propafenone for human beta receptors, was approximately 1/40 that of propranolol. These observations suggest that in clinical doses, propafenone is likely to induce a modest degree of beta-blocking action, especially when the adrenergic tone is high. It has been shown that antiarrhythmic effects of class I agents may be reversed by beta-adrenergic stimulation, as assessed by electrophyslogic study (EPS).27 It has also been shown that adjunctive therapy with beta antagonists enhances ventricular arrhythmia suppression by class I agents, as assessed by ambulatory monitoring and exercise testing.28 Thus, propafenone's beta blocking activity may confer upon the drug a unique advantage as compared with other class I agents. At very high concentrations, propafenone can inhibit the slow inward calcium current.29 Its calcium entry blocking potency is about 1/100 that of verapamil and probably does not play a significant role clinically.

CLINICAL EFFICACY

Ventricular Premature Complexes and Nonsustained Ventricular Tachycardia

There have been numerous placebo-controlled trials investigating the effectiveness of oral propafenone in the suppression of ventricular premature complexes (VPCs).30-33 In general, propafenone was administered in doses ranging from 450 mg per day (150 mg every 8 h) to 900 mg per day (300 mg every 8 h). Throughout this dosage range, the studies were consistent in showing that propafenone was significantly more effective than placebo. In a recent multi-center double-blind, randomized, placebo-controlled study involving 226 patients,34 there was a clear-cut dose-dependent suppression of ventricular ectopy, with more striking effect on ventricular couplets and ventricular tachycardia (VT) beats than on total VPCs. Compared to placebo at two weeks, 337.5 mg/day reduced VPCs by 70.8 percent (p<0.05), 450 mg/day by 82.0 percent (p<0.01), 675 mg/day by 90.2 percent (p<0.01) and 900 mg/day reduced VPCs by 95.3 percent (p<0.01). Many other studies report favorable results, variable from 60 percent of patients exhibiting over 50 percent suppression of VPCs24 to 92 percent exhibiting 90 to 100 percent suppression.25 In the majority of patients, over a 90 percent suppression of couplets and nonsustained VT was observed.

Propafenone compares very favorably with other agents. It has been found to be at least as efficacious and well tolerated as quinidine,26,27 mexiletine,28 and flecainide.29 Hodges30 compared propafenone to quinidine in a large double-blind placebo-controlled parallel study involving 105 patients. Two dosages were used for each drug (600 mg/day and 900 mg/day for propafenone vs 800 mg/day and 1600 mg/day for quinidine). Both drugs significantly reduced ventricular ectopy at both dose levels. There was no significant difference between both drugs in effectiveness (with a higher percentage responding to propafenone). However, significantly more (p<0.01) patients receiving quinidine (31 percent) dropped out of the study than patients receiving propafenone (9 percent), mainly related to diarrhea with the former agent. Propafenone 300 mg every 8 hours was compared to disopyramide 200 mg every 8 hours in a double-blind, placebo-controlled randomized crossover study.31 For greater than 90 percent VPC reduction and abolition of nonsustained VT, there were more responders with propafenone than with disopyramide. The drug has also been used efficaciously and safely when added to class IA agents.15 The combination of propafenone with procainamide or quinidine resulted in more VPC suppression than either drug alone (27 VPC/h vs 211 VPC/h, p<0.001). The effective dosage of propafenone used in combination therapy was significantly less than that used in monotherapy (480 mg/d vs 730 mg/d, p<0.001).

Hammill et al32 described the long-term efficacy of propafenone in 45 patients who had previously been shown to be refractory to a mean of 3.8 antiarrhythmic drugs. Thirty patients (67 percent) responded to propafenone during the dose-ranging phase of the study with decreases in total VPCs, pairs, and runs of 95 percent, 98 percent, and 95 percent, respectively. During a subsequent period of 12.4 months, the administration of propafenone was effective and well tolerated in 22 (73 percent) of the 30 patients; was discontinued due to side effects in seven patients (23 percent); and was discontinued due to ventricular tachycardia in only one patient (4 percent). This study and others in smaller groups of patients30 have indicated that patients treated with propafenone for up to
four years have continued good suppression of total
VPCs and excellent suppression of paired beats and
runs.
It is long known that the presence of ventricular
ectopy post-myocardial infarction (MI) is a risk factor
for higher mortality, independent of left ventricular
function. However, previous trials of antiarrhythmic
therapy in post-MI patients have failed to demonstrate
any benefit. Initially, this was felt to be due to the
small sample sizes studied and the lack of specific
attention towards ventricular arrhythmia recognition
and control. Unfortunately, the recently published
larger, better designed, placebo-controlled Cardiac
Arrhythmia Suppression Trial (CAST) showed that use
of certain agents (flecainide and encainide) in the
early post-MI phase (6 days to 2 years) actually caused
harm (with a 2.5 fold increase in mortality). Notably,
propafenone has not been used in the study and a
direct extrapolation of the trial results to this agent
(being also class IC) is not justified, especially since
propafenone uniquely possesses beta-blocking activ-
ity, which may be beneficial in post-MI patients.
Nonetheless, in the absence of positive data, the drug
should be avoided in post-MI patients with asymp-
tomatic or minimally symptomatic nonsustained ventric-
ular arrhythmias. In the significantly symptomatic
patients with nonsustained ventricular arrhythmias,
therapy will need to be individualized, with careful
assessment of the risk-benefit ratio, and clear under-
standing that its usage in these patients has not been
approved by the Food and Drug administration (FDA).

Sustained Ventricular Tachycardia

Sustained VT is frequently defined as VT lasting at
least 30 s or requiring intervention (such as direct
current cardioversion) for termination. At least five
studies exist that examine the effectiveness of propa-
fenone in suppressing sustained VT, as assessed by
EPS. The majority of the patients evaluated were
refractory to or intolerant of other antiarrhythmic
agents. Favorable results were reported in four of the
five studies with sustained VT induction abolished
from two of 16 patients (13 percent) to five of six
patients (83 percent).

The frequency of non-inducibility probably does
not place this drug much above the other available
conventional antiarrhythmic agents like quinidine or
procainamide. In one study, however, patients with
inducible but slowed and well-tolerated VT on propa-
fenone were discharged on therapy with the drug,
and five (70 percent) of seven patients remained
asymptomatic on follow up (mean 11 months). The
authors concluded that initiation of VT by EPS on
propafenone did not preclude a favorable outcome.
In a large study by Waller et al using other drugs, it
is found that patients with sustained VT still inducible
but "beneficially" affected (as defined by tachycardia
cycle length increasing by 100 ms and not producing
severe symptoms) have a higher VT recurrence rate
than noninducible patients, but significantly reduced
total mortality and sudden death mortality as com-
pared to inducible patients without the beneficial
response. In fact, this reduction in mortality is similar
to that seen in the noninducible patients. The above
two studies suggest that in patients in whom sustained
VT is still inducible on propafenone, but sufficiently
slowed and well tolerated, a clinical trial may be
worthwhile.

As assessed noninvasively by ambulatory monitor-
ing and exercise testing, VT salvos also respond
favorably, with 60 percent of the patients showing
complete elimination.

Supraventricular Tachycardias

Even though Knoll has not yet sought FDA approval
for propafenone usage in supraventricular tachycar-
dias (SVT), the drug holds much promise.

Both the intravenous as well as the oral formulations
have been well assessed. One placebo-controlled,
randomized, double-blind crossover study evaluated
the efficacy of intravenous propafenone in three forms
of SVT: AV reciprocating tachycardia using a bypass
tract (14 patients), AV nodal reentrant tachycardia
(three patients), and intra-atrial reentrant tachycardia
(three patients). Propafenone was infused in a dosage
of 2 mg/kg over 10 min. It acutely terminated SVT in
15 (75 percent) of 20 patients, vs none of the 11 patients
receiving placebo (p<0.01). Its mechanism was prob-
ably related to increasing refractoriness and decreasing
conduction velocity in the atria, AV node, and acces-
sory pathway. In one patient, in whom the initiation
of intra-atrial tachycardia was facilitated by isoprote-
renol, the drug's beta-blocking effect contributed to
its effectiveness. No adverse effects were evident. The
authors concluded that intravenous propafenone was
at least as effective as intravenous verapamil in the
acute termination of reentrant SVT. Because of its
additional depressive effects on the atria, accessory
bypass tracts, and the ventricles, however, intravenous
propafenone should have a wider clinical application
than intravenous verapamil, especially in cases involv-
ing suspicion of ventricular preexcitation or when the
differentiation between SVT with aberration and VT
is unclear.

Intravenous propafenone is also effective in con-
verting recent-onset atrial fibrillation and flutter (less
than 15 days) to sinus rhythm. A dose of 2 mg/kg of
propafenone resulted in conversion of 47 (62 percent)
of 68 patients with fibrillation and 5 (33 percent) of 15
patients with flutter within 29 ± 24 minutes. The
success rate was inversely proportional to arrhythmia
duration (27 percent efficacy in arrhythmia lasting
over 48 hours) and echocardiographic left atrial size (49 ± 12 mm in nonconverters vs 39 ± 7 mm in converters, p<0.0005). In nonconverters, the ventricular rate decreased from 141 ± 26 to 104 ± 22 beats per minute (p<0.0005). Oral propafenone is similarly helpful in suppression of drug refractory atrial fibrillation and flutter. In one study of 53 patients, complete control was achieved in 34 with partial control in 6 more (overall 77 percent), with mean dose of 700 ± 190 mg and follow-up of 9 ± 6 months. These patients failed an average of 3 ± 2 drugs previously. Such effectiveness in atrial fibrillation and flutter is quite remarkable. However, it should be appreciated that these studies were not placebo-controlled.

The efficacy of oral propafenone in the Wolff-Parkinson-White syndrome has been fairly well studied. It was found that approximately 80 percent of patients improved on the oral agent, either with no recurrence of tachyarrhythmia or with decreased recurrences, and with slower, self-terminating attacks which were well tolerated. Because the drug prolongs the refractoriness of the accessory pathway, it also holds promise for prophylaxis against the potentially life-threatening atrial flutter-fibrillation in this syndrome by decreasing the ventricular response. It appears to be effective also in accessory pathways with short antegrade effective refractory periods, which typically do not respond well to agents like quinidine and procainamide.

Oral propafenone has also been found useful for AV nodal reentrant tachycardia and atrial tachycardia. Interestingly, in the so-called adrenergically dependent atrial tachycardia and fibrillation (with the arrhythmia occurring predominantly during the day, being triggered by effort or emotion), propafenone was actually more effective than either quinidine or amiodarone.

**Dosage and Administration**

Only the oral formulation is currently available in the United States, as tablets of 150 mg and 300 mg. Eventually, a 225 mg tablet will be introduced. The usual dosage ranges from 150 mg to 300 mg three times a day. Because of non-linear kinetics, a three-fold increase in dosage may lead to a ten-fold elevation in plasma concentration (as in changing from 150 mg twice a day to 300 mg three times a day). A corresponding non-linear rise in efficacy and side-effects is possible and should be watched for. A stepwise increase from 150 mg to 225 mg to 300 mg three times a day every three to four days may be considered, even though one does not necessarily have to start at the lowest dose. Dosing should be guided more by therapeutic endpoints or side effects rather than plasma levels. Excessive QRS prolongation may require dosage reduction. Concurrent doses of digoxin, warfarin, propanolol and especially metoprolol may need to be decreased.

The drug is extensively metabolized by the liver, and a significant portion of metabolites are excreted in the urine. Therefore, it should be administered cautiously to patients with impaired hepatic or renal function. Severe liver failure would increase the bioavailability of propafenone and prolong its half-life to about 9 h. Thus, the initial dosage should be decreased to 20 to 30 percent of the normal dose in patients with hepatic dysfunction. In severe renal failure, no clearcut guidelines exist as to dosage reduction, and a close clinical follow-up would be necessary.

There is no firm recommendation on the intravenous dosage. The loading dose reported in the literature is usually 2 mg/kg, infused over 10-15 min. This may be followed by a continuous infusion of 0.5 to 2 mg/min.

**Adverse Reactions**

One of the strong advantages of propafenone is its favorable side-effect profile. Severe side effects are uncommon and the drug is generally well tolerated. Intolerance could be frequently minimized by decreasing the dosage. Drug discontinuation occurs in only about 20 percent of all cases. The more important side effects follow.

**Proarrhythmia**

All antiarrhythmic drugs have proarrhythmic potential, as defined by the appearance of new arrhythmias or worsening of previously existent arrhythmias. In patients treated for ventricular ectopy, this may be observed clinically as an increase in VPC frequency, conversion of nonsustained to sustained VT, or the new appearance of VT or ventricular fibrillation. For propafenone, clinically significant proarrhythmia occurred in about 5 percent of all cases reported in a large study involving a heterogeneous population of 774 patients. From CAST, it is appreciated that the proarrhythmic risk in post-MI patients with flecainide and encainide is sustained over time, and is not readily apparent in the early phases of usage. There is also an increased risk of nonarrhythmic deaths. Whether similar patients on propafenone are subject to the same seemingly unpredictable "late" events is unknown, but close follow-up is certainly essential. Furthermore, it is known that the proarrhythmic tendency of currently available agents increases with the presence of compromised left ventricular function or sustained ventricular tachyarrhythmia. In these patients, propafenone should be started with slow titration, under monitoring conditions in a hospital. If a patient has sustained VT, the efficacy and perhaps the proarrhythmic tendency with propafenone may be more expediently defined by EPS.
There is a recent report of two cases of sustained ventricular tachyarrhythmia (VT and ventricular flutter) in patients receiving flecainide for atrial fibrillation, both immediately post-exercise on a treadmill. The reliability of exercise testing as a tool for exposing latent ventricular proarrhythmia with propafenone (and indeed, with any agent) is unknown, but the test should be considered part of the routine assessment. Further validation is necessary.

Conduction Disturbances

Because of the drug's conduction-slowing effects, first-degree AV block, bundle branch block, and intraventricular conduction delay are occasionally reported, but usually do not require drug discontinuation. Complete AV block is rare. As with most antiarrhythmic agents, propafenone should be avoided in patients with pre-existing AV conduction disturbances and in those with sick sinus syndrome who do not have a permanent pacemaker.

Because of the drug's prominent rate dependency, sometimes a patient with SVT on propafenone may actually present with a wide complex tachycardia, mimicking VT. This may lead to the erroneous diagnosis of ventricular proarrhythmia.

Myocardial Depressant Effects

Propafenone has been shown to exert a mild negative inotropic effect. Right-heart catheterization studies, using intravenous propafenone, have revealed a mild asymptomatic increase in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistance, and a mild depression of cardiac indices. Likewise, a mild decrease in left ventricular ejection fraction (LVEF) has been reported in patients receiving the oral drug. Generally, it is an effective and well-tolerated agent for the management of patients with VT who have a history of congestive heart failure. In one study, two of 13 patients with LVEF less than 40 percent had worsening of heart failure. In the same study, another 14 patients had a small but significant decrease in LVEF from 52 ± 19 percent to 48 ± 11 percent, with the effect more marked if the baseline EF was less than 50 percent. Therefore, patients who have poor myocardial function should be optimized hemodynamically before initiation of therapy, and they should be closely watched for signs of worsening heart failure.

Gastrointestinal Side Effects

Propafenone is very well tolerated in terms of gastrointestinal side effects, and is superior to quinidine in this respect. About 20 percent of patients may report some form of adverse effect, usually mild, which may include constipation, nausea/vomiting, and uncommonly, diarrhea. Because the drug is secreted by the salivary glands, 5 to 10 percent of patients may notice a bitter taste. This has rarely been bothersome enough to require drug discontinuation.

Neurologic Side Effects

These occur in about 20 percent of cases, the majority with daily doses of 900 mg or more. Poor metabolizers appear to be more susceptible. Dizziness is the most common, followed by paresthesia, ataxia, change in mental status and tremors. Seizures are exceedingly rare.

Asthmogenicity

Very uncommonly, propafenone has been reported to worsen dyspnea in severe chronic obstructive lung disease, presumably related to its beta-blocking effect. In patients with mild intermittent asthma, there was no significant change in pulmonary function test measurements on treatment with propafenone (up to high dose of 300 mg every 8 h) when compared with placebo, but the mean provocative dose of methacholine required to reduce forced expiratory volume in one second (FEV1) by 20 percent was significantly decreased with the high dose, suggesting that bronchial provocation may be a more sensitive measure of the asthmogenicity of the agent. Even though bronchospasm is a rare adverse effect, the drug should still be administered with caution to patients with airway disease.

Miscellaneous

Not infrequently, propafenone can cause a positive antinuclear antibody titer, which may revert to normal with continued treatment. Unlike procainamide, there has only been one case of clinical lupus reported in the world literature, which resolved after discontinuation of the drug.

Conclusions

Propafenone is a new class IC agent with unique, mild, beta-blocking effects. It has two active metabolites which may contribute to antiarrhythmic action. It has been shown to be efficacious in the treatment of a wide variety of ventricular and supraventricular arrhythmias. Moreover, it has a favorable side-effect profile and high patient acceptance rate. However, it should be administered cautiously in patients with poor left ventricular function, as the proarrhythmic and myocardial depressant effects of the drug may be exaggerated in this group. It should not be used in early post MI patients with asymptomatic or mildly symptomatic ventricular ectopy, in view of the recent CAST findings. Future placebo-controlled mortality trials with propafenone are needed in these patients. In the United States, the drug has been approved for use in malignant ventricular arrhythmias. It has the potential of making a significant impact on antiarrhyth-
mic drug therapy here, as it has already done in Europe and Canada.

References
The relationship between ventricular arrhythmias, left ventricular dysfunction and mortality in the two years after myocardial infarction. Circulation 1984; 69:250-58

Furberg CD. Effect of antiarrhythmic drugs on mortality after myocardial infarction. Am J Cardiol 1983; 52:32C-36C


Counsel P, Leclercq JF, Hassayag P. European experience with the antiarrhythmic efficacy of propafenone for supraventricular and ventricular arrhythmias. Am J Cardiol 1984; 54:60D-66D


Prescribing information. Rytmon (propafenone) product package insert


