PRODUCT MONOGRAPH

NU-PROPAFENONE

Propafenone Hydrochloride Tablets

150 mg

Antiarrhythmic Agent

Control # 089683

NU-PHARM INC.
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PRODUCT MONOGRAPH

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150 mg

THERAPEUTIC CLASSIFICATION

Antiarrhythmic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Propafenone is an antiarrhythmic agent which possesses class Ic properties in the modified electrophysiological classification of Vaughan-Williams. It has a direct stabilizing action on myocardial cell membranes. The electrophysiological effect of propafenone manifests itself as a reduction of the upstroke velocity (Phase 0) of the monophasic action potential, while phase 4 spontaneous automaticity is depressed. Diastolic excitability threshold is increased and effective refractory period prolonged. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces the fast inward sodium current.

In addition to a local anesthetic effect, approximately equal to procaine, propafenone has weak beta-blocking activity. Clinical trials employing isoproterenol challenge and exercise testing suggest that the affinity of propafenone for beta-adrenergic receptors, as calculated from dose ratios and drug concentrations, is about 1/40 that of propranolol. Propafenone also inhibits the slow calcium influx at high concentrations; however, this action is weak (approximately 1/100 of verapamil) and does not contribute to its antiarrhythmic effect.

Electrophysiology

Electrophysiology studies have shown that propafenone prolongs atrioventricular conduction and in some instances significantly lengthens sinus nodal recovery times with a non-significant effect on sinus cycle length. AV nodal conduction time (AH interval) as well as His-Purkinje conduction time (HV interval) are prolonged. Propafenone increases atrial, AV nodal and ventricular effective refractory periods. Propafenone causes a dose-dependent increase in the PR interval and QRS complex duration. Non-significant increases in the QT_c interval and occasional slowing of the heart rate have also been observed.

Hemodynamics

Propafenone can exert a negative inotropic effect on the myocardium. Increases in pulmonary capillary wedge pressure and systemic and pulmonary vascular resistance, with a concurrent mild depression of cardiac output and cardiac index, have occurred following propafenone administration. Decreases in left ventricular function have been recorded in patients with depressed baseline function.

Pharmacokinetics and Metabolism

Following oral administration, propafenone is nearly completely absorbed but undergoes extensive first-pass hepatic metabolism resulting in a dose-dependent absolute bioavailability ranging from 3-40%. Bioavailability is enhanced by administration of the drug with food. Peak plasma concentrations occur within 3 hours. There is a non-linear increase in both plasma concentration and bioavailability with increase in dosage, presumably due to saturation of first pass hepatic metabolism as the liver is exposed to higher concentrations of propafenone. This departure from dose linearity occurs when single doses above 150 mg are given. A 300 mg dose gives plasma levels six times that of a 150 mg dose. Similarly, for a 3-fold increase in daily dose from 300 to 900 mg/day there is a 10-fold increase in steady-state plasma concentration.

Patients may be categorized into fast (90%) or slow (10%) metabolizers of propafenone, resulting in low or high plasma concentrations respectively. This variability in metabolism is thought to be due to a genetically determined deficiency in one pathway. Propafenone undergoes extensive hepatic metabolism with <1% excreted as unchanged drug. In man, the major metabolites are: 5–hydroxypropafenone (5-OHP) and N-depropylpropafenone (NDPP); both occurring in concentrations less than 20% of the parent compound. In vitro preparations and animal studies have shown that the 5-OHP metabolite possesses antiarrhythmic and beta-adrenoreceptor blocking activity comparable to propafenone. For fast metabolizers of propafenone, the elimination half-life is 5.5 ± 2.1 hours; for slow metabolizers, the elimination half-life is 17.2 ± 8.0 hours. In slow metabolizers, as opposed to fast metabolizers, a linear relationship between propafenone dose and plasma concentration was observed. Slow metabolizers had higher propafenone plasma concentrations which they required for suppression of arrhythmia since they did not produce the active metabolite 5-OHP. These higher propafenone plasma concentrations

may lead to clinically evident beta-blockade. Despite these differences in pharmacogenetics, steady-state conditions are achieved after 3-4 days in all patients.

Therapeutic plasma levels of propafenone appear to be in the range of 0.5 - 2.0 mcg/mL. Propafenone is 97% bound to plasma proteins.

Comparative Bioavailability

Two comparative bioavailability studies were performed using healthy human volunteers - one under fasting conditions and one under fed conditions. The rate and extent of absorption of propafenone following administration of a single 300 mg (one 300 mg tablet) dose of NU-PROPAFENONE and RYTHMOL were measured and compared. The results are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Propafenone (Dose: 1 x 300 mg) From Measured Data - Under Fasting Conditions

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Nu-Propafenone	Rythmol ® †	
AUC_T (ng•hr/mL)	1325 2679 (155)	1255 2641 (165)	103.5
AUC_I (ng•hr/mL)	1372 2871 (165)	1301 2838 (176)	103.5
C_{max} (ng/mL)	269 371 (86)	252 352 (88)	104.9
T_{max} (hr)*	3.31 (30)	3.20 (27)	
$t_{1/2}$ (hr)*	3.09 (89)	3.09 (89)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Rythmol ® is manufactured by Knoll Pharma Inc. Canada , and was purchased in Canada.

Summary Table of the Comparative Bioavailability Data Propafenone (Dose: 1 x 300 mg) From Measured Data - Under Fed Conditions			
Parameter	Geometric Mean Arithmetic Mean (CV%) Nu-Propafenone	Rythmol ® †	Ratio of Geometric Means (%)**
AUC_T (ng•hr/mL)	1494 2204 (106)	1394 2112 (109)	108.1
AUC_I (ng•hr/mL)	1539 2274 (111)	1437 2193 (118)	108.0
C_{max} (ng/mL)	340 419 (57)	321 408 (65)	106.6
T_{max} (hr)*	3.12 (36)	3.23 (34)	
$t_{1/2}$ (hr)*	2.72 (54)	2.70 (60)	

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Rythmol ® is manufactured by Knoll Pharma Inc. Canada , and was purchased in Canada.

INDICATIONS AND CLINICAL USE

No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

NU-PROPAFENONE (propafenone HCl) is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia. Propafenone may also be used for the treatment of patients with documented symptomatic ventricular arrhythmias when the symptoms are of sufficient severity to require treatment. Because of the proarrhythmic

effects of propafenone, its use should be reserved for patients in whom, in the opinion of the physician, the benefit of treatment clearly outweighs the risk.

For patients with sustained ventricular tachycardia, propafenone therapy should be initiated in the hospital. Initiation in hospital may also be required for certain other patients depending on their cardiac status and underlying cardiac disease.

The effects of propafenone in patients with recent myocardial infarction have not been adequately studied and, therefore, its use in this condition cannot be recommended.

There is no evidence from controlled clinical trials that the use of propafenone favourably affects survival or the incidence of sudden death.

CONTRAINDICATIONS

NU-PROPAFENONE (propafenone HCl) is contraindicated in the presence of the following: Severe or uncontrolled congestive heart failure (see WARNINGS); cardiogenic shock; sinoatrial, atrioventricular and intraventricular disorders of impulse conduction and sinus node dysfunction (e.g. sick sinus syndrome) in the absence of an artificial pacemaker; severe bradycardia (less than 50 beats/min.); marked hypotension; bronchospastic disorders; severe disorders of electrolyte balance; severe hepatic failure (see PRECAUTIONS); known hypersensitivity to the drug.

WARNINGS

Mortality

The results of the Cardiac Arrhythmia Suppression Trials (CAST) in post-myocardial infarction patients with asymptomatic ventricular arrhythmias showed a significant increase in mortality and in the non-fatal cardiac arrest rate in patients treated with flecainide and encainide compared with a matched placebo group. CAST was continued using a revised protocol with the moricizine and placebo arms only. The trial was prematurely terminated because of a trend towards an increase in mortality in the moricizine treated group.

The applicability of these results to other populations or other antiarrhythmic agents is uncertain, but at present it is prudent to consider these results when using any antiarrhythmic agent.

Proarrhythmic Effects

Propafenone may cause new or worsen existing arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes. It is therefore essential that each patient administered propafenone be evaluated clinically and electrocardiographically prior to, and during therapy to determine whether the response to propafenone supports continued treatment.

Overall in clinical trials with propafenone, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event (0.7% was an increase in PVCs, 4.0% a worsening, or new appearance, of VT or VF). Of the patients who had worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign

arrhythmias which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study (see above) suggests that a risk is present throughout treatment.

Congestive Heart Failure

During treatment with oral propafenone in patients with depressed baseline function (mean EF=33.5%), no significant decreases in ejection fraction were seen. In clinical trial experience, new or worsened CHF has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to propafenone. Of the patients with congestive heart failure probably related to propafenone, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to propafenone developed rarely (<0.2%) in patients who had no previous history of CHF.

Propafenone exerts both beta blockade and a dose related direct negative inotropic effect on myocardium. Therefore, patients with congestive heart failure should be compensated before receiving NU-PROPAFENONE (propafenone HCl), and then closely monitored with careful attention being given to the maintenance of cardiac function. If congestive heart failure worsens, NU-PROPAFENONE should be discontinued (unless congestive heart failure is due to the cardiac arrhythmia) and, if indicated, restarted at a lower dosage only after adequate cardiac compensation has been established.

Caution should be exercised when using NU-PROPAFENONE in patients with minimal cardiac reserve or in those who are receiving other drugs with negative inotropic potential.

Effects on Cardiac Conduction

NU-PROPAFENONE slows cardiac conduction which may result in a dose-related prolongation of PR interval and QRS complex, development of first or higher degree AV block, bundle branch block and intraventricular conduction delay (see ADVERSE REACTIONS). Therefore, development of signs of increasing depression of cardiac conductivity during NU-PROPAFENONE therapy requires a reduction in dosage or a discontinuation of NU-PROPAFENONE unless the ventricular rate is adequately controlled by a pacemaker.

Hematologic Disturbances

Agranulocytosis has been reported infrequently in patients taking propafenone. The onset is generally within 4-6 weeks and presenting symptoms have included fever, fatigue, and malaise. Agranulocytosis occurs in less than 0.1% of patients taking propafenone. Patients should be instructed to immediately report fever, fatigue, malaise or any signs of infection, especially in the first three months of therapy. Prompt discontinuation of NU-PROPAFENONE therapy is recommended when a decreased white blood cell count or other signs and symptoms warrant consideration of agranulocytosis/granulocytopenia. Cessation of propafenone therapy is usually followed by recovery of blood counts within two weeks.

Nonallergic Bronchospasm (e.g. chronic bronchitis, emphysema)

Patients with bronchospastic disease should, in general, not receive NU-PROPAFENONE or other agents with beta-adrenergic blocking activity (see CONTRAINDICATIONS).

PRECAUTIONS

Effects on Pacemaker Threshold

Patients with permanent pacemakers should have their existing thresholds re-evaluated after initiation of or change in NU-PROPAFENONE (propafenone HCl) therapy because of a possible increase in endocardial stimulation threshold.

Use in Patients with Impaired Hepatic Function

Since propafenone is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function (see CONTRAINDICATIONS). Administration of propafenone to these patients results in an increase in bioavailability to approximately 70% compared to 3-40% for patients with normal liver function, prolongation of the half life, a decrease in the systemic clearance, and a reduction in the serum protein binding of the drug. As a result, the dose of NU-PROPAFENONE given to patients with impaired hepatic function should be reduced (see DOSAGE AND ADMINISTRATION). It is important to monitor electrocardiographic intervals for signs of excessive pharmacological effects (see SYMPTOMS AND TREATMENT OF OVERDOSAGE) and/or adverse reactions, until an individualized dosage regimen has been determined.

Use in Patients with Impaired Renal Function

To date there is no experience with use of oral propafenone in patients with impaired renal function. Since a considerable percentage of propafenone metabolites are excreted in the urine (18.5 - 38% of the dose/48 hrs), NU-PROPAFENONE should be used cautiously in patients with renal impairment and only after consideration of the benefit/risk ratio. These patients should be carefully monitored for signs of toxicity (see SYMPTOMS AND TREATMENT OF OVERDOSAGE). The dose in these patients has not been determined.

Neuromuscular Dysfunction

Exacerbation of myasthenia gravis has been reported during propafenone therapy.

Elevated ANA Titers

In long term studies, positive antinuclear antibody (ANA) titers have been reported in 21% of patients receiving propafenone. However, it is impossible to determine what exact percentage of patients had a new positive ANA titer as a result of propafenone therapy. This laboratory finding has not been associated with clinical symptoms. One case of Lupus-like syndrome has been reported which resolved upon discontinuation of therapy. Laboratory evaluation for antinuclear antibodies should be performed initially and at regular intervals. It is recommended that patients in whom an abnormal ANA test has occurred be evaluated regularly. If worsening elevation of ANA titers or clinical symptoms are detected, NU-PROPAFENONE should be discontinued.

Impaired Spermatogenesis

Clinical evaluation of spermatogenesis was undertaken in 11 normal subjects given oral propafenone 300 mg b.i.d. for 4 days, which was then increased to 300 mg t.i.d. for an additional 4 days. Patients were followed for 128 days post-treatment and demonstrated a 28% reduction in semen sample volume following the last dose (day 8) and a 27% reduction in sperm count, on day 72. FSH and testosterone levels were also slightly decreased. Neither the decrease in sperm count nor the decrease in sample volume were sustained beyond the single visit in which they occurred, and both values remained within the laboratories normal reference range. Reduced spermatogenesis was also observed in animal experiments. The significance of these findings is uncertain.

Use in the Elderly

A slight increase in the incidence of dizziness was observed in elderly patients. Because of the possible increased risk of impaired hepatic or renal function in this age group, NU-PROPAFENONE should be used with caution. The effective dose may be lower in these patients.

Use in Children

The use of NU-PROPAFENONE in children is not recommended, since safety and efficacy has not been established.

Use in Pregnancy

Propafenone has been shown to be embryotoxic in the rat when given in doses of 600 mg/kg and in the rabbit when given in doses of 150 mg/kg. In a perinatal and postnatal study in rats, propafenone produced dose dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

There are no studies in pregnant women. NU-PROPAFENONE should be used during pregnancy only when the potential benefit outweighs the risk to the fetus.

Labour and Delivery

It is not known whether the use of propafenone during labour or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labour or increases the need for forceps delivery or other obstetrical intervention.

Nursing Mothers

It is not known whether propafenone is excreted in human milk. Because of possible serious adverse reactions in nursing infants, an alternative method of infant feeding should be considered when the use of NU-PROPAFENONE is considered essential.

Drug Interactions

Quinidine: Small doses of quinidine completely inhibit the hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (see ACTIONS AND CLINICAL PHARMACOLOGY). There is, as yet, too little information to recommend concomitant use of propafenone and quinidine.

Digitalis: Propafenone produces dose-related increases in serum digoxin levels ranging from approximately 35% at 450 mg/day to 85% at 900 mg/day of propafenone without affecting digoxin renal clearance. These elevations of digoxin levels were maintained for up to 16 months during concomitant administration. Plasma digoxin levels of patients on concomitant therapy should be measured and digoxin dosage should ordinarily be reduced when propafenone is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.

Beta-antagonists: In a study involving healthy subjects, concomitant administration of propafenone and propranolol has resulted in substantial increases in propranolol plasma concentration and elimination half-life with no change in propafenone plasma levels from control values. Similar observations have been reported with metoprolol. Propafenone appears to inhibit the hydroxylation pathway for the two beta-antagonists (just as quinidine inhibits propafenone metabolism). Increased plasma concentrations of metoprolol could overcome its relative cardioselectivity. In propafenone clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects. While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone.

Warfarin: Concurrent administration of propafenone and warfarin leads to a 39% increase in warfarin plasma levels with a corresponding prolongation of prothrombin times of approximately 25%. It is therefore recommended that in patients treated with NU-PROPAFENONE and warfarin concomitantly, prothrombin time should be carefully monitored and the dose of warfarin adjusted as necessary.

Cimetidine: Concomitant administration of propafenone and cimetidine resulted in a 20% increase in plasma concentrations of propafenone. Therefore, patients should be carefully monitored and the dose of NU-PROPAFENONE adjusted when appropriate.

Local anesthetics: Concomitant use of local anesthetics and propafenone may increase the risk of central nervous system side effects.

Desipramine: Concomitant administration of propafenone and desipramine may result in elevated serum desipramine levels. Both desipramine, a tricyclic antidepressant, and propafenone are cleared by oxidative pathways of demethylation and hydroxylation carried out by the hepatic P-450 cytochrome.

Cyclosporine: Propafenone therapy may increase levels of cyclosporine.

Theophylline: Propafenone may increase theophylline concentration during concomitant therapy with the development of theophylline toxicity.

Rifampin: Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.

ADVERSE REACTIONS

In 2127 patients treated with propafenone in North American controlled and open clinical trials, the most common adverse reactions reported were dizziness (12.5%), nausea and/or vomiting (10.7%), unusual taste (8.8%) and constipation (7.2%). The adverse effects judged to be most severe were aggravation or induction of arrhythmia (4.7%), congestive heart failure (3.7%), and ventricular tachycardia (3.4%). The incidences for these three adverse reactions in patients with a previous history of MI were 6.9%, 5.3% and 5.5%, while in patients without a history of MI the incidences were 3.0%, 2.4% and 1.8%, respectively. Approximately 20% of patients had propafenone discontinued due to adverse reactions.

Adverse reactions were dose related and occurred most frequently during the first month of therapy.

The following adverse events were observed in greater than one percent of patients.

	Incidence By Total Daily Dose			Overall Incidence At Any Dose	% Patients who Discontinued
	450 mg	600 mg	900 mg	(N=2127)	
CARDIOVASCULAR SYSTEM					
Dyspnea	2.2%	2.3%	3.6%	5.3%	1.6%
Proarrhythmia	2.0	2.1	2.9	4.7	4.7
Angina	1.7	2.1	3.2	4.6	0.5
Congestive Heart Failure	0.8	2.2	2.6	3.7	1.4
Ventricular Tachycardia	1.4	1.6	2.9	3.4	1.2
Palpitations	0.6	1.6	2.6	3.4	0.5
First Degree AV Block	0.8	1.2	2.1	2.5	0.3
Syncope	0.8	1.3	1.4	2.2	0.7
QRS Duration, Increased	0.5	0.9	1.7	1.9	0.5
Bradycardia	0.5	0.8	1.1	1.5	0.5
PVC's	0.6	0.6	1.1	1.5	0.1
Edema	0.6	0.4	1.0	1.4	0.2
Bundle Branch Block	0.3	0.7	1.0	1.2	0.5
Atrial Fibrillation	0.7	0.7	0.5	1.2	0.4
Intraventricular Conduction Delay	0.2	0.7	0.9	1.1	0.1
Hypotension	0.1	0.5	1.0	1.1	0.4
CENTRAL NERVOUS SYSTEM					
Dizziness	3.6%	6.6%	11.0%	12.5%	2.4%
Headaches	1.5	2.5	2.8	4.5	1.0
Blurred Vision	0.6	2.4	3.1	3.8	0.8
Ataxia	0.3	0.6	1.5	1.6	0.2
Insomnia	0.3	1.3	0.7	1.5	0.3
Tremor(s)	0.3	0.8	1.1	1.44	0.3
Drowsiness	0.6	0.5	0.7	1.2	0.2
GASTROINTESTINAL					
Nausea and/or Vomiting	2.4	6.1	8.9	10.7	3.4
Unusual Taste	2.5	4.9	6.3	8.8	0.7
Constipation	2.0	4.1	5.3	7.2	0.5
Dyspepsia	1.3	1.7	2.5	3.4	0.9
Diarrhea	0.5	1.6	1.7	2.5	0.6
Dry Mouth	0.9	1.0	1.4	2.4	0.2
Anorexia	0.5	0.7	1.6	1.7	0.4
Abdominal Pain/Cramping	0.8	0.9	1.1	1.7	0.4
Flatulence	0.3	0.7	0.9	1.2	0.1

	Incidence By Total Daily Dose			Overall Incidence At Any Dose	% Patients who Discontinued
	450 mg	600 mg	900 mg	(N=2127)	
OTHER					
Fatigue	1.8	2.8	4.1	6.0	1.0
Rash	0.6	1.4	1.9	2.6	0.8
Weakness	0.6	1.6	1.7	2.4	0.7
Atypical Chest Pain	0.5	0.7	1.4	1.8	0.2
Anxiety	0.7	0.5	0.9	1.5	0.6
Diaphoresis	0.6	0.4	1.1	1.4	0.3
Pain, Joints	0.2	0.4	0.9	1.0	0.1

In addition, the following adverse reactions were reported less frequently than either in clinical trials or in marketing experience *(adverse events from marketing experience are given in italics*). Causality and relationship to propafenone therapy cannot necessarily be judged from these events.

Cardiovascular System: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia, torsades de pointes.

Nervous System: Abnormal dreams, abnormal speech, abnormal vision, *apnea, coma*, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo.

Gastrointestinal: A number of patients with liver abnormalities associated with propafenone therapy have been reported in foreign post-marketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome.

Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), gastroenteritis, hepatitis (0.3%).

Hematologic: Agranulocytosis (see WARNINGS), anemia, bruising, granulocytopenia, *increased bleeding time*, leukopenia, purpura, thrombocytopenia.

Other: Alopecia, eye irritation, *hyponatremia/inappropriate ADH secretion,* impotence, increased glucose, *kidney failure*, positive ANA (0.7%), *lupus erythematosus,* muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus.

SYMPTONS AND TREATMENT OF OVERDOSAGE

The symptoms of overdose include hypotension, somnolence, convulsions, bradycardia, conduction disturbances, ventricular tachycardia and/or ventricular fibrillation.

If ingestion is recent, perform gastric lavage or induce emesis. Supportive measures such as mechanical respiratory assistance and cardiac massage may be necessary.

Defibrillation and the use of a temporary pacemaker, as well as infusion of isoproterenol and dopamine have been effective in controlling cardiac rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam.

Detoxification measures such as forced diuresis, hemoperfusion and hemodialysis have not proven useful.

DOSAGE AND ADMINISTRATION

The dose of NU-PROPAFENONE (propafenone HCl) must be individually determined on the basis of patient's response and tolerance. The usefulness of monitoring plasma levels for optimization of therapy has not been established. The recommended dose titration regimen can be used for both fast and slow metabolizers (see ACTIONS AND CLINICAL PHARMACOLOGY).

The initial dose of NU-PROPAFENONE is 150 mg given every 8 hours (450 mg/day). Dosage may be increased at 3 to 4 day intervals to 300 mg every 12 hours (600 mg/day). Should a further increase in dosage be necessary, a maximum dose of 300 mg every 8 hours (900 mg/day) may be given.

In those patients in whom widening of the QRS complex (>0.12 sec) or prolongation of PR interval (>0.24 sec) occurs, the dosage of NU-PROPAFENONE should be reduced.

Administration of NU-PROPAFENONE with food is recommended.

In patients with mild to moderate hepatic insufficiency (see PRECAUTIONS), NU-PROPAFENONE therapy should be initiated with 150 mg given once (150 mg/day) daily. The dosage may be increased at a minimum of 4 day intervals to 150 mg twice (300 mg/day) daily then to 150 mg every 8 hours (450 mg/day) and, if necessary, to 300 mg every 12 hours (600 mg/day).

There is no information on dosing with propafenone in patients with renal impairment. NU-PROPAFENONE should be used cautiously in these patients and only after consideration of the benefit/risk ratio. These patients should be carefully monitored for signs of toxicity. Lower doses

may be required (see PRECAUTIONS).

In elderly patients, the effective dose of NU-PROPAFENONE may be lower (see PRECAUTIONS).

There is no information on the appropriate regimen for the transfer from lidocaine to NU-PROPAFENONE.

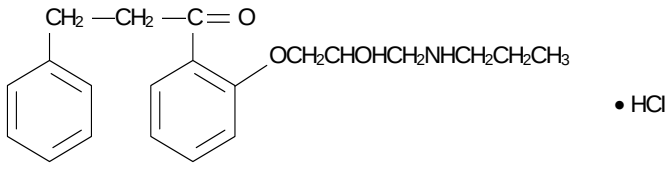
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: propafenone hydrochloride

Chemical Name: 2'-(2-hydroxy-3-propylamino-propoxy)-3-phenylpropiophenone hydrochloride

Structural Formula:



Molecular Formula: $C_{21}H_{27}NO_3 \bullet HCl$

Molecular Weight: 377.92

Description: Propafenone hydrochloride occurs as colourless crystals or white crystalline powder

with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol.

Composition

In addition to propafenone hydrochloride, each film-coated tablet contains the non-medicinal ingredients methylcellulose, croscarmellose sodium, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

Stability and Storage Recommendations

Store at room temperature 15 to 30°C (59 to 86°F).

AVAILABILITY OF DOSAGE FORMS

NU-PROPAFENONE 150 mg: Each round, white, film-coated, biconvex, tablet engraved 'APO' over 'P150' on one side contains 150 mg propafenone hydrochloride. Available in HDPE bottles of 100.

PHARMACOLOGY

Electrophysiology

The antiarrhythmic effect of propafenone HCl has been demonstrated in a number of different animal models. Electrically-induced ventricular fibrillation was controlled by propafenone (2 mg/kg i.v.) in the guinea pig and rabbit. Chloroform- and adrenaline-induced arrhythmias were reduced or abolished by propafenone in the cat (1 mg/kg i.v., 2-10 mg/kg i.d.) and dog (1 mg/kg i.v., 10 mg/kg oral) as were arrhythmias induced by calcium chloride, glycoside and coronary ligature in the dog (1-4 mg/kg i.v.). Aconitine-induced arrhythmias were also controlled by propafenone in the rabbit (3 mg/kg i.v.).

Propafenone can be classified as an antiarrhythmic drug with a membrane stabilizing effect.

Hemodynamics

In the dog, the force of ventricular contraction and blood pressure were not affected by doses of 3 mg/kg i.v. However, after higher doses of 12 mg/kg i.v. or in hearts predamaged by coronary ligature, or when administering beta-blockers concomitantly, a fall in blood pressure, a reduction in the heart rate and contractility, and an increase in ECG-intervals (PR and QRS) have been seen.

Other

Structural similarities between propafenone and propranolol prompted several animal investigations into the possible beta-blocking effects of propafenone. A $beta_1$-sympatholytic action on isolated heart preparations (guinea pigs) and a $beta_2$-sympatholytic action on the coronary arteries and tracheal muscles (bovine) have been demonstrated *in vitro*. *In vivo* studies in rats showed that the antiarrhythmic effect occurred with i.v. doses seven times lower than necessary for the beta-blocking effect (ED_{50} at 0.437 mg/kg and 3.25 mg/kg respectively). However, the *in vitro* beta-blocking effect of propafenone occurred in the same dose range as the antiarrhythmic effect.

In *in vitro* studies of bovine coronary arteries, propafenone (56.0 mg/L) yielded a relaxing effect weaker than that of etafenone, papaverine, hexobendine, fendiline and oxifedrine but stronger than that of theophylline, aminophylline and carbocromen. In bovine tracheal muscle and guinea pig colon, the potency of propafenone was the same as that of papaverine. *In vivo*, canine duodenum tone decreased slightly after i.v. propafenone, 0.5-4.0 mg/kg, with a marked decrease

of the amplitude of peristalsis following propafenone, 1.0-4.0 mg/kg.

The local anesthetic activity of propafenone was demonstrated in the cornea of conscious guinea pigs with a 0.5% solution of propafenone.

TOXICOLOGY

Acute Toxicology

LD_{50} Values

Species	Route	Sex	LD_{50}	(95% Confidence Interval)
Mouse	oral	male	650	(445-888) mg/kg
		female	605	(434-840) mg/kg
	i.v.	male	29.3	(26.6-32.7) mg/kg
		female	31.1	(28.3-35.7) mg/kg
Rat (Adult)	oral	male	1,316	(978-1,729) mg/kg
		female	1,250	(263-5,934) mg/kg*
	i.v.	male	18.6	(16.8-22.0) mg/kg
		female	16.8	(14.4-19.4) mg/kg
Rat (Juvenile)	oral	male	3,556	(2731-4885) mg/kg
		female	2,902	(2090-4484) mg/kg
	i.v.	male	23.0	(16.0-32.0) mg/kg
		female	23.1	(16.1-31.8) mg/kg

*90% confidence interval

In an acute oral dose tolerance study in dogs with 2 animals per dose level, no dogs died at 350 mg/kg, 1 dog died at 500 mg/kg and both dogs died at 650 mg/kg. In a similar study in cats, no animals died at 60 mg/kg and both cats died at the 100 mg/kg dose level.

Primary symptoms of toxicity were ataxia, attenuated reflexes and tonic-clonic convulsions.

Subacute and Chronic Toxicity

The studies are summarized in Table 1. For all studies, animals in each group were equally divided by sex.

Table 1

Species	Route Of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. Animals Per Dose Group	No. of Deaths per Dose Group	Toxic Effects
Rabbit	i.v.	3 weeks	0 0.3 0.5 1.0	4 4 4 4	0 0 0 0	Dose related reduction in body weight increases and elevated SGPT values were observed in the high dose group. High dose group had significantly increased heart weights with focal muscle cell degeneration. Reduced spermatogenesis was found on histological examination in all groups.
Rat (Wistar)	i.v.	4 weeks	0 0.35 1.75 3.5	30 30 30 30	0 0 0 0	Changes were observed in the 3.5 mg/kg group. Sedation, tremor and reduced alertness were noted as well as reduction in body weight gain and food and water consumption. Clinical laboratory tests revealed decreases in erythrocyte count and serum urea, sodium and phosphorus values. Increases in serum chloride were also noted.
Rat (Wistar)	oral (gavage)	4 weeks	0 30 150 300	20 20 20 20	0 0 0 0	A decrease in serum sodium values was observed in rats receiving 300 mg/kg.

Table 1

Species	Route Of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. Animals Per Dose Group	No. of Deaths per Dose Group	Toxic Effects
Rat (Wistar)	oral (gastric tube)	6 months	0 90 270 (180) 600 (360)	30 30 30 30	0 0 3 11	Due to high mortality, the intermediate and high doses were reduced after eight weeks. Death was preceded by weight loss or reduced weight gain. Intermediate doses produced sedation and reduced reflexes. Sedation, apathy, ataxia, impaired coordination, shaggy skin, loose stool and intermittent tonic-clonic convulsions occurred in the high dose group. Histopathology revealed a dose related increase in fatty liver cells and kidney protein cylinders in the tubuli. Nephritis was observed in the high dose group. Focal to complete degeneration of the tubular epithelial cells in the testes was observed equally in all dose groups.
Rat (Sprague-Dawley)	oral (gavage)	26 weeks	0 90 180 500 (360)	52 52 52 52	0 0 14 27	Due to high mortality, the high dose was decreased after 6 weeks. Primarily in the high dose group, observations included unkempt coat, sedation, ataxia and apathy. Inhibition of body weight gain occurred in all groups. Inflammatory renal lesions (nephritis and nephrohydrosis) caused by precipitations of propafenone in the upper tubules was noted in several high dose and one intermediate dose animal.
Dog (Beagle)	i.v.	4 weeks	0 0.3 1.0 5.0	6 6 6 6	0 0 0 0	The 5 mg/kg animals showed a reduction in body weight and food consumption and increased restlessness, timidity, anxiety and shaggy coats. Tremor, reduced responses and spontaneous defecation were observed immediately post injection. ECG tracings taken at the end of the study revealed significant heart rate reduction. Laboratory evaluations revealed significantly lowered LDH, BUN, Na, CI and inorganic phosphorus. Complete cessation of spermatogenesis was observed on histopathology.

Table 1

Species	Route Of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. Animals Per Dose Group	No. of Deaths per Dose Group	Toxic Effects
Dog (Beagle)	i.v.	4 weeks	0 1.0 2.2 5.0	6 6 6 6	0 0 0 0	The 5 mg/kg group showed a decrease in serum potassium.
Dog (Mongrel)	oral	4 weeks	0 20 50 100	2 2 2 2	0 0 0 0	Reduction in body weight and increased heart and liver weights were observed in the high dose group.
Dog (Beagle)	oral	6 months	0 30 120 240 (180) (210) (240)	6 6 6 6	0 0 0 1	The following effects were observed in the 120 mg/kg group: sedation, intermittent tremor, reduced body weight gain and food consumption. Prothrombin time was also shortened. Due to one death and the marked deterioration of remaining animals in the 240 mg/kg group, the dose was reduced to 180 mg/kg at 9 weeks and gradually increased to 240 mg/kg at the thirtieth week. At this dose, animals exhibited apathy, sedation, ataxia, convulsions, vomiting, salivation, diarrhea, reduced body weight gain and food intake, reduced prothrombin time, decreased LDH values and increased uric acid.

Table 1

Species	Route Of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. Animals Per Dose Group	No. of Deaths per Dose Group	Toxic Effects
Dog (Beagle)	oral	52 weeks	0 30 60 120	10 10 10 10	0 0 1 3	Vomiting was observed in the 60 mg/kg dosed dogs. The 120 mg/kg dogs exhibited vomiting, ataxia and tremor with tonic-clonic spasm. Biochemical analysis showed decreased total protein and globulins. One animal at 60 mg/kg and 3 animals at 120 mg/kg died. Probable cause of death: circulatory collapse.
Monkey (Rhesus)	i.v.	4 weeks	0 2.0 5.0	4 4 4	0 0 0	A dose related decrease in body weight gain was reported. All animals treated showed a decrease in the ejaculation volume and sperm count. Death of all spermatozoa was observed in the high dose group. The following was observed on histopathology: inhibition of spermatogenesis in the 2.0 mg/kg group and more severe disorders of spermatogenesis (including absence of spermatozoa maturation, severe degree of atypical nucleii with hyperchromasie and an increased number of nucleus pycnosis) in the 5.0 mg/kg dose group. Sperm counts returned to normal within 8 weeks post study.

Reproduction and Teratology Studies

Fertility and General Reproductive Performance: SPF albino rats (24/sex/dose) received 0, 30, 90, 270 mg/kg/day of propafenone p.o. (gavage). Males were treated for 70 days prior to mating and females began treatment 14 days prior to mating. Both continued treatment for a maximum of 14 days during the mating period. Propafenone did not produce any adverse effects on fertility but increased the time required for mating.

Male Wistar rats (20/group) and male albino rabbits (10/group) received oral propafenone at doses of 0 or 150 mg/kg (rats) and 0 or 120 mg/kg (rabbits) over 10 weeks (6 days/week). On the last day of treatment in the rat and after termination of treatment in the rabbit, each male was paired with 2 non-treated females. There was no effect in either species on fertility, mating behaviour nor litter size.

Teratology Studies: Female Wistar rats (20/group) received oral propafenone (gavage) at doses of 0, 90, 270 or 600 mg/kg from the 5th to the 15th day of pregnancy. There was no evidence of teratogenicity at any dose. An embryotoxic effect (i.e. increased resorption rates and decreased fetal weights), was detected at the highest dose level. This dose was already toxic to dams as evidenced by reduced weight gain.

White pregnant female New Zealand rabbits received oral (gavage) propafenone at doses of 0, 15, 30 or 150 mg/kg/day from the 6th to the 18th day of pregnancy. Fetuses of the intermediate and high dose group showed variations (retarded ossification of the skull, the coccygeal vertebra and end-phalanx). The number of resorbed and dead fetuses was increased in the high dose group. This dose was toxic to the dam as evidenced by reduced weight gain and increased mortality.

Spermatogenesis

Intravenous administration of propafenone in doses of 0.3, 0.5 and 1.0 mg/kg for 3 weeks to NZ-rabbits (2/dose) resulted in reduced spermatogenesis. The dose of 1.0 mg/kg produced degenerated spermatogenic epithelium in the testes of all animals.

Additional studies of spermatogenesis were performed in the monkey, dog and rabbit. After i.v. administration of 2 and 5 mg/kg propafenone per day to monkeys for 4 weeks, decreased spermatogenesis occurred, but was reversible 8 weeks after discontinuation of propafenone. Minor alterations in the spermatogram (oligospermia) were observed in dogs administered 5 mg/kg i.v. for 4 weeks and rabbits administered 3.5 and 5 mg/kg i.v. for 6 days. The phenomenon was reversible 4 weeks after discontinuation of propafenone. No injury to the parenchyma of the testes occurred, nor did electron microscopy demonstrate any changes in the spermatogenic epithelium of rabbits.

Mutagenicity Study

The mutagenic potential of propafenone was investigated in bacteria *in vitro* (Salmonella/microsome assay) as well as in Chinese hamsters, rats and mice *in vivo*. No indication of mutagenic activity was detected in any of these studies.

Carcinogenicity Studies

Propafenone was administered in doses of 60, 180 and 540 (360) mg/kg to NMR mice for 104 weeks. After 21 weeks, the maximum dose was reduced to 360 mg/kg for the remainder of the study. Sprague-Dawley rats were given doses of 30, 90 and 270 mg/kg in the food for 30 months. In these studies propafenone was not carcinogenic.

BIBLIOGRAPHY

1. Baker BJ, Dinh H, Kroskey D, et al. Effect of propafenone on left ventricular ejection fraction. Am J Cardiol 1984; 54: 20D-22D.

2. Brodsky MA, Allen BJ, Abate D, Henry WL. Propafenone therapy for ventricular tachycardia in the setting of congestive heart failure. Am Heart J 1985; 110: 794-799.

3. Chilson DA, Heger JJ, Zipes DP, et al. Electrophysiologic effects and clinical efficacy of oral propafenone therapy in patients with ventricular tachycardia. J Am Coll Cardiol 1985; 5: 1407-1413.

4. Connolly SJ, Kates RE, Lebsack CS, et al. Clinical pharmacology of propafenone. Circulation 1983; 68: 589-596.

5. Connolly SJ, Lebsack CS, Winkle RA, et al. Propafenone disposition kinetics in cardiac arrhythmia. Clin Pharmacol Ther 1984; 36: 163-168.

6. De Soyza N, Terry L, Murphy ML, et al. Effect of propafenone in patients with stable ventricular arrhythmias. Am Heart J 1984; 108: 285-289.

7. Hill MR, Gotz VP, Harman E, et al. Evaluation of the asthmogenicity of propafenone, a new antiarrhythmic drug. Chest 1986; 90: 698-702.

8. Hodges M. Role of propafenone in the treatment of ventricular premature beats. J Electrophysiol 1987; 1: 536-542.

9. Lee JT, Koremer HK, Silberstein DJ, et al. The role of genetically determined polymorphic drug metabolism in the beta-blockade produced by propafenone. N Eng J Med 1990; 322: 1764-1768.

10. Naccarella F, Bracchetti D, Palmierri M, et al. Comparison of propafenone and disopyramide for treatment of chronic ventricular arrhythmias: placebo-controlled double-blind, randomized crossover study. Am Heart J 1985; 109: 833-840.

11. Podrid PJ, Lown B. Propafenone: a new agent for ventricular arrhythmia. J Am Coll Cardiol 1984; 4: 117-125.

12. Podrid PJ, Lampert S, Graboys B, et al. Aggravation of arrhythmia by antiarrhythmic drugs - incidence and predictors. Am J Cardiol 1987; 59: 38E-44E.

13. Rabkin SW, Rotem CE, Boroomand-Rashti K, Bar-Shlomo B. Propafenone for the treatment of severe ventricular arrhythmias. Can Med Assoc J 1984; 131: 601-603.

14. Salerno DM, Granrud G, Sharkey P, et al. A controlled trial of propafenone for treatment of frequent and repetitive ventricular premature complexes. Am J Cardiol 1984; 53: 77-83.

15. Shen EN. Propafenone: a promising new antiarrhythmic agent. Chest 1990; 98: 434-441.

16. United States Food and Drug Administration. Review and evaluation of pharmacology and toxicology data of NDA 19-151 (original summary). Rythmonorm (propafenone hydrochloride). October 26,1983; 1-23.