# PRODUCT MONOGRAPH

**[Pr]TEVA-PROPRANOLOL**
(Propranolol Hydrochloride)

10, 20, 40 and 80 mg Tablets

USP

Beta-Adrenergic Receptor Blocking Agent

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Date of Preparation:
September 19, 2011

Submission Control#: 149953

NAME OF DRUG

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(Propranolol Hydrochloride)

(10, 20, 40 and 80 mg)

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PHARMACOLOGIC CLASSIFICATION

Beta-adrenergic receptor blocking agent

## ACTIONS

TEVA-PROPRANOLOL (propranolol hydrochloride) is a beta-adrenergic receptor blocking agent. It has no other autonomic nervous system activity. TEVA-PROPRANOLOL is a competitive antagonist which specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites.

When access to beta-adrenergic receptor sites is blocked by TEVA-PROPRANOLOL, the Chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Beta- adrenergic blockade is useful in some clinical conditions in which sympathetic activity is excessive or inappropriate, and therefore detrimental to the patient. Sympathetic stimulation is however, vital in some situations, (e.g. in patients with A-V· block or with a severely' damaged: heart) and should, be preserved. The basic objective of beta- adrenergic blockade is to decrease adverse sympathetic stimulation but not to degree that impairs necessary sympathetic support. Beta-blockade results in bronchial constriction by interfering with endogenously or exogenously induced bronchodilation. (See CONTRAINDICATIONS AND WARNINGS).

The mechanism of the antihypertensive effects of TEVA-PROPRANOLOL has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2)

inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. It has been suggested, but not established, that propranolol hydrochloride may achieve a better antihypertensive effect in patients with normal or elevated plasma renin activity than those with low PRA

TEVA-PROPRANOLOL may reduce the oxygen requirement of the heart at any level of effort by blocking catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, TEVA-PROPRANOLOL may increase oxygen requirements by increasing left ventricular fiber length, and diastolic pressure, and systolic ejection period. When the net effect is beneficial in anginal patients, it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks.

TEVA-PROPRANOLOL exerts antiarrhythmic effects in concentrations producing beta-adrenergic blockade, which appears to be its principal antiarrhythmic mechanism of action. Beta-adrenergic blockade is of importance in the management of arrhythmias caused by increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

TEVA-PROPRANOLOL is almost completely absorbed from the gastro-intestinal tract and undergoes extensive presystemic (or ‘first pass’) elimination due to its high hepatic clearance. Interindividual variations in circulating drug concentrations due to this ‘first pass effect’ have been documented and differ according to a number of factors including genetic make-up. Peak plasma concentrations of propranolol are attained in 60-90 minutes. The plasma half-life is approximately 3 hours whereas the duration of pharmacological effect is longer.

## INDICATIONS

A) HYPERTENSION

TEVA-PROPRANOLOL (propranolol hydrochloride) is indicated in the treatment of mild to moderate hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. TEVA-PROPRANOLOL may, however, in certain patients be used alone or as an initial agent in those patients in whom, in the judgment of the physician, treatment should be started with a beta-blocker rather than a diuretic. The combination of TEVA-PROPRANOLOL with thiazide-like diuretics and/or peripheral vasodilators has been shown to be compatible and generally more effective than TEVA-PROPRANOLOL alone. Experience with most commonly used antihypertensive agents has not suggested evidence of incompatibility.

TEVA-PROPRANOLOL is not recommended for the emergency treatment of hypertensive crises.

B) ANGINA PECTORIS

TEVA-PROPRANOLOL is indicated for the prophylaxis of angina pectoris.

C) CARDIAC ARRHYTHMIAS

1) Supraventricular arrhythmias
   a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with Wolff-Parkinson-White syndrome (see W-P-W under WAKNINGS).

   b) Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.

   c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short-

term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy (see Thyrotoxicosis under WARNINGS).

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2) Tachyarrhythmias of digitalis intoxication.
If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they may be reversible with TEVA-PROPRANOLOL. Severe bradycardia may occur (See SYMPTOMS AND TREATMENT OF OVERDOSAGE).

D) MIGRAINE

TEVA-PROPRANOLOL is indicated for the prophylaxis of migraine headache. It is not indicated for the treatment of acute migraine attacks.

E) HYPERTROPHIC SUBAORTIC STENOSIS

TEVA-PROPRANOLOL is useful in the management of hypertrophic subaortic stenosis, especially for the treatment of exertional or other stress-induced angina, palpitations, and syncope. TEVA-PROPRANOLOL may also improve exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-adrenergic receptor stimulation. Clinical improvement may be temporary.

F) PHEOCHROMOCYTOMA

After primary treatment with an alpha-adrenergic blocking agent has been instituted, TEVA-PROPRANOLOL may be useful as adjunctive therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use TEVA-PROPRANOLOL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure rise. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed. In the event of hemorrhage or shock, producing both beta- and alpha-blockade is contraindicated since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

In inoperable or metastatic pheochromocytoma, TEVA-PROPRANOLOL may be useful as an adjunct to the management of symptoms due to excessive beta-adrenergic receptor stimulation.

## CONTRAINDICATIONS

TEVA-PROPRANOLOL (Propranolol hydrochloride) is contraindicated in:

1) bronchospasm including bronchial asthma;
2) allergic rhinitis during the pollen season;
3) sinus bradycardia and greater than first degree block;
4) cardiogenic shock;
5) right ventricular failure secondary to pulmonary hypertension;
6) congestive heart failure (See WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with TEVA-PROPRANOLOL.

## WARNINGS

### CARDIAC FAILURE

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure; therefore, inhibition by means of beta-adrenergic blockade is a potential hazard as it may further depress myocardial contractility and precipitate cardiac failure.

TEVA-PROPRANOLOL (propranolol hydrochloride) acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by TEVA-PROPRANOLOL's negative inotropic effect. The effects of TEVA-PROPRANOLOL and digitalis are additive in depressing A-V conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE

Continued depression of the myocardium over a period of time can in some patients, lead to cardiac failure. In rare instances, this has been observed during TEVA-PROPRANOLOL therapy. Therefore, at the first sign of symptoms of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely:

a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, TEVA-PROPRANOLOL should be withdrawn immediately.

b) If tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until threat of cardiac failure is over.

ABRUPT CESSATION OF THERAPY IN ANGINA PECTORIS

Severe exacerbation of angina and the occurrence of myocardial infarction have been reported in some patients with angina pectoris following abrupt discontinuation of propranolol hydrochloride therapy. Therefore, when discontinuation of TEVA-PROPRANOLOL is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. In situations of greater urgency, TEVA-PROPRANOLOL dosage should be reduced stepwise, in four days under close observation. If angina markedly worsens, or acute coronary insufficiency develops, it is recommended that treatment with TEVA-PROPRANOLOL be reinstituted promptly, at least temporarily. In. addition, patients with angina pectoris should be warned against abrupt discontinuation of TEVA-PROPRANOLOL.

OCULOMUCOCUTANEOUS SYNDROME

Various skin rashes and conjunctival xerosis have been reported in patients treated with beta-blockers including TEVA-PROPRANOLOL. A severe oculomucocutaneous syndrome, whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the long-term use of one beta- adrenergic blocking agent. This syndrome has not been observed with TEVA-PROPRANOLOL, however, physicians should be alert to the possibility of such reactions and discontinue treatment if they occur.

IN PATIENTS WITH THYROTOXICOSIS

Possible deleterious effects from long-term use of TEVA-PROPRANOLOL have not yet been adequately appraised. Special consideration should be given to TEVA-PROPRANOLOL's potential for aggravating congestive heart failure. TEVA-PROPRANOLOL may mask the clinical signs of developing or continuing hyperthyroidism or its complications, and may give a false impression of improvement. Therefore, abrupt withdrawal of TEVA-PROPRANOLOL may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This may be another instance where TEVA-PROPRANOLOL should be withdrawn slowly by reducing dosage. Propranolol hydrochloride does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

TEVA-PROPRANOLOL should be used with caution since several cases have been reported in which, after propranolol hydrochloride treatment, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one patient, this occurred after an initial dose of 5 mg of propranolol hydrochloride.

IN PATIENTS UNDERGOING ELECTIVE OR EMERGENCY SURGERY

The management of patients with angina, being treated with beta-blockers and undergoing elective or emergency surgery, is controversial because beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, but abrupt discontinuation of therapy with TEVA-PROPRANOLOL may be followed by severe

complications. (See WARNINGS). Some patients receiving beta-adrenergic blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

For these reasons, in patients with angina undergoing elective surgery, TEVA-PROPRANOLOL should be withdrawn gradually following the recommendation given under Abrupt Cessation of Therapy. (See WARNINGS). According to available evidence, all clinical and physiologic effects of beta-blockade are no longer present 48 hours after cessation of medication.

In emergency surgery, since TEVA-PROPRANOLOL is a competitive inhibitor of beta-adrenergic receptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol or levarterenol.

Anesthesia with agents which maintain cardiac contractility by virtue of their effect on catecholamine release (e.g. ether) should be avoided in patients on TEVA-PROPRANOLOL therapy.

IN PATIENTS PRONE TO NON-ALLERGIC BRONCHOSPASM
(e.g. Chronic Bronchitis, Emphysema, Bronchiectasis), TEVA-PROPRANOLOL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-adrenergic receptors.

IN PATIENTS WITH DIABETES AND IN THOSE SUBJECT TO HYPOGLYCEMIA
TEVA-PROPRANOLOL, because of its beta-adrenergic blocking activity, may block premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY

The safe use of TEVA-PROPRANOLOL in pregnancy has not been established. Use of any drug in pregnancy or in women of child-bearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Perinatal complications, such as small placenta and intra-uterine growth retardation, have been reported in a few cases where the mother took propranolol hydrochloride during pregnancy. Some infants born to mothers treated with propranolol hydrochloride were reported to have hypoglycemia and/or bradycardia.

USE IN CHILDREN

While experience with propranolol hydrochloride in children under 12 is limited, the indications for which TEVA-PROPRANOLOL is recommended occur infrequently in childhood. Although reports fail to indicate that children respond in a manner different from the adult, physicians are advised to undertake treatment with caution.

## PRECAUTIONS

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflux bradycardia and heart-block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm, and norepinephrine to overcome hypotension.

Some slowing of heart due to unopposed vagal activity is usual in patients receiving TEVA-PROPRANOLOL (propranolol hydrochloride), however, occasionally severe bradycardia occurs and may lead to vertigo, syncopal attacks or orthostatic hypotension. Patients,

especially those with limited cardiac reserve should be monitored for signs of excessive bradycardia. Should the patient become symptomatic the dose of TEVA-PROPRANOLOL should be decreased or, if necessary, the drug should be discontinued. If it is essential to correct the bradycardia intravenous atropine or isoproterenol should be considered.

It has been reported that administration of propranolol hydrochloride to control cardiac arrhythmias in acute myocardial infarction has caused marked reduction in cardiac output. Therefore, the doses of TEVA-PROPRANOLOL should be kept to the minimum in patients with severe myocardial infarction. Prior administration of other antiarrhythmic cardiac depressant drugs, such as procainamide or quinidine may potentiate the cardiac-depressant activities of TEVA-PROPRANOLOL. Prior digitalization may be indicated and atropine should be at hand to control bradycardia.

The combination of TEVA-PROPRANOLOL with a thiazide-like diuretic and/or peripheral vasodilator produces a greater fall in blood pressure than either drug alone. This occurs regardless of which drug is administered first. The same degree of blood pressure control can be achieved by lower than usual dosages of each drug. Therefore, when using such combined therapy, careful monitoring of the dosages is required until the patient is stabilized.

Patients receiving catecholamine depletion drugs such as reserpine or guanethidine should be closely observed if TEVA-PROPRANOLOL is administered concomitantly. The added catecholamine blocking action of this drug may produce an excessive reduction of the resting sympathetic nervous activity.

In patients on long-term treatment with TEVA-PROPRANOLOL, laboratory determinations should be made at regular intervals. The drug should be used with caution in patients with impaired renal and hepatic functions.

## ADVERSE REACTIONS

The most serious adverse effects that may be encountered with TEVA-PROPRANOLOL (propranolol hydrochloride) are congestive heart failure and bronchospasm (See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea, abdominal pain) are the most common adverse effects reported. Other less frequently reported adverse effects are: (in descending order) cold extremities and exacerbation of Reynaud's phenomenon; congestive heart failure; sleep disturbances including vivid dreams; dizziness, fatigue and bronchospasm. Reported adverse effects, according to organ systems are recorded below:

CARDIOVASCULAR

Congestive heart failure (See WARNINGS); secondary effects of decreased cardiac output which could include: syncope, vertigo, lightheadedness, decreased renal perfusion and rarely, postural hypotension; intensification of A-V block and hypotension; severe bradycardia; claudication and cold extremities, Raynaud's phenomenon; palpitations; precordial pain.

CENTRAL NERVOUS. SYSTEM

Dizziness, lethargy, weakness, drowsiness, headache, insomina, fatigue, anore**xia,** anxiety, mental depression, poor concentration, reversible amnesia and catatonia, vivid dreams with or without insomnia, hallucinations, paresthesia, incoordination.

GASTROINTESTINAL

Nausea, vomiting, epigastric distress, anorexia, bloating, mild diarrhea, constipation.

RESPIRATORY

Bronchospasm; laryngospasm and respiratory distress. (See CONTRAINDICATIONS and WARNINGS).

DERMATOLOGIC

A few cases of erythematous rashes and increase of facial acneiform lesions have been reported; urticaria; exfoliative psoriasiform eruption.

OTHERS

Reduction or loss of libido; reversible alopecia and rarely: diminution and loss of hearing; tinnitus, visual disturbances; diminished vision; conjunctivitis; thrombocytopenic purpura; pharyngitis and agranulocytosis, fever combined with aching and sore throat; urinary retention associated with repeated bouts of paroxysmal tachycardia; flushing of face.

CLINICAL LABORATOKY TESTING FINDINGS

Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, and lactate dehydrogenase have been reported.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE;.

Several reports in the published literature describe cases in which propranolol hydrochloride was used as a suicide agent. In most cases, other agents, e.g. alcohol, have also been involved. One patient who was thought to have ingested 3,600 mg of propranolol hydrochloride died. Survival of patients taking higher single doses has, however, also been reported.

The common signs to be expected in overdosage are bradycardia, hypotension, bronchospasm, or acute cardiac failure. If overdosage occurs, in all cases therapy with TEVA-PROPRANOLOL should be discontinued and the patient observed closely. In addition the following therapeutic measures are suggested:

BRADYCARDIA

Administer atropine incrementally in 0.6 mg doses. If there is no response to vagal blockade, administer isoproterenol cautiously.

CARDIAC FAILURE

Digitalization and Diuretics

HYPOTENSION

Vasopressors, e.g. levarterenol or epinephrine. (See Precaution concerning the use of epinephrine in B-blocked patients).

BRONCHOSPASM

Administer isoproterenol and aminophylline.

## DOSAGE AND ADMINISTRATION

HYPERTENSION

Therapeutic, response to a given dosage varies between patients, therefore, dosage must be indivually titrated and should be carefully monitored. In the treatment of hypertension TEVA-PROPRANOLOL (propranolol hydrochloride) may be started by administering the drug in two equal daily doses of 40 mg. This may be increased, if necessary, in one week, to 80 mg twice daily, before breakfast and at bedtime. If necessary, the drug may be increased to 160 mg twice daily. For most patients the dosage is within the range of 160-320 mg daily. A small number of patients may respond to 80 mg daily. Experience to date suggests that in some resistant patients increasing the dosage above 320 mg/day may have an additional effect. Doses above 320 mg/day should be given on a t.i.d. or q.i.d. regimen.

The time course of full blood pressure response is variable. The anti-hypertensive effect will usually occur within 3 to 7 days after reaching the effective dose. The maximum decrease in blood pressure may occur 2 to 4 weeks after initiation of treatment.

ANGINA PECTORIS

Dosage must be individualized. Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at 3 to 7 day intervals until optimum response is obtained. Although individual patients may respond at any dosage level,

the average optimum dosage appears to be 160 mg/day. Occasionally, in resistant patients, dosage as high as 320-400 mg/day have been administered with beneficial results. If treatment is to be discontinued, reduce dosage gradually over a period of about two weeks (See WARNINGS).

ARRHYTHMIAS

10-30 mg three or four times daily, before meals and at bedtime.

MIGRAINE

Dosage must be individualized. The initial dose is 40 mg twice daily. The dose may then be gradually increased until optimum migraine prophylaxis is achieved. The usual effective dose range is 80 - 160 mg/day.

HYPERTROPHIC SUBAORTIC STENOSIS

20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA

| | |
|---|---|
| Pre-operatively | - 60 mg daily, in divided doses, for three days before surgery, concomitantly with an alpha-receptor blocking agent. |
| Malignant cases | -30 mg daily, in divided doses. |

## AVAILABILITY

TEVA-PROPRANOLOL TABLETS 10 mg

Orange coloured round bi-convex compressed tablets, engraved N 10 on one side and bisect on the reverse, containing 10 mg propranolol hydrochloride.

Supplied in bottles of 100 and 1000 and in boxes of 100 (as unit dose strips).

TEVA-PROPRANOLOL TABLETS 20 mg

Blue coloured hexagonal shaped bi-convex compressed tablets, engraved modified N on one side and 2|0 on the reverse, containing 20 mg propranolol hydrochloride.

Supplied in bottles of 100 and 1000 and in boxes of 100 (as unit dose strips).

TEVA-PROPRANOLOL TABLETS 40 mg

Green coloured round bi-convex compressed tablets, engraved $\frac{N}{40}$ one side and bisect on the reverse, containing 40 mg propranolol hydrochloride.

Supplied in bottles of 100, 1000 and 5000 and in boxes of 100 (as unit dose strips).

TEVA-PROPRANOLOL TABLETS 80mg

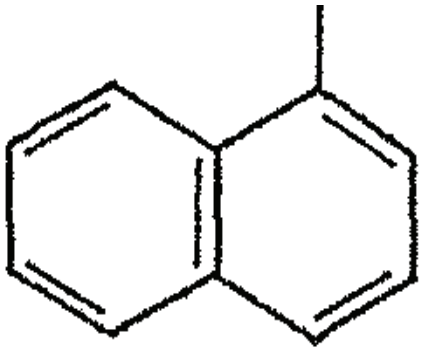
Yellow coloured round bi-convex compressed tablets, engraved $\frac{N}{80}$ on one side and bisect on the reverse, containing 80 mg propranolol hydrochloride.

Supplied in bottles of 100 and 1000 and in boxes of 100 (as unit dose strips).

## CHEMISTRY

Propranolol Hydrochloride

$O\text{-}CH_2CHOHCH_2NHCH(CH_3)HCl$



Molecular Formula: $C_{16}H_{22}C1NO_2$ Molecular Weight: 295.81

Chemical Name: 1-(isopropylamino)-3-(1-napthyloxy-2-propanol hydrochloride.

Description: Propranolol hydrochloride is a stable, colorless, crystalline solid with a melting point of 163-l64°C. It is readily soluble in water and ethanol and insoluble in non-polar solvents.

PHARMACOKINETICS

Propranolol hydrochloride is rapidly and almost completely absorbed from the gastrointestinal tract. A large part of the absorbed drug is lost to the systemic circulation due to the first pass metabolism in the liver. After repeated administration, the first pass removal process becomes saturated and, at steady state, the plasma concentration is proportional to the dose, although there is some variation between patients as to the blood levels achieved at a given dose. In addition, correlation of plasma level to therapeutic effect varies considerably with propranolol hydrochloride as with some other beta-blockers. This lack of correlation is most marked in the treatment of angina and hypertension.

The circulating drug is more than 90% bound to serum proteins. Propranolol hydrochloride is rapidly and extensively metabolized and excreted by the kidney. Over 20 metabolites have been identified. One of these, the 4-hydroxy metabolite, found only after oral administration, has beta-adrenergic blocking properties. The biological half-life of propranolol hydrochloride (i.e. the serum concentration of the unchanged drug) is about four hours. The duration of pharmacologic effect is longer.

## PHARMACOLOGY

Propranolol hydrochloride is a competitive antagonist of endogenous and exogenous sympathomimetic amines at the beta-adrenergic receptors ($Beta_l$ and $Beta_2$). Chemically it is a racemic mixture of equal amounts of levo and dextro isomers. The levo isomer is responsible for most of the beta-receptor blocking activity.

CARDIOVASCULAR EFFECTS

Intravenous administration of propranolol to cats and dogs produced a fall in heart rate by blocking endogenous sympathetic activity to the heart. In anesthetized dogs, propranolol

produced dose-related decrease in heart rate, cardiac contractile force, and small depressions in blood pressure, and cardiac output. These effects have also been demonstrated in man. A reduction in oxygen consumption and increased right atrial pressure were observed in human myocardium.

Human and animal studies with propranolol have demonstrated competitive and reversible blockade of the increased heart rate and increased force of contraction produced by isoproterenol, adrenaline, noradrenaline and stellate ganglion stimulation. Propranolol reduced the pressor response of noradrenaline, potentiated that of adrenaline, but did not effect the response of phenylephrine.

Epstein and associates studied 16 human subjects under conditions of maximal and submaximal exercise. Propranolol 0.15 mg/kg intravenously, was sufficient to reduce by tenfold the sensitivity of heart rate to isoproterenol.

Blockade of beta-adrenergic receptors in the peripheral vasculature has little if any effect on circulation or blood pressure. Administered intra-arterially, propranolol causes a brief vasodilation unrelated to beta-adrenergic receptor blockade.

Amounts of propranolol which completely abolished the increase in heart rate produced by stimulation of the right stellate ganglion in anesthetized cats did not affect the bradycardia produced by vagal stimulation.

Propranolol causes no observable response when it interacts with beta-receptors in the absence of a primary agonist such as epinephrine or isoprenaline indicating a lack of intrinsic sympathomimetic activity.

Lucchesi et al demonstrated in dogs that propranolol was effective in reversing or preventing several types of experimentally-induced cardiac arrhythmias.

In animal experiments, at concentrations much higher than those necessary for complete beta-adrenergic blockade, propranolol exerts a local anesthetic effect. This has also been termed a "membrane stabilizing" or "quinidine-like" effect. This property of propranolol has been demonstrated in vitro with human myocardium only at a minimum concentration of 10 mg/L which is about 100 times greater than that required for inhibition of exercise tachycardia or suppression of ectopic beats. This is, therefore, not thought to be an important property of propranolol in the doses used in clinical practice and there are no in vivo methods for demonstrating this effect in man.

Plasma renin activity is inhibited by propranolol.

RESPIRATORY EFFECTS

Propranolol increases airway resistance by inhibiting the sympathetic innervation of the bronchi. This effect is small in most normal individuals where it can only be demonstrated by measuring forced expiry volume ($FEV_1$). In asthmatics and patients with other bronchospastic diseases however, this effect is marked and potentially dangerous.

Injection of propranolol reduced $FEV_1$ with dyspnoea, cough and dizziness in two of eleven patients with chronic obstructive lung disease. When given the drug orally (40 mg q.i.d.) five of these eleven patients reported dyspnoea. Propranolol has been reported to potentiate bronchospasm induced by histamine, acetylcholine, methylcholine or allergen and this potentiation is greater in asthmatics than in non-asthmatic subjects.

Central Nervous System Effects

Propranolol hydrochloride readily crosses the blood/brain barrier. In some animal experiments it has been shown to display central muscle relaxant, sedative and anticonvulsant properties. To date, none of these effects can be directly attributed to blockade of beta-adrenergic receptors in the central nervous system. One publication, suggests that propranolol's CNS activity may be attributable to a glycol metabolite.

Metabolic Activity

Propranolol hydrochloride may produce hypoglycemia but this effect appears to be rare and its mechanism is not clear. Propranolol also impairs the sympathetically mediated rebound response to hypoglycemic symptoms (See WARNINGS).

Propranolol hydrochloride inhibits the rise in plasma free fatty acids induced by sympathomimetic amines. It also inhibits the lipolytic action of catecholamines in isolated adipose tissues of several animal species.

## TOXICOLOGY

Acute Oral Toxicity ($LD_{50}$)

Mice: 620 mg/kg

Rats: 638 mg/kg

Chronic Toxicity

It has been reported that a toxicity study of 18 months duration was conducted in four groups of rats (one control and three experimental) each consisting of 25 males and 25 females. All animals received medication by tube directly into the stomach for the first six months and thereafter received the drug in the diet.

A number of animals who received the highest dose (150 mg/kg) developed bronchospasm soon after receiving the drug. A variety of pathologic lesions were observed in both the control and experimental groups. Dilatation of both ventricles was noted in a number of high-dose experimental rats that died spontaneously during the early part of the experiment. Spontaneous myocarditis consisting of minor lymphocytic infiltration was observed in both groups. Testicular atrophy and reduction or absence of corpora lutea was seen in both the control and experimental groups.

It has been reported that a one-year toxicity test was carried out in 32 dogs in both sexes, divided into four groups (control and propranolol 60, 20 and 5 mg/kg).A patchy edema and a slight increase in the size of the lymphoid follicles of the mucosa in the fundus of the stomach were seen and were attributed to mild irritation caused by prolonged dosing with high doses of propranolol.

It has been reported that the carcinogenic potential of propranolol hydrochloride was investigated in mice and rats by chronic administration of the compound in the diet for 78 weeks at varying concentrations to provide dosage levels of 10, 50 and 150 mg/kg/day. Control groups of mice and rats were fed the same diet without compound. After 78 weeks of administration, the mice were kept alive for an additional two months and the rats for six months withdrawal period. At the termination of the experiment, gross and microscopic pathologic investigations revealed that in mice the incidence of benign and malignant neoplasms was similar in control and all treated groups. Thus, no compound-related, tumorigenic effect was observed at any dose level. Similarly, no tumorigenic effect was found in the rat. The tumor incidence was lower in female rats treated with 150 mg/kg/day propranolol than in any of the other groups. This was attributed to the markedly decreased body weight gains in this group.

It has been reported that to determine the effects of propranolol hydrochloride in rats on fertility, pregnancy, the developing fetus, and newborns up to the time of weaning, various dose levels of the drug were administered either by gastric intubation or in the feed. The drug was also fed to rabbits in their diet. In some studies in rats a non-dose related increase in resorption sites and neonatal deaths were observed. No teratogenic effects were noted in either species. Furthermore, the compound had no adverse effect on fertility, pregnancy, parturition, or lactation.

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