



unresponsive to the usual doses of epinephrine used to treat allergic reaction.

**Clinical Laboratory Tests**

In patients with hypertension, use of propranolol has been associated with elevated levels of serum potassium, serum transaminases and alkaline phosphatase. In severe heart failure, the use of propranolol has been associated with increases in Blood Urea Nitrogen.

**Drug Interactions**

Caution should be exercised when propranolol is administered with drugs that have an effect on CYP2D6, 1A2, or 2C19 metabolic pathways. Coadministration of such drugs with propranolol may lead to clinically relevant drug interactions and changes on its efficacy and/or toxicity (see **Drug Interactions in PHARMACOKINETICS AND DRUG METABOLISM**).

Cardiovascular Drugs

*Antiarrhythmics*

Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol.

Quinidine increases the concentration of propranolol and produces greater degrees of clinical beta-blockade and may cause postural hypotension.

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with β-blockers such as propranolol.

The clearance of lidocaine is reduced with administration of propranolol. Lidocaine toxicity has been reported following coadministration with propranolol.

Caution should be exercised when administering propranolol with drugs that slow A-V nodal conduction, e.g., digitalis, lidocaine and calcium channel blockers.

*Digitalis Glycosides*

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

*Calcium Channel Blockers*

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.

There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers.

Coadministration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high-degree heart block, and heart failure.

*ACE Inhibitors*

When combined with beta-blockers, ACE inhibitors can cause hypotension, particularly in the setting of acute myocardial infarction.

The antihypertensive effects of clonidine may be antagonized by beta-blockers. Propranolol should be administered cautiously to patients withdrawing from clonidine.

*Alpha Blockers*

Prazosin has been associated with prolongation of first dose hypotension in the presence of beta-blockers.

Postural hypotension has been reported in patients taking both beta-blockers and terazosin or doxazosin.

*Reserpine*

Patients receiving catecholamine-depleting drugs, such as reserpine, should be closely observed for excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

*Inotropic Agents*

Patients on long-term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation. Epinephrine is therefore not indicated in the treatment of propranolol overdose (see **OVERDOSAGE**).

*Isoproterenol and Dobutamine*

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing evaluation for myocardial ischemia.

Non-Cardiovascular Drugs

*Nonsteroidal Anti-Inflammatory Drugs*

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor blocking agents.

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.

*Antidepressants*

The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers by interfering with the beta blocking activity of propranolol.

*Anesthetic Agents*

Methoxyflurane and trichloroethylene may depress myocardial contractility when administered with propranolol.

*Warfarin*

Propranolol when administered with warfarin increases the concentration of warfarin. Prothrombin time, therefore, should be monitored.

*Neuroleptic Drugs*

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

*Thyroxine*

Thyroxine may result in a lower than expected T<sub>3</sub> concentration when used concomitantly with propranolol.

*Alcohol*

Alcohol, when used concomitantly with propranolol, may increase plasma levels of propranolol.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

In dietary administration studies in which mice and rats were treated with propranolol hydrochloride for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is, respectively, about equal to and about twice the maximum recommended human oral daily dose (MRHD) of 640 mg propranolol hydrochloride. In a study in which both male and female rats were exposed to propranolol hydrochloride in their diets at concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol hydrochloride in bacteria (*S. typhimurium* strain TA 1538).

**Pregnancy: Pregnancy Category C**

In a series of reproductive and developmental toxicology studies, propranolol hydrochloride was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day, but not at doses of 80 mg/kg/day (equivalent to the MRHD on a body surface area basis), treatment was associated with embryotoxicity (reduced litter size and increased resorption rates) as well as neonatal toxicity (deaths). Propranolol hydrochloride also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (about 5 times the maximum recommended human oral daily dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation, small placentas, and congenital abnormalities have been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers received propranolol at parturition have exhibited bradycardia, hypoglycemia, and/or respiratory depression. Adequate facilities for monitoring such infants at birth should be available. Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

Propranolol is excreted in human milk. Caution should be exercised when propranolol is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of propranolol in pediatric patients have not been established.

Bronchospasm and congestive heart failure have been reported coincident with the administration of propranolol therapy in pediatric patients.

**Geriatric Use**

Clinical studies of propranolol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## ADVERSE REACTIONS

The following adverse events were observed and have been reported in patients using propranolol.

**Cardiovascular:** Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

**Central Nervous System:** Light-headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose-related.

**Gastrointestinal:** Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

**Allergic:** Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm, and respiratory distress.

**Respiratory:** Bronchospasm.

**Hematologic:** Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

**Autoimmune:** Systemic lupus erythematosus (SLE).

**Skin and mucous membranes:** Stevens-Johnson Syndrome, toxic epidermal necrolysis, dry eyes, exfoliative dermatitis, erythema multiforme, urticaria, alopecia, SLE-like reactions, and psoriasisform rashes. Oculomucocutaneous syndrome involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

**Genitourinary:** Male impotence; Peyronie’s disease.

## OVERDOSAGE

Propranolol is not significantly dialyzable. In the event of overdose or exaggerated response, the following measures should be employed:

General: If ingestion is or may have been recent, evacuate gastric contents, taking care to prevent pulmonary aspiration.

Supportive Therapy: Hypotension and bradycardia have been reported following propranolol overdose and should be treated appropriately. Glucagon can exert potent inotropic and chronotropic effects and may be particularly useful for the treatment of hypotension or depressed myocardial function after a propranolol overdose. Glucagon should be administered as 50 to 150 mcg/kg intravenously followed by continuous drip of 1 to 5 mg/hour for positive chronotropic effect. Isoproterenol, dopamine or phosphodiesterase inhibitors may also be useful. Epinephrine, however, may provoke uncontrolled hypertension. Bradycardia can be treated with atropine or isoproterenol. Serious bradycardia may require temporary cardiac pacing.

The electrocardiogram, pulse, blood pressure, neurobehavioral status and intake and output balance must be monitored. Isoproterenol and aminophylline may be used for bronchospasm.

## DOSAGE AND ADMINISTRATION

**General**

Because of the variable bioavailability of propranolol, the dose should be individualized based on response.

**Hypertension**

The usual initial dosage is 40 mg propranolol hydrochloride twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure control is achieved. The usual maintenance dosage is 120 mg to 240 mg per day. In some instances a dosage of 640 mg a day may be required. The time needed for full antihypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3-times-daily therapy may achieve better control.

**Angina Pectoris**

Total daily doses of 80 mg to 320 mg propranolol hydrochloride, when administered orally, twice a day, three times a day, or four times a day, have been shown to increase exercise tolerance and to reduce ischemic changes in the ECG. If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See **WARNINGS**.)

**Atrial Fibrillation**

The recommended dose is 10 mg to 30 mg propranolol hydrochloride three or four times daily before meals and at bedtime.

**Myocardial Infarction**

In the Beta-Blocker Heart Attack Trial (BHAT), the initial dose was 40 mg t.i.d., with titration after 1 month to 60 mg to 80 mg t.i.d. as tolerated. The recommended daily dosage is 180 mg to 240 mg propranolol hydrochloride per day in divided doses. Although a t.i.d. regimen was used in the BHAT and a q.i.d. regimen in the Norwegian Multicenter Trial, there is a reasonable basis for the use of either a t.i.d. or b.i.d. regimen (see **PHARMACODYNAMICS AND CLINICAL EFFECTS**). The effectiveness and safety of daily dosages greater than 240 mg for prevention of cardiac mortality have not been established. However, higher dosages may be needed to effectively treat coexisting diseases such as angina or hypertension (see above).

**Migraine**

The initial dose is 80 mg propranolol hydrochloride daily in divided doses. The usual effective dose range is 160 mg to 240 mg per day. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, propranolol hydrochloride therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

**Essential Tremor**

The initial dosage is 40 mg propranolol hydrochloride twice daily. Optimum reduction of essential tremor is usually achieved with a dose of 120 mg per day. Occasionally, it may be necessary to administer 240 mg to 320 mg per day.

**Hypertrophic Subaortic Stenosis**

The usual dosage is 20 mg to 40 mg propranolol hydrochloride three or four times daily before meals and at bedtime.

**Pheochromocytoma**

The usual dosage is 60 mg propranolol hydrochloride daily in divided doses for three days prior to surgery as adjunctive therapy to alpha-adrenergic blockade. For the management of inoperable tumors, the usual dosage is 30 mg daily in divided doses as adjunctive therapy to alpha-adrenergic blockade.

## HOW SUPPLIED

Propranolol Hydrochloride Tablets, USP, 10 mg are orange, round, convex, scored tablets, debossed “54” bisect “82” on one side and debossed “V” on the reverse side. They are available as follows:

- Bottles of 100: 0603-5482-21
- Bottles of 1000: 0603-5482-32

Propranolol Hydrochloride Tablets, USP, 20 mg are blue, round, flat faced, beveled edge, scored tablets, debossed “54” bisect “83” on one side and debossed “V” on the reverse side. They are available as follows:

- Bottles of 100: 0603-5483-21
- Bottles of 1000: 0603-5483-32

Propranolol Hydrochloride Tablets, USP, 40 mg are green, round, convex, scored tablets, debossed “54” bisect “84” on one side and debossed “V” on the reverse side. They are available as follows:

- Bottles of 100: 0603-5484-21
- Bottles of 1000: 0603-5484-32

Propranolol Hydrochloride Tablets, USP, 60 mg are pink, round, convex, scored tablets, debossed “54” bisect “85” on one side and debossed “V” on the reverse side. They are available as follows:

- Bottles of 100: 0603-5485-21

Propranolol Hydrochloride Tablets, USP, 80 mg are yellow, round, convex, scored tablets, debossed “54” bisect “86” on one side and debossed “V” on the reverse side. They are available as follows:

- Bottles of 100: 0603-5486-21
- Bottles of 500: 0603-5486-28

**Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].**

**Dispense in a well-closed, light-resistant container as defined in the USP.**

**Protect from light.**

	Distributed by: <b>Par Pharmaceutical</b> Chestnut Ridge, NY 10977	
Issued: 06/18		OS5482H-01-1-01