8013989-9093

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

PROMOTIL TR

(Propranolol Hydrochloride Timed Release Capsules)

COMPOSITION

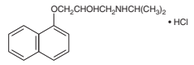
PROMOTIL TR 40
Each timed release capsule contains :
Propranolol Hydrochloride I.P. 40 mg
Approved colours used in empty hard gelatin capsule shell.

PROMOTIL TR 60
Each timed release capsule contains :
Propranolol Hydrochloride I.P. 60 mg
Approved colours used in empty hard gelatin capsule shell.

PROMOTIL TR 80
Each timed release capsule contains :
Propranolol Hydrochloride I.P. 80 mg
Approved colours used in empty hard gelatin capsule shell.

DESCRIPTION

Propranolol hydrochloride is a synthetic beta-adrenergic receptor-blocking agent chemically described as (RS)-1-isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride. Its structural formula is:



Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol; slightly soluble in chloroform; practically insoluble in ether. Its molecular weight is 295.80.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Propranolol hydrochloride is a nonselective, beta-adrenergic receptor-blocking agent. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol hydrochloride, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

The mechanism of the antihypertensive effect of propranolol hydrochloride has not been established. Among the factors that may be involved in contributing to the antihypertensive action 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. Propranolol has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

The mechanism of the antimigraine effect of propranolol has not been established.

Pharmacokinetics

Peak blood concentration levels following dosing with propranolol hydrochloride timed release (TR) occur at about 6 hours, and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24 hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65%. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hour, and then decline exponentially.

Propranolol TR should not be considered a simple mg-for-mg substitute for conventional propranolol. When changing to propranolol TR from conventional propranolol, a possible need for retitration upwards should be considered, especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, Propranolol TR has been therapeutically equivalent to the same mg dose of conventional Propranolol as assessed by 24- hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Propranolol TR can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE

Hypertension

Promotil TR is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. It is not indicated in the management of hypertensive emergencies.

Angina pectoris due to coronary atherosclerosis

Promotil TR is indicated for the long-term management of patients with angina pectoris.

Migraine

Promotil TR is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established, and propranolol is not indicated for such use.

Hypertrophic subaortic stenosis

Promotil TR is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. It also improves exercise performance.

CONTRAINDICATIONS

Promotil TR is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure, unless the failure is secondary to a tachyarrhythmia treatable with propranolol.

WARNINGS

Hypersensitivity reactions, including anaphylactic reactions, have been associated with the administration of propranolol.

Cardiac failure

Beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

In patients without a history of heart failure

Continued use of beta blockers can lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or propranolol should be discontinued (gradually, if possible).

In patients with angina pectoris

Abrupt discontinuation of propranolol can lead to exacerbation of angina and, in some cases, myocardial infarction. Therefore, when discontinuation of propranolol is planned, the dosage should be gradually reduced over at least a few weeks.

Nonallergic bronchospasm (e.g., Chronic Bronchitis, Emphysema)

Beta blockers should be administered with caution in patients with bronchospasm since it may block bronchodialation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

Major surgery

Propranolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension.

Diabetes and hypoglycemia

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure in patients on propranolol. Acute increases in blood pressure have occurred after insulin-induced hypoglycemia in patients on propranolol.

Thyrotoxicosis

Abrupt withdrawal of propranolol may lead to an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

In patients with Wolff-Parkinson-White Syndrome

Some cases reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker

PRECAUTIONS

General

Propranolol should be used with caution in patients with impaired hepatic or renal function. It is not indicated for the treatment of hypertensive emergencies.

Patients should be told that propranolol may interfere with the glaucoma screening test because beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Withdrawal may lead to a return of increased intraocular pressure.

Risk of anaphylactic reaction

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Clinical laboratory tests

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

Drug Interactions

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be taken when patients receiving a beta blocker are administered a calcium channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported.

Haloperidol, when coadministered with propranolol, hypotension and cardiac arrest has been reported.

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

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Phenytoin, *phenobarbitone* and *rifampicin* accelerate propranolol clearence.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

Carcinogenesis, mutagenesis, impairment of fertility

There was no evidence of drug related tumorigenesis when propranolol was administered in rats and mice up to 18 months at doses of up to 150 mg/kg/day. There were no effects on fertility when both male and female rats were exposed to propranolol at concentrations of up to 0.05%, from 60 days prior to mating and throughout pregnancy and lactation for two generations.

Pregnancy: Category C

Intrauterine growth retardation, small placentas, and congenital abnormalities have been reported in neonates whose mothers received propranolol during pregnancy. Neonates whose mothers are receiving propranolol at parturition have exhibited bradycardia, hypoglycemia and/or respiratory depression. Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Propranolol is excreted in human milk. Caution should be taken when administered to a nursing mother.

Pediatrics

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

Geriatric use

Reports have 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.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

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, reversible mental depression progressing to 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.

Gastrointestinal

Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, and ischemic colitis.

Allergic

Hypersensitivity reactions, including anaphylactic reactions, pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory

Bronchospasm.

Hematologic

Agranulocytosis, nonthrombocytopenic purpura, and thrombocytopenic purpura.

Autoimmune

Systemic lupus erythematosus (extremely rare).

Miscellaneous

Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker have not been associated with propranolol.

Skin

Stevens - Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria.

DOSAGE AND ADMINISTRATION

If patients are switched from conventional propranolol to propranolol timed release, care should be taken to assure that the desired therapeutic effect is maintained. Propranolol TR should not be considered a simple mg-for-mg substitute for propranolol. Propranolol TR has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

Hypertension

The usual initial dosage is 80mg Promotil TR once daily, whether used alone or added to a diuretic. The dosage may be increased to 120mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160mg once daily. In some instances a dosage of 640mg may be required.

Angina pectoris

Starting with 80mg Promotil TR once daily, dosage should be gradually increased at three to seven day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160mg once daily. In angina pectoris, the value and safety of dosage exceeding 320mg per day have not been established. If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks.

Migraine

The initial oral dose is 80mg Promotil TR once daily. The usual effective dose range is 160 to 240mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

Hypertrophic subaortic stenosis

Promotil TR 80mg to 160mg once daily.

Pediatric Dosage

Limited data is available on the use of the drug in pediatric group. Hence an adequate direction for use is not possible.

OVERDOSE

Propranolol is not significantly dialyzable. In the event of overdosage 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.

Bradycardia

Administer atropine (0.25 to 1.0mg); if there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac failure

Digitalization and diuretics.

Hypotension

Vasopressors, e.g., levarterenol or epinephrine (there is evidence that epinephrine is the drug of choice).

Bronchospasm

Administer isoproterenol and aminophylline.

EXPIRY DATE:

Do not use after the date of expiry.

STORAGE:

Store in a cool dry place, protected from light.

PRESENTATION

Promotil TR 40, 60 and 80 are available in blister strip pack of 10 Capsules.

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TORRENT PHARMACEUTICALS LTD.
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