CIPLAR Tablets (Propranolol)

Composition

CIPLAR-10
Each tablet contains:
Propranolol hydrochloride IP..... 10 mg

CIPLAR-40
Each tablet contains:
Propranolol hydrochloride IP..... 40 mg

Dosage Form

Tablets

Pharmacology

Pharmacodynamics

Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor agonist agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. At dosages greater than required for beta-blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antihypertensive effect of propranolol has not been established. Factors that may contribute to the antihypertensive action include: (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. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use of propranolol. Effects on plasma volume appear to be minor and somewhat variable.

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 net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade, and this appears to be its principal antiarrhythmic mechanism of action. In dosages greater than required for beta-blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

The specific mechanism of propranolol's antitremor effects has not been established, but $beta_2$ (noncardiac) receptors may be involved. A central effect is also possible. Clinical studies have demonstrated that propranolol is of benefit in exaggerated physiological and essential (familial) tremor.

Pharmacokinetics

Absorption

Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. Peak plasma concentrations occur about 1 to 4 hours after an oral dose.

Administration of protein-rich foods increase the bioavailability of propranolol by about 50% with no change in time to peak concentration, plasma binding, half-life, or the amount of unchanged drug in the urine.

Distribution

Approximately 90% of circulating propranolol is bound to plasma proteins (albumin and $alpha_1$ acid glycoprotein). The binding is enantiomer-selective. The S(-)-enantiomer is preferentially bound to alpha1 glycoprotein and the R(+)-enantiomer preferentially bound to albumin. The volume of distribution of propranolol is approximately 4 liters/kg.

Propranolol crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

Metabolism and Elimination

Propranolol is extensively metabolized with most metabolites appearing in the urine. Propranolol is metabolized through three primary routes: aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain oxidation, and direct glucuronidation. It has been estimated that the percentage contributions of these routes to total metabolism are 42%, 41% and 17%, respectively, but with considerable variability between individuals. The four major metabolites are propranolol glucuronide, naphthyloxylactic acid and glucuronic acid, and sulfate conjugates of 4-hydroxy propranolol.

In vitro studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic CYP2D6. Side-chain oxidation is mediated mainly by CYP1A2 and to some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6.

Propranolol is also a substrate of CYP2C19 and a substrate for the intestinal efflux transporter, pglycoprotein (p-gp). Studies suggest however that p-gp is not dose-limiting for intestinal absorption of propranolol in the usual therapeutic dose range.

In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance of 4-hydroxy propranolol was significantly higher and of naphthyloxyactic acid significantly lower in EMs than PMs.

The plasma half-life of propranolol is from 3 to 6 hours.

Enantiomers

Propranolol is a racemic mixture of two enantiomers, R(+) and S(-). The S(-)-enantiomer is approximately 100 times as potent as the R(+)-enantiomer in blocking beta-adrenergic receptors. In normal subjects receiving oral doses of racemic propranolol, S(-)-enantiomer concentrations exceeded those of the R(+)-enantiomer by 40-90% as a result of stereoselective hepatic metabolism. Clearance of the pharmacologically active S(-)-propranolol is lower than R(+)-propranolol after intravenous and oral doses.

Special Populations

Geriatric

In a study of 12 elderly (62-79 years old) and 12 young (25-33 years old) healthy subjects, the clearance of S(-)-enantiomer of propranolol was decreased in the elderly. Additionally, the half-life of both the R(+)- and S(-)-propranolol were prolonged in the elderly compared with the young (11 hours vs. 5 hours).Clearance of propranolol is reduced with aging due to decline in oxidation capacity (ring oxidation and side-chain oxidation). Conjugation capacity remains unchanged. In a study of 32 patients age 30 to 84 years given a single 20-mg dose of propranolol, an inverse correlation was found between age and the partial metabolic clearances to 4-hydroxypropranolol (40HP-ring oxidation) and to naphthoxylactic acid (NLA-side chain oxidation). No correlation was found between age and the partial metabolic clearance to propranolol glucuronide (PPLG-conjugation).

Gender

In a study of 9 healthy women and 12 healthy men, neither the administration of testosterone nor the regular course of the menstrual cycle affected the plasma binding of the propranolol enantiomers. In contrast, there was a significant, although non-enantioselective diminution of the binding of propranolol after treatment with ethinyl estradiol. These findings are inconsistent with another study, in which administration of testosterone cypionate confirmed the stimulatory role of this hormone on propranolol metabolism and concluded that the clearance of propranolol in men is dependent on circulating concentrations of testosterone. In women, none of the metabolic clearances for propranolol showed any significant association with either estradiol or testosterone.

Race

A study conducted in 12 Caucasian and 13 African-American male subjects taking propranolol, showed that at steady state, the clearance of R(+)- and S(-)-propranolol were about 76% and 53% higher in African-Americans than in Caucasians, respectively. Chinese subjects had a greater proportion (18% to 45% higher) of unbound propranolol in plasma compared to Caucasians, which was associated with a lower plasma concentration of alpha1 acid glycoprotein.

Renal Impairment

In a study conducted in 5 patients with chronic renal failure, 6 patients on regular dialysis, and 5 healthy subjects, who received a single oral dose of 40 mg of propranolol, the peak plasma concentrations (C_{max}) of propranolol in the chronic renal failure group were 2 to 3-fold higher (161±41 ng/mL) than those observed in the dialysis patients (47±9 ng/mL) and in the healthy subjects (26±1 ng/mL). Propranolol plasma clearance was also reduced in the patients with chronic renal failure. Studies have reported a delayed absorption rate and a reduced half-life of propranolol in patients with renal failure of varying severity. Despite this shorter plasma half-life, propranolol peak plasma levels were 3-4 times higher and total plasma levels of metabolites were up to 3 times higher in these patients than in subjects with normal renal function. Chronic renal failure has been associated with a decrease in drug metabolism via downregulation of hepatic cytochrome P450 activity resulting in a lower “first-pass” clearance. Propranolol is not significantly dialyzable.

Hepatic Impairment

Propranolol is extensively metabolized by the liver. In a study conducted in 7 patients with cirrhosis

and 9 healthy subjects receiving 80-mg oral propranolol every 8 hours for 7 doses, the steady-state unbound propranolol concentration in patients with cirrhosis was increased 3-fold in comparison to controls. In cirrhosis, the half-life increased to 11 hours compared to 4 hours

Indications

- Hypertension
- Angina Pectoris Due to Coronary Atherosclerosis
- Atrial Fibrillation
- Myocardial Infarction
- Migraine
- Essential Tremor
- Hypertrophic Subaortic Stenosis
- Pheochromocytoma

Dosage and Administration

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

Hypertension

The usual initial dosage is **CIPLAR-40** 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 **CIPLAR**, 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.

Atrial Fibrillation

The recommended dose is 10 mg to 30 mg **CIPLAR** 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 dose is 180-240 mg **CIPLAR** per day in divided doses. Although a t.i.d regimen was used in the Beta-Blocker Heart Attack Trial (BHAT) & a qid 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. 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.

Migraine

The initial dose is 80 mg **CIPLAR** 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, **CIPLAR** 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 **CIPLAR-40** 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 **CIPLAR** three or four times daily before meals and at bedtime.

Pheochromocytoma

The usual dosage is 60 mg **CIPLAR** 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.

Contraindications

- Cardiogenic shock
- Sinus bradycardia and greater than first degree block
- Bronchial asthma
- Hypersensitivity to propranolol hydrochloride

Warnings and Precautions

Hypertensive Emergencies, Glaucoma, Anaphylactic Reaction

Propranolol is not indicated for the treatment of hypertensive emergencies.

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

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.

Drug Interactions

Antiarrhythmics

Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol. The area under curve (AUC) of propafenone is increased by more than 200% by co-administration of propranolol. Quinidine increases the concentration of propranolol and produces greater degrees of clinical beta-blockade and may cause postural hypotension. The metabolism of propranolol is reduced by co-administration of quinidine, leading to a two-to three-fold increased blood concentration and greater degrees of clinical beta-blockade. Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with beta-blockers such as propranolol. The metabolism of lidocaine is inhibited by co-administration of propranolol, resulting in a 25% increase in lidocaine concentrations. 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.

Antidepressants

The hypotensive effects of monoamine oxidase (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.

Angiotensin Converting Enzyme (ACE) Inhibitors

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

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.

Anti-ulcer Drugs

Co-administration of propranolol with cimetidine, a non-specific CYP450 inhibitor, increased propranolol AUC and C_{max} by 46% and 35%, respectively. Co-administration with aluminum hydroxide gel (1200 mg) may result in a decrease in propranolol concentrations. Co-administration of metoclopramide with the long-acting propranolol did not have a significant effect on propranolol's pharmacokinetics.

Alcohol

Concomitant use of alcohol may increase plasma levels of propranolol.

Benzodiazepines

Propranolol can inhibit the metabolism of diazepam, resulting in increased concentrations of diazepam and its metabolites. Diazepam does not alter the pharmacokinetics of propranolol. The pharmacokinetics of oxazepam, triazolam, lorazepam, and alprazolam are not affected by co-administration of propranolol.

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. The mean C_{max} and AUC of propranolol are increased respectively, by 50% and 30% by co-administration of nisoldipine and by 80% and 47%, by co-administration of nicardipine. The mean C_{max} and AUC of nifedipine are increased by 64% and 79%, respectively, by co-administration of propranolol. Propranolol does not affect the pharmacokinetics of verapamil and norverapamil. Verapamil does not affect the pharmacokinetics of propranolol. There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers. Co-administration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high-degree heart block, and heart failure.

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

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

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.

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.

Migraine Drugs
Administration of zolmitriptan or rizatriptan with propranolol resulted in increased concentrations of zolmitriptan (AUC increased by 56% and C_{max} by 37%) or rizatriptan (the AUC and C_{max} were increased by 67% and 75%, respectively).

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.

Neuroleptic Drugs
Co-administration of long-acting propranolol at doses greater than or equal to 160 mg/day resulted in increased thioridazine plasma concentrations ranging from 55% to 369% and increased thioridazine metabolite (mesoridazine) concentrations ranging from 33% to 209%. Co-administration of chlorpromazine with propranolol resulted in a 70% increase in propranolol plasma level. Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Reserpine
Patients receiving-depleting drugs such as 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.

Lipid Lowering Drugs
Co-administration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations. Co-administration of propranolol with lovastatin or pravastatin, decreased 18% to 23% the AUC of both, but did not alter their pharmacodynamics. Propranolol did not have an effect on the pharmacokinetics of fluvastatin.

Interactions with Substrates, Inhibitors or Inducers of Cytochrome P-450 Enzymes
Because propranolol's metabolism involves multiple pathways in the cytochrome P-450 system (CYP2D6, 1A2, 2C19), co-administration with drugs that are metabolized by, or effect the activity (induction or inhibition) of one or more of these pathways may lead to clinically relevant drug interactions.

Substrates or Inhibitors of CYP2D6
Blood levels and/or toxicity of propranolol may be increased by co-administration with *substrates or inhibitors of CYP2D6* (eg. amiodarone, cimetidine, delavudin, fluoxetine, paroxetine, quinidine, and ritonavir). No interactions were observed with either ranitidine or lansoprazole.

Substrates or Inhibitors of CYP1A2
Blood levels and/or toxicity of propranolol may be increased by co-administration with *substrates or inhibitors of CYP1A2*, (eg. imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan).

Substrates or Inhibitors of CYP2C19
Blood levels and/or toxicity of propranolol may be increased by co-administration with *substrates or inhibitors of CYP2C19* (eg. fluconazole, cimetidine, fluoxetine, fluvoxamine, tenioposide, and tolbutamide). No interaction was observed with omeprazole.

Inducers of Hepatic Drug Metabolism
Blood levels of propranolol may be decreased by co-administration with *inducers of hepatic drug metabolism* (eg. rifampin, ethanol, phenytoin, and Phenobarbital). Cigarette smoking also induces hepatic metabolism and has been shown to increase up to 77% the clearance of propranolol, resulting in decreased plasma concentrations.

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

Theophylline
Co-administration of theophylline with propranolol decreases theophylline oral clearance by 30% to 52%.

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

Angina Pectoris

There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks and the

patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Cardiac Failure

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, some have been shown to be highly beneficial when used with close follow-up in patients with a history of failure who are well compensated and are receiving additional therapies, including diuretics as needed. 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, in some cases, lead to cardiac failure.

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

In general, patients with bronchospastic lung disease should not receive beta- blockers. Propranolol should be administered with caution since it may provoke a bronchial asthmatic attack by blocking bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in labile insulin-dependent diabetics. In these patients, it may be more difficult to adjust the dosage of insulin.

Propranolol therapy, particularly when given to infants and children, diabetic or not, has been associated with hypoglycemia, especially during fasting as in preparation for surgery. Hypoglycemia has been reported in patients taking propranolol after prolonged physical exertion and in patients with renal insufficiency.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by 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.

Wolff-Parkinson-White Syndrome

Beta-adrenergic blockade in patients with Wolff-Parkinson-White Syndrome and tachycardia has been

associated with severe bradycardia requiring treatment with a pacemaker. In one case, this result was reported after an initial dose of 5 mg propranolol.

Pheochromocytoma

Blocking only the peripheral dilator (beta) action of epinephrine with propranolol leaves its constrictor (alpha) action unopposed. In the event of hemorrhage or shock, there is a disadvantage in having both beta- and alpha-blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

Hypersensitivity and Skin Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of propranolol. Cutaneous reactions, including toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol.

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.

Renal Impairment

CIPLAR should be used with caution in patients with impaired renal function. Propranolol is not significantly dialyzable.

Hepatic Impairment

CIPLAR should be used with caution in patients with impaired hepatic function.

Pregnancy

Category C
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.

Lactation

Propranolol is secreted in human milk. Caution should be exercised when **CIPLAR** 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.

Undesirable Effects

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 psoriasiform 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 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.

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 50-150 mcg/kg intravenously followed by continuous drip of 1-5 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.

Packaging Information

CIPLAR-10: Blister pack of 15 tablets
CIPLAR-40: Blister pack of 15 tablets

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