Inderal®
(propranolol hydrochloride)
Tablets

Rx only

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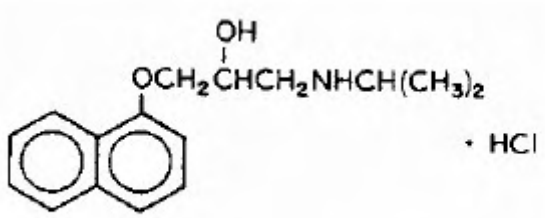
DESCRIPTION

Inderal® (propranolol hydrochloride) is a synthetic beta-adrenergic receptor blocking agent chemically described as 2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride,(±)-. Its molecular and structural formulae are:



$C_{16}H_{21}NO_2 \cdot HCl$

Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80.

Inderal is available as 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration.

The inactive ingredients contained in Inderal Tablets are: lactose, magnesium stearate, microcrystalline cellulose, and stearic acid. In addition, Inderal 10 mg and 80 mg Tablets contain FD&C Yellow No. 6 and D&C Yellow No. 10; Inderal 20 mg Tablets contain FD&C Blue No. 1; Inderal 40 mg Tablets contain FD&C Blue No. 1, FD&C Yellow No. 6, and D&C Yellow No. 10; Inderal 60 mg Tablets contain D&C Red No. 30.

CLINICAL PHARMACOLOGY

General

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.

Mechanism of Action
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 of propranolol 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 Inderal is of benefit in exaggerated physiological and essential (familial) tremor.

PHARMACOKINETICS AND DRUG METABOLISM
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 $alpha_1$ 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, p-glycoprotein (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 alpha$_1$ acid glycoprotein.

Renal Insufficiency
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 Insufficiency
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 (see **PRECAUTIONS**).

Drug Interactions
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 (see **Drug Interactions** under **PRECAUTIONS**).

Substrates or Inhibitors of CYP2D6
Blood levels and/or toxicity of propranolol may be increased by co-administration with substrates or inhibitors of CYP2D6, such as 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, such as 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, such as 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 such as 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.

Cardiovascular Drugs
Antiarrhythmics
The AUC of propafenone is increased by more than 200% by co-administration of propranolol.

The metabolism of propranolol is reduced by co-administration of quinidine, leading to a two-three fold increased blood concentration and greater degrees of clinical beta-blockade.

The metabolism of lidocaine is inhibited by co-administration of propranolol, resulting in a 25% increase in lidocaine concentrations.

Calcium Channel Blockers
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.

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