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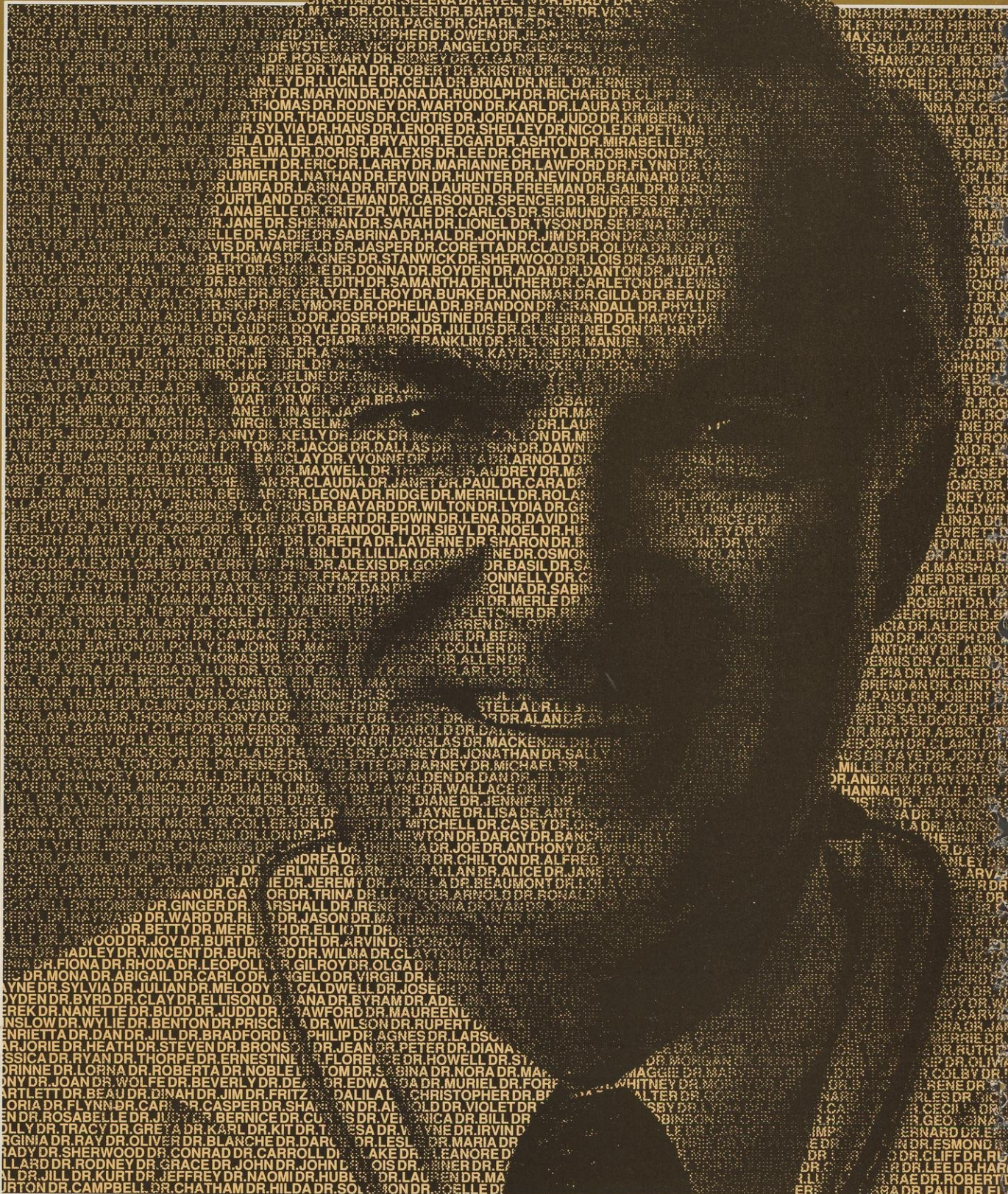
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# ...THINK



# AGAIN!

Recent data on INDERAL® LA prove it's the preferred propranolol for tolerability and promoting patient compliance...

## INDERAL® LA outperforms propranolol HCl tablets

In a comparative study<sup>1</sup> involving 1,768 hypertensives on previous propranolol or INDERAL tablet therapy—54% of the patients stated they felt “better” or “much better” on INDERAL LA.

Patient compliance with once-daily INDERAL LA was also significantly improved.<sup>1</sup> Eight out of ten patients demonstrated *perfect* compliance on INDERAL LA, compared with only 55% of patients receiving multi-dosed propranolol.

## The “preferred beta blocker” of 3 out of 4 doctors who’ve tried it

In a recent survey<sup>2</sup> of 4,120 physicians who evaluated INDERAL LA in their patients, nearly all rated it good to excellent for tolerability and for promoting patient compliance. Based on their first-hand experience, 3 out of 4 of these doctors choose INDERAL LA as their “preferred beta blocker in hypertension” —and prefer to prescribe it before ACE inhibitors, calcium-channel blockers, or alpha blockers. Forty-nine percent also prefer to prescribe INDERAL LA before diuretics.

Try INDERAL LA in your practice and see for yourself...

HYPERTENSIVE PATIENTS CAN

*Feel like a*

MILLION\*

ONCE-DAILY  
**INDERAL® LA**  
(PROPRANOLOL HCl) LONG ACTING CAPSULES  
60, 80, 120, 160 mg

\*like the more than one million patients who have taken INDERAL LA for all its indications.

Please see next page for brief summary of prescribing information.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree and bronchial asthma.

**W** WYETH  
AYERST



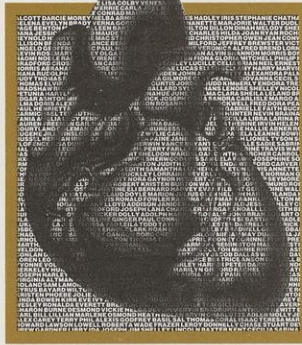
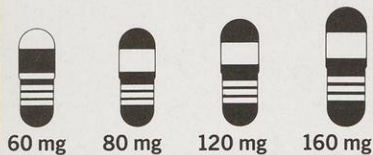
THE AMERICAN  
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PHARMACEUTICAL  
ROUNDTABLE®

feel like a

MILLION

ONCE-DAILY  
**INDERAL<sup>®</sup> LA**  
(PROPRANOLOL HCl)  
LONG ACTING CAPSULES  
60, 80, 120, 160 mg

The one you know best  
keeps looking better \*



BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

**INDERAL<sup>®</sup> LA** brand of propranolol hydrochloride (Long Acting Capsules)

**DESCRIPTION.** Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

**CLINICAL PHARMACOLOGY.** Inderal is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by Inderal, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Inderal LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with Inderal LA 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% of the AUCs for a comparable divided daily dose of Inderal Tablets. 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) hours then decline exponentially.

Inderal LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to Inderal LA 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, Inderal LA has been therapeutically equivalent to the same mg dose of conventional Inderal as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Inderal LA can provide effective beta blockade for a 24-hour period.

**INDICATIONS AND USAGE.** **Hypertension:** Inderal LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Inderal LA is not indicated in the management of hypertensive emergencies.

**Angina Pectoris Due to Coronary Atherosclerosis:** Inderal LA is indicated for the long-term management of patients with angina pectoris.

**Migraine:** Inderal LA 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:** Inderal LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Inderal LA also improves 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-receptor stimulation. Clinical improvement may be temporary.

**CONTRAINDICATIONS.** Inderal is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with Inderal.

**WARNINGS. 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, 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, in some cases, 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 Inderal should be discontinued (gradually, if possible).

**IN PATIENTS WITH ANGINA PECTORIS,** there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of Inderal therapy. Therefore, when discontinuance of Inderal 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 Inderal therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute Inderal therapy and take other measures appropriate for the management of unstable 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.

**Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS.** Inderal should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

**MAJOR SURGERY:** The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Inderal (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

**DIABETES AND HYPOGLYCEMIA:** Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

**THYROTOXICOSIS:** Beta 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<sub>4</sub> and reverse T<sub>3</sub>, and decreasing T<sub>3</sub>.

**IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME,** several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

**PRECAUTIONS. GENERAL:** Propranolol should be used with caution in patients with impaired hepatic or renal function. Inderal (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

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

**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 Inderal (propranolol HCl) 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 exercised 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.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and rifampin accelerate propranolol clearance.

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<sub>3</sub> 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:** Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

**PREGNANCY:** Pregnancy Category C. Inderal has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. Inderal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**NURSING MOTHERS:** Inderal is excreted in human milk. Caution should be exercised when Inderal is administered to a nursing woman.

**PEDIATRIC USE:** Safety and effectiveness in children have not been established.

**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. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

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

**Allergic:** Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

**Respiratory:** Bronchospasm.

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

**Auto-immune:** In extremely rare instances, systemic lupus erythematosus has been reported.

**Miscellaneous:** Alopecia, LE-like reactions, psoriasisiform 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 (practolol) have not been associated with propranolol.

**DOSAGE AND ADMINISTRATION.** Inderal LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from Inderal Tablets to Inderal LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. Inderal LA should not be considered a simple mg-for-mg substitute for Inderal. Inderal LA 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—Dosage must be individualized.** The usual initial dosage is 80 mg Inderal LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

**ANGINA PECTORIS—Dosage must be individualized.** Starting with 80 mg Inderal LA 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 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

**MIGRAINE—Dosage must be individualized.** The initial oral dose is 80 mg Inderal LA once daily. The usual effective dose range is 160-240 mg 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, Inderal LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

**HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg Inderal LA once daily.**

**PEDIATRIC DOSAGE—**At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

\*The appearance of these capsules is a registered trademark of Wyeth-Ayerst Laboratories.

References:

- Sanderson JH: Half-Inderal LA therapy in general practice. *BR J Clin Pract* 1987;41(7):833-838.
- Data on file, Wyeth-Ayerst Laboratories.

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