Inderal advertisement.

[s.l.]: [s.n.], 1976

ANGINA PECTORIS:

Initial, prudent management involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. Until 1973, for many patients in whom these conventional measures had failed and for whom coronary bypass surgery was not possible, life-styles were likely to be limited. Many had to give up the work that provided much of the meaning in their lives. The term "cardiac cripple" only begins to suggest the toll that such a loss can exact.

Then, in the early part of this decade, INDERAL was introduced, and the prospects for many patients with moderate to severe angina significantly improved.

INDERAL can permit many patients with angina a more normal, more active life

"The value of beta-adrenergic blockade in angina is established beyond question."[1] In many trials conducted over 12 years of worldwide clinical use, INDERAL has been found in a substantial majority of patients to decrease the frequency of anginal attacks, reduce the need for intermittent nitroglycerin, and increase exercise tolerance.[2-13] For some, the combined effect of these benefits means the ability to carry on work that, without INDERAL (propranolol hydrochloride), would have been precluded.

Combined use with nitroglycerin

During angina prophylaxis, the patient may benefit from the ability of INDERAL and nitroglycerin to complement the actions of each other. All the major determinants of myocardial oxygen demand tend to be reduced by the concomitant use of these drugs.

Candidates for INDERAL therapy: selected patients with moderate to severe angina not responsive to conventional measures

INDERAL is indicated for the many patients in whom conventional measures for the treatment of angina have failed to provide a satisfactory response, and in whom angina results from relatively little effort or frequent precipitating factors. INDERAL is contraindicated in patients with congestive

failure unless it is secondary to a tachyarrhythmia treatable with INDERAL. It is also contraindicated in patients with heart block of greater than first degree, and in those with bronchial asthma. *Please refer to the Brief Summary of Prescribing Information on the last page of this advertisement for additional contraindications.*

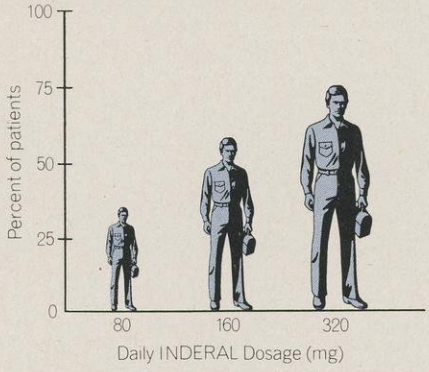
While the net physiologic effect produced by INDERAL is usually positive in patients selected according to the criteria above, it may not be so in some patients. Treatment should therefore be carefully monitored. If the overall result of INDERAL therapy is advantageous, the benefit should manifest itself by delayed onset of pain during exercise. *INDERAL should not be continued unless there is reduced pain or increased work capacity.*

Effective INDERAL prophylaxis: a question of individualized dosage titration

Start with 10-20 mg three or four times daily, before meals and at bedtime. Increase dosage gradually until optimal response is obtained, assessing results every three to seven days during titration. While individual response may vary, the average dosage appears to be 160 mg per day. Occasionally, dosages as high as 320 mg may be needed for fully effective management. In angina pectoris, the value and safety of dosages above this level have not been established.

Several investigators have shown that promising antianginal effects achieved with moderate dosages of INDERAL were substantially bettered when dosages were increased.[2-4,14] Alderman, *et al.*, for example, found in a study of 17 subjects that the numbers of patients experiencing a marked reduction in the frequency of anginal attacks more than doubled as the daily INDERAL dosage was raised from 80 mg to 160 mg and finally to 320 mg.[4]

Percent of patients with 25% or greater reduction in number of anginal attacks with upward titration of INDERAL dosage relative to placebo.*



*Adapted from Alderman, *et al.*[4]: A double-blind, crossover study of 17 patients on INDERAL vs placebo

Decreased heart rate is part of the normal action of INDERAL[1]

In angina pectoris, a slowing of the heart rate is an integral part of the mode of action of INDERAL, *i.e.*, a reduction in the overall oxygen requirements of the heart. While INDERAL dosage should be reduced or discontinued if symptomatic bradycardia occurs, "In general, patients tolerate heart rates as low as 50 beats per minute well."[15]

Untoward cardiac effects are relatively infrequent[1,16-20]

Congestive failure: Inhibition with beta-blockade carries the potential risk of depressing myocardial contractility and precipitating cardiac failure in patients with, or in rare instances, without a history of such failure.

At the first sign or symptom of impending cardiac failure, the patient should be fully digitalized and/or given a diuretic, and the response closely observed. If cardiac failure continues, INDERAL should be immediately withdrawn, keeping in mind the need to avoid abrupt discontinuation unless it is required by overriding clinical considerations. If the congestive failure is caused by a tachyarrhythmia that is being controlled with INDERAL, the agent may be continued with extreme caution if digitalis, a diuretic agent, and dietary sodium restriction are used concomitantly.

Avoid abrupt withdrawal

There have been reports of exacerbation of angina and, in some cases, myocardial infarction following abrupt discontinuance of INDERAL. All patients should be cautioned against interruption or cessation of therapy without the physician's advice. If discontinuance is indicated, the daily dosage of INDERAL should be diminished gradually over a period of several weeks until withdrawal is complete.

Please see last page of advertisement for prescribing information.

Ayerst®

Often increases work capacity in selected patients with angina pectoris

Inderal®

(propranolol hydrochloride)

BRIEF SUMMARY

(For full prescribing information, see package circular.)

INDERAL® Brand of propranolol hydrochloride

A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

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

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATION

Angina Pectoris Due to Coronary Atherosclerosis

The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, 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.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

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.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta-blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

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

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; 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

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

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.*

Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. 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 several weeks. (See WARNINGS.)

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.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): 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.

HOW SUPPLIED

INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCES

1. Conolly, M.E., Kersting, F., and Dollery, C.T.: Progr. Cardiovasc. Dis. *19*:203-234 (Nov./Dec.) 1976. **2.** Mizgala, H.F., Khan, A.S., and Davies, R.O.: Can. Med. Assoc. J. *100*:756-764 (Apr. 26) 1969. **3.** Prichard, B.N.C., and Gillam, P.M.S.: Br. Heart J. *33*:473-480 (July) 1971. **4.** Alderman, E.L., Davies, R.O., Crowley, J.J., *et al.*: Circulation *51*:964-975 (June) 1975. **5.** Keelan, P.: Br. Med. J. *1*:897-898 (Apr. 3) 1965. **6.** Gianelly, R.E., Goldman, R.H., Treister, B., *et al.*: Ann. Intern. Med. *67*:1216-1225 (Dec.) 1967. **7.** Sandler, G., Clayton, G.A., and Thornicroft, S.G.: Br. Med. J. *3*:224-227 (July 27) 1968. **8.** Battock, D.J., Alvarez, H., and Chidsey, C.A.: Circulation *39*:157-169 (Feb.) 1969. **9.** Zsotér, T.T., and Beanlands, D.S.: Arch. Intern. Med. *124*:584-587 (Nov.) 1969. **10.** Wolfson, S., Heinle, R.A., Herman, M.V., *et al.*: Am. J. Cardiol. *18*:345-353 (Sept.) 1966. **11.** Davies, R.O., Mizgala, H.F., and Khan, A.S.: Clin. Research (Abstr.) *17*:635 (Dec.) 1969. **12.** Miller, R.R., Olson, H.G., Pratt, C.M., *et al.*: Clin. Pharmacol. Ther. *18* (No. 5, Pt. 1):598-605 (Nov.) 1975. **13.** Chhetri, M.K., Neelkantan, C., and Guha, S.R.: Indian Heart J. *21*:273-286 (July) 1969. **14.** Gillam, P.M.S., and Prichard, B.N.C.: Am. J. Cardiol. *18*:366-369 (Sept.) 1966. **15.** Shand, D.G.: N. Engl. J. Med. *293*:280-285 (Aug. 7) 1975. **16.** Greenblatt, D.J., and Koch-Weser, J.: Am. Heart J. *86*:478-484 (Oct.) 1973. **17.** Shand, D.G.: D.M., Chicago Year Book Medical Publishing Inc. (Oct.) 1974, pp. 1-31. **18.** Zacharias, F.J., Cowen, K.J., Prestt, J., *et al.*: Am. Heart J. *83*:755-761 (June) 1972. **19.** Holland, O.B., and Kaplan, N.M.: N. Engl. J. Med. *294*:930-936 (Apr. 22) 1976. **20.** Simpson, F.O.: Drugs *7*:85-105, 1974.

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