Propranolol in the Office Treatment of Angina Pectoris

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The concept of differing adrenergic receptors was first postulated by Ahlquist in 1948 and has been generally accepted. An adrenergic receptor may be defined as the specific molecular site or structure in or on the surface of effector cells with which molecules of adrenergic agents react in order to elicit the characteristic response of the cell. The effects of an adrenergic substance such as adrenaline are mediated through two different receptors:

1. Alpha receptors, chiefly associated with excitatory effects such as vasoconstriction and the contraction of smooth muscle of uterus, nictitating membrane and ureter and of the pupillary dilator muscle; but with one inhibitory effect responsible for intestinal muscle relaxation.

2. Beta receptors, mostly concerned with inhibitory effects such as vasodilatation and the inhibition of bronchial and uterine smooth muscle, as well as one important excitatory effect, namely myocardial stimulation. This latter effect results in an increase in rate and force of contraction of the heart, with consequent increased cardiac output and oxygen consumption.

Blockade of adrenergic receptors is now possible. Alpha blockade can be brought about by dibenamine, phenoxybenzamine (Dibenzyline) and phentolamine (Rogitine). Beta blockade can be effected by dichlorisoproterenol, first described and used in animals in 1959 by Powell and Slater. Pronethalol (Alderlin) has been studied in animals and man but was discarded because of the development of tumours in mice. Propranolol (Inderal) has been studied in animals and man and has been the subject of four international symposia.7-10

The effects of propranolol on the heart muscle are to decrease cardiac rate and output, and to reduce oxygen consumption and cardiac work. The extent of these changes resulting from beta adrenergic blockade varies with the underlying degree of sympathetic activity. The effect on the blood pressure of normotensive individuals is minimal. While cardiac output decreases, there is a compensatory increase in total peripheral resistance through reflex mechanisms. It has been suggested that propranolol may potentiate the effects of antihypertensive agents in patients with elevated blood pressure.11, 12

The fall in cardiac output is apparently due partly to the reduction in heart rate and can be partially abolished by the administration of atropine sulfate.12 This reduction occurs in normal subjects at rest and, more important, during exercise, as well as in patients with hypermetabolic states such as hyperthyroidism and tachyarrhythmias.

The use of propranolol in the treatment of angina pectoris was first suggested by Black, Duncan and Shanks.9 The theoretical basis for this idea was that propranolol, by reducing cardiac work and oxygen consumption, would lessen the frequency and severity of the pain of cardiac ischemia. The drug has no important effect on the calibre of coronary arteries in man.

The present trial was designed as a double-blind crossover study in an office setting, based on a consulting practice in internal medicine. Its purpose was to determine the value of propranolol as compared to a placebo in the treatment of angina, by methods applicable to such a setting, and using the patient's own evaluation of the drug's effect as well as a more objective record of the number of attacks of pain and the number of nitroglycerin tablets consumed.

Selection of Patients

Fourteen patients were asked to enter this trial and were selected in so far as they were living within access of the doctor's office, were ambulant, reasonably intelligent and co-operative and had remained symptomatically unchanged for at least the preceding four months. The trial included patients who were easily controlled on nitroglycerin alone and who had been referred by their physicians either because of the frequency or severity of anginal pain or because of the disability it caused. Most were already taking so-called long-acting vasodilator drugs and these were discontinued at the beginning of the trial, though nitroglycerin, hypoten- sive agents and digitalis were continued where applicable. Cases of co-existent bronchial asthma and/or cardiac failure were excluded.

The ages of the patients ranged from 38 to 65 years; there were 12 men and 2 women. All
had angina of effort of varying severity and fre-
frequency. Five had previous infarction and all except one had S-T and T wave abnormalities either at rest or after the Master two-step test (Table I).

**Design of Study**

Patients were allocated to the propranolol or the placebo group using a table of random numbers. Evaluation of the patient’s symptomatic and physical status was initially carried out, followed by one month’s treatment on one or other drug with assessment by one of us (B.J.S.H.) at the end of periods of two and four weeks, using a standardized questionnaire. The patient was also given a diary card on which a daily record of severity and frequency of pain and nitroglycerin consumption was entered. At the end of one month a second supply of identical tablets was given, after which similar observations were made at intervals of two weeks.

Identical scored tablets had been prepared containing inert placebo and 40 mg. propranolol, respectively. At the start of each monthly period of treatment, one-half of each tablet was given twice daily for two days, then one-half tablet every six hours for two days and finally one full tablet every six hours. The final daily dose of propranolol was therefore 160 mg. per day. At the end of the trial the code was broken and the results, based on the above observations, were tabulated by the same observer.

Blood pressure and pulse rate were observed with the patient supine on the couch with the shoulders raised 45°. Determinations were undertaken only after the patient had been interviewed. Pulse rate was measured over a half-minute period, and diastolic pressure was taken as the Korotkoff sounds changed.

**Results**

Results were assessed by noting, first, subjective increase or diminution in symptoms as far as severity of anginal pain and estimated pain threshold were concerned; secondly, objective improvement or regression as estimated by the daily frequency of anginal episodes and by the number of nitroglycerin tablets consumed (Table II).

It will be seen that some cases improved subjectively and objectively, some subjectively and not objectively, and some the reverse. The results of treatment with the drug can be condensed as follows: Marked improvement: Cases 1, 4 and 12. Moderate improvement: Cases 5, 8, 9 and 14. Slight improvement: Case 2. No improvement: Cases 3, 6, 7, 10 and 13.

Five patients showed no clear benefit from propranolol. Four patients must be considered as placebo reactors, as they demonstrated effects on both medications. One such patient (No. 13) had a clear clinical history of angina pectoris; after an episode of congestive heart failure and brief hospitalization during the placebo period, no further anginal symptoms were elicited. While this patient is not considered to have benefited from propranolol, this observation is presented with reservation. Of the eight patients who improved while taking the drug, a balance of their subjective and objective performances determined their placement in the three grades. In general, a noticeable slowing of pulse rate was found when the drug was being taken, but no consistent effect was noted on the blood pressure.

**Adverse Effects**

Adverse effects were noted in some patients while taking the drug, and in others while taking the placebo; these are summarized in Table III. Dizziness was the most common mild ad-
verse reaction and was sometimes described as "light-headedness". It was most frequent in the mornings in the propranolol group, but it was also quite frequently noted in the placebo group. Gastrointestinal effects were not pronounced, but three patients in the propranolol group complained of a feeling of tightness and swelling of extremities and sometimes of the face, without any objective edema. Mild side effects seemed to be more common in the propranolol group.

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<th>Case No.</th>
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Two cases of acute left ventricular failure occurred, requiring hospitalization for short periods. Because of the experimental and clinical evidence that the sympathetic nervous system plays a significant role in the maintenance of adequate circulation in the failing heart, and the reported provocation of failure by propranolol, the dosage schedule was temporarily stopped in these cases for a few days until the heart had again become compensated. No further episodes of failure occurred and both patients were maintained satisfactorily on digoxin during the remainder of the trial. Later it was learned that both had been taking placebo medication when congestive failure was noted, and had remained compensated during propranolol and digoxin therapy.

**DISCUSSION**

Obviously caution must be exercised in evaluating the results of a clinical trial of this nature using a comparatively small number of patients, when changes would not reach significance. The limitations of the double-blind method are well known, but the results of this trial indicate that propranolol is an effective agent and does alleviate the symptoms of angina in some cases. The circumstances under which the trial was carried out, i.e., office practice, permit prediction of the experience of physicians who will use this drug in the future. As in other trials of drugs used for relieving angina, a well-marked placebo effect was noted but the results were better with propranolol, and 8 of the 13 patients completing the trial were improved. Perhaps a longer "run in" period would have minimized this placebo effect. A possible observer bias could have been introduced into this trial because of the demonstrable effectiveness of propranolol in lowering the pulse rate, but this is something which could not be avoided.

The response of the individual patient to the drug was not predictable. Although no cases of emotionally induced angina were included in the trial, the response did not seem to be related to the emotional constitution of the individual. No direct relationship could be obtained between the relief of anginal pain and the observed effects on pulse rate, but decrease in the latter was apparent in those patients who derived the most benefit. No relationship was found to the length of history or severity of symptoms, although the most dramatic relief occurred in a patient who developed status anginosus. It is possible that an increase in dosage might have achieved improvement in an additional number of cases and, in fact, doses of propranolol as high as 400 mg. a day have been
given. The absence of severe side effects due to the propranolol in this trial would certainly encourage one to prescribe higher dosage if benefit is not first achieved with the administration of 20 to 40 mg. every six hours; it is likely that dosage should be individualized. Finally, it is worth pointing out that the four serious complications in this trial all occurred while the patients were taking the placebo, and that care must be taken not to ascribe serious adverse effects to the active drug in a condition in which the natural occurrence of these complications is frequent and unpredictable.

**Summary**

Propranolol in doses of 160 mg. per day or placebo were used in a double-blind trial in 14 patients with angina of effort who were observed under conditions encountered in an office practice. The drug was more effective than placebo in relieving the symptoms of angina, and no serious adverse effects attributable to the drug were encountered. The drug seemed to be most beneficial in patients complaining of severe pain and in patients with status anginosus.

**Résumé**

Chez 14 malades présentant une crise angineuse à l'effort et qui ont été observés dans les conditions d'une pratique privée normale, on a expérimenté, dans une étude à double inconnue, le propranolol à doses de 160 mg et un placebo. Le médicament s'est révélé plus actif que le placebo pour soulager les symptômes angineux et il n'a donné lieu à aucune réaction contraire. Il fut très avantageux chez les malades se plaignant de douleurs très vives et chez ceux qui présentaient des crises subitrantes (status anginosus).

Our thanks are due to the staff of Ayerst Laboratories Ltd. for preparing the material for this trial.

**References**

7. Symposium on propranolol (Inderal), the first adrenergic beta receptor blocking agent in practice, *Cardiologia (Basel)*, 49: (Suppl. 3): 1, 1968.