# EFFECT OF PRONETHALOL IN ANGINA PECTORIS

BY

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The problem of assessing the numerous new drugs offered to clinicians is continuously increasing. It is not always possible, even if desirable, to mount a substantial and definitive therapeutic trial for each new drug in a single department. In these circumstances close observation of a few patients in several centres may provide data adequate to justify more general distribution of a new drug, with minimal diversion of workers from their other tasks. The animal pharmacology of a new adrenergic beta-receptor blocking agent, pronethalol, has been reported by Black and Stephenson (1962), and some aspects of the human pharmacology by Dornhorst and Robinson (1962). It was thought that pronethalol might prove to be beneficial in angina because its restraining effect on tachycardia should reduce the cardiac work, and thus decrease requirements of myocardial oxygen at any given level of exercise.

## REPORT OF CLINICAL TRIAL FROM MEDICAL UNIT AND M.R.C. STATISTICAL UNIT, UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL, LONDON

BY

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### Design of Trial

The aim was to make a double-blind comparison of placebo with the *maximum tolerated dose* of pronethalol. This dose was found for each patient by increasing the dose of pronethalol at weekly intervals until mild side-effects occurred, then reducing the dose slightly and maintaining it for at least one week prior to the trial proper. Initially 150 mg. q.d.s. was given as the starting dose, but later this was reduced to 100 mg. q.d.s. The maximum tolerated dose was selected both because of the obvious disadvantage of a fixed dose and of the well-known therapeutic effect of increased frequency of out-patient attendance in angina. Relief at a lower dosage might have been only a placebo effect, and if pronethalol was really more effective than placebo this would be more likely to be shown in a double-blind study using maximum tolerated doses. This design also provided more information on the acute side-effects of the drug.

Each patient was given placebo for two periods and pronethalol for two periods, each period being of two weeks' duration. There are six different ways in which this can be done, and it was arranged that each of these ways should be used once for every six patients entering the trial. Within this restriction the allocation was at random.

*Recording of Data.*—Patients were asked to take glyceryl trinitrate as usual for the attacks of pain, but not prophylactically, and to keep a record of the attacks of pain and number of tablets taken. They were given a record sheet for each week, each day being divided into four periods starting at the time pronethalol (or placebo) was taken. They were asked to fill in their sheet at the end of each period and to record the time of onset of any attacks of angina, their duration; to assess severity as mild, moderate, or severe; to note the number of glyceryl trinitrate tablets consumed; and to record any comments they desired. Patients were supplied with a known number of glyceryl trinitrate tablets, and this number was recorded on their sheet and checked with the number remaining in the bottle when they attended at the next visit. Clinicians saw the same patients weekly and recorded their progress without reference to previous assessment sheets. Patients were asked standard questions, and their subjective impressions and any complaints of side-effects were noted.

*Assessment.*—See results.

*Selection of Patients.*—The case-notes of over 100 patients with a diagnosis of angina were examined and only 21 of these subjects were considered to be suitable for this study of a new drug—that is, those having at least two attacks of angina regularly each week, and without other disease or complications that might make the trial of a new drug inadvisable. The pain had to be of characteristic nature, site, and radiation, brought on by exertion, relieved by rest and/or glyceryl trinitrate, and lasting one to three minutes. Of these patients, nine had to be withdrawn during the early stage before the double-blind study began, for the following reasons: (1) hypersensitivity in two patients (measles-like rash in 2nd week in one, and angio-neurotic oedema, "collapse" 2nd day in the other); (2) diarrhoea in one patient (refused to continue); (3) depression in one patient on a high dose—he then went abroad; (4) angina subsided, apparently spontaneously in one patient; (5) fatal myocardial infarct in one patient; (6) one patient objected to having his tablets "mucked about"; and (7) two defaulted.

### Results

*Maximum Tolerated Dosage Used in Double-blind Trial.*—(1) 100 mg. q.d.s., 1 patient; (2) 150 mg. q.d.s., 2 patients; (3) 200 mg. q.d.s., 6 patients; (4) 250 mg. q.d.s., 1 patient; (5) 350 m.g. q.d.s., 1 patient; (6) 400 mg. q.d.s., 1 patient.

#### Effectiveness of Pronethalol in Relieving Angina of Effort

The results have been analysed from three aspects: (1) number of attacks of pain experienced by each patient during the trial, when on pronethalol and placebo (see Table)—each attack was scored as one, regardless of severity of duration; (2) number of glyceryl trinitrate tablets consumed (see Table); and (3) subjective feeling of the patients, whether they felt generally better when taking the drug, apart from relief of pain. The Table shows, for each of the 12 patients who completed the trial, the total number of attacks and the total number of glyceryl trinitrate tablets consumed during the eight weeks of the trial. The figures in each column represent the sum of four weeks' experience for each patient.

| Patients | No. of Attacks of Pain | | No. of Glyceryl Trinitrate Tablets Taken | |
|---|---|---|---|---|
| | Pronethalol | Placebo | Pronethalol | Placebo |
| 1 | 7 | 14 | 8 | 18 |
| 2 | 16 | 23 | 13 | 25 |
| 3 | 29 | 71 | 30 | 72 |
| 4 | 25 | 34 | 14 | 25 |
| 5 | 15 | 17 | 15 | 17 |
| 6 | 1 | 8 | 4 | 9 |
| 7 | 0 | 2 | 0 | 6 |
| 8 | 2 | 7 | 0 | 0 |
| 9 | 0 | 3 | 0 | 3 |
| 10 | 348 | 323 | 377 | 346 |
| 11 | 65 | 79 | 58 | 57 |
| 12 | 41 | 55 | 67 | 89 |

Since the number of attacks and the number of glyceryl trinitrate tablets used were closely associated from week to week and from patient to patient, statistical analysis has been carried out only on the number of attacks. Of the 12 patients, 11 had fewer attacks on pronethalol than on placebo. This event in itself is statistically significant ($P=0.003$) and has the advantage over other analyses of being independent of any assumptions.

The figures have also been analysed using a standard "analysis of variance" technique, after transforming the variable to log (number of attacks +1). This transformation makes the distribution more nearly symmetrical, and the variability more nearly equal in the different groups, as required for the analysis. The difference between the placebo and pronethalol figures is found to be significant at the 1% level. There is no evidence in this small series that the drug is any better for some patients than for others.

The figures have been examined for any carry-over effect from one two-weeks period to the next. There is no evidence of any such effect.

The subjective reports of the patients week by week were expressed as much better (+2), better (+1), same (0), worse (−1), and much worse (−2). Examination of these results showed only a marginal benefit in favour of the drug which was insignificant.

#### Side-effects

Side-effects met with in the three trials are discussed below, but it should be made clear that in this trial side-effects were deliberately provoked in order to find the maximum tolerated dose. Therefore it should not be inferred that their frequency represents what would be seen in ordinary therapeutic use, and in fact, when the dose was adjusted for the trial proper, side-effects became minimal or disappeared.

*Avoidance of Side-effects.*—It is thought important to start with a low dose, say 50 or 100 mg. q.d.s., which may be increased by 50 mg. per dose about every seven days. A slight cumulative effect is suspected with this regime, and at higher doses 14-day intervals between increases of dose are provisionally recommended.

### Conclusions

It is concluded that pronethalol is effective, in the maximum tolerated doses used in this trial, in reducing both the number of attacks of pain and the consumption of glyceryl trinitrate tablets in patients with angina pectoris. Despite these benefits patients did not feel better in themselves: indeed, several commented spontaneously that during the trial they had had less pain, but did not feel as well as before, when they changed from placebo to drug. It may well be that the use of higher doses than were needed for relief in some patients may have impaired their sense of well-being.

### Summary

Pronethalol has been assessed in a small double-blind trial of 12 patients with severe angina of effort. In each patient the dose was increased until symptoms occurred and then reduced slightly.

Pronethalol significantly reduced the number of attacks of pain and the number of glyceryl trinitrate tablets consumed, when compared with a placebo, but with the high and only just subtoxic doses used there was no evidence that the patients felt significantly better while on treatment.

Side-effects sufficient to force withdrawal occurred in three of the total of 24 patients given the drug (two cases of hypersensitivity, one of diarrhoea).

In over 500 patient-weeks of observation two patients died, probably of cardiac infarction—one while taking pronethalol and one while taking a placebo.

## REPORT OF CLINICAL TRIAL FROM MEDICAL UNIT, ST. GEORGE'S HOSPITAL, LONDON

BY

B. ROBINSON T. PILKINGTON

Fifteen patients (2 women and 13 men) were selected for trial using the following criteria: (*a*) they complained of typical angina occurring several times a day; (*b*) the symptoms had been present for at least three months and had not altered appreciably during that time; (*c*) E.C.G. showed ischaemic changes at rest or on exercise (patients with myocardial infarct were not excluded); and (*d*) apart from angina they were fit to do their daily work.

*Trial.*—The drug and an indistinguishable dummy tablet were each taken for two periods of a fortnight in random sequence. The dosage schedule was 100 mg. three times daily for the first two days, followed by 200 mg. three times daily for the remaining 12 days. In one small woman, however, the maximum dose was only 400 mg. daily.

*Assessment.*—One observer was in possession of the code and interviewed the patients *solely* about side-effects. He was responsible for terminating the trial if this seemed advisable. He had no information about the effect of the drug on angina. The other observer recorded the comments of the patients about the angina. They were

asked to state whether the drug had altered their symptom in any way. Since no patient complained of increasing angina during the trial, their statements were recorded as benefit—that is, less angina—or no benefit.

*Results.*—Four patients (3 men and 1 woman) withdrew because of severe nausea and dizziness in three and an extensive rash in the fourth. A fifth patient was withdrawn from the trial because of left ventricular failure on the drug, although he had on a previous occasion taken the drug without ill effect and benefited. The analysis of effectiveness concerns only the 10 patients who completed all four periods and is weighted in favour of the drug, since those who dropped out had the most severe side-effects. The 10 patients expressed their opinion about the drug as follows:

| | Benefit | No Benefit | Total |
|---|---|---|---|
| Drug .. .. .. | 14 | 6 | 20 |
| Dummy .. .. | 3 | 17 | 20 |
| Total .. | 17 | 23 | 40 |

$$\chi^2 = \frac{40\,([14 \times 17 - 18] - 20)^2}{20 \times 20 \times 17 \times 23} = 10.23. \quad P < 0.01.$$

Six patients consistently preferred the drug and claimed no benefit on any occasion from the placebo.

## REPORT OF CLINICAL TRIAL FROM STOCKPORT INFIRMARY

BY

R. M. FULTON K. G. GREEN

### Design of Trial

In order to assess the efficiency of pronethalol we treated 18 patients in an "open" trial, in which the patients were aware that two preparations were being used and when treatment was changed, but not that one preparation was inactive.

All the patients had severe classical angina of effort with several attacks of pain daily and most were specially referred because treatment with TNT and a variety of long-acting vasodilators was not adequately controlling their pain.

We gave each patient 200 mg. orally and examined him an hour later. Except in a few patients with an initially slow heart rate, we found that bradycardia occurred within the hour and lasted for three to six hours. Therefore, 200 mg. appeared to be an active dose, and we decided to give 200 mg. thrice daily at approximately five-hourly intervals, starting on waking. In a few cases we modified the timing to suit individual activities.

An hour after the initial dose we inquired about side-effects, particularly dizziness, which we found to be the most frequent initial complaint. If the patient had any such symptom we started treatment with 100 mg. daily and increased the dose gradually to 200 mg. t.d.s. over a period of four or five days.

In this preliminary trial 13 of the 18 claimed improvement. A double-blind trial was then carried out on 10 patients, 7 of them having already claimed benefit from the drug.

*Withdrawals from the Trial.*—Of the 13 "successes" in the "open" investigation, six did not participate in the "double-blind" trial—three died, one from proved and two from presumptive infarctions (two were receiving pronethalol and one the placebo at the time); one defaulted; and one developed a rash.

In the double-blind trial patients were given 200 mg. of drug or placebo t.d.s., except one who had 100 mg. t.d.s. because we knew that he developed diarrhoea on the higher dose. All patients except one had two fortnightly periods on drug and placebo in random order. The exception was a man whose symptoms were so severe during the first placebo period that we decided to maintain him on the drug.

### Assessment of Double-blind Trial

Patients were interviewed fortnightly by one or other of us, or both separately. We had originally recorded the number of glyceryl trinitrate tablets used, and asked the patients to fill in record cards daily; but we abandoned both methods. The tablet count was misleading because some patients were able to increase the scope and speed of their activity, and for this very reason did not necessarily reduce their tablet consumption. The aim of the cards was for the patient to refer the frequency of his pain to his pretreatment state, but we found that patients tended to forget their baseline and to compare one day with the preceding one.

We concluded that the best method of assessment was a careful inquiry into the patient's daily activity. Each had some individual yardstick such as walking to the bus-stop, climbing stairs to the office, etc., and by inquiring about these points it was possible to decide whether his effort-tolerance was static or improved.

### Results

The results of 39 fortnightly periods are tabulated according to the benefit obtained from drug or placebo. The results showed a significant advantage in favour of pronethalol ($P = 0.001$).

| | Benefit | No Benefit | Total |
|---|---|---|---|
| Pronethalol .. .. | 17 | 3 | 20 |
| Placebo .. .. | 5 | 14 | 19 |
| Total .. | 22 | 17 | 39 |

In 5 of the 10 patients benefit coincided with periods on the drug every time. In the remaining five the pattern was confused. No patient obtained benefit on placebo periods only.

We found no relation between the amount of improvement and the degree of bradycardia.

### Comment

At the dosage used (200 mg. t.d.s.), where improvement in exercise tolerance resulted, we did not find that this was accompanied by any deterioration in the patients' general well-being. This was confirmed by the fact that the five

patients who were consistently improved by the drug have all continued with treatment for periods up to 10 months. Attempts to reduce dosage have resulted in increased pain.

That three of the seven "successes" in the "open" trial failed to benefit consistently from the drug in the "blind" trial confirms the well-known fact that anginal patients are prone to placebo responses.

As a result of the trial we consider that pronethalol may be useful in the management of about half the patients with severe angina pectoris.

**Summary**

Pronethalol was assessed first in an "open" trial on 18 patients and subsequently in a double-blind trial on 10 patients.

The drug was found to be significantly better than the placebo in reducing frequency of pain or improving exercise tolerance.

Mild side-effects were frequent, but could usually be avoided by low initial dosage.

## SIDE-EFFECTS SEEN IN THE THREE TRIALS

This section summarizes the unwanted effects seen in the three trials in angina pectoris reported above, and also those seen during a simultaneous trial in cardiac arrhythmias (Stock and Dale, 1963), and represents the experience of a total of 104 patients. An attempt is made to classify these effects provisionally according to the supposed likely site of action, and they are mentioned approximately in the order of frequency of occurrence within each group.

Figures for the incidence of most side-effects would be misleadingly high owing to the different ways the drug was used and because during the trials all workers discovered that the effects attributed to the nervous system, and also diarrhoea, could be avoided by starting with a lower dose than at first thought necessary and increasing it more slowly. Figures are therefore not given. Skin reactions, attributable to hypersensitivity, would not be expected to be similarly avoidable.

*Nervous System.*—Paraesthesiae, "walking on air" and feeling "tight all over," were reported occasionally. Polyneuritis occurred in one patient, but attribution to the drug is uncertain. Nausea and vomiting (these can occur with intravenous as well as oral administration), fatigue, dizziness, insomnia, dreams, depression, and unsteady gait were fairly common. Defective ocular fixation when the head was moved occurs after intravenous injection of above 1 mg./kg. (Dornhorst and Robinson, 1962). Seeing several images on entering bright light and spontaneous appearance of flashing lights were also reported.

*Cardiac Effects.*—Stock and Dale comment on the precipitation of heart failure by pronethalol and suggest a mechanism. There was also one case of heart failure that might be attributable to the drug in the angina pectoris trials. Extreme cardiac slowing, amounting even to brief arrest, has occurred under circumstances where vagal slowing would normally be expected.

*Alimentary Tract.*—Diarrhoea, with or without nausea and vomiting (also see above under "nervous system"), occurred especially with high initial doses.

*Hypersensitivity.*—Skin rashes occurred in six cases (four erythematous, two urticarial).

*Deaths While Taking Pronethalol.*—Three patients died during the angina pectoris trials. One was proved to have had a myocardial infarct and two were diagnosed as having infarcts on clinical grounds only. There is no reason to attribute these deaths to the drug.

### Comment

As stated above, the side-effects attributed to an effect on the C.N.S. and alimentary tract could generally be avoided by starting oral therapy with a low dose, say 50 mg., two to four times a day and increasing it about once a week.

It seems likely that vagal activity, added to the slowing effect of pronethalol on the heart, could be dangerous. If pronethalol were used in an attempt to treat a supraventricular tachycardia great caution would be advisable in carrying out manœuvres designed to exploit vagal action, such as carotid sinus massage or pressure on the eyeball.

## CONCLUSIONS

Pronethalol has been shown to be capable of giving some relief of angina pectoris in each trial.

Side-effects, particularly nausea, dizziness, and other mild central nervous system effects, were frequent (largely owing to the trial designs). They can usually be avoided by careful adjustment of the dose.

A suitable dosage schedule would be 50 mg. orally three or four times a day, increased by 50 mg. on all doses weekly until relief was obtained or side-effects occurred. If relief had not occurred with a total daily dose of 800 mg., or after appreciable cardiac slowing, a higher dose was unlikely to be beneficial. The margin between the dose that is useful and that causing side-effects is often small.

We are indebted to I.C.I. Pharmaceuticals for the supply of tablets used in the trials.

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