Double-blind Trial of Propranolol (Inderal) in Angina Pectoris

PATRICK KEELAN,* M.D., M.R.C.P., M.R.C.P.I.

Brit. med. J., 1965, 1, 897–898

Propranolol (I.C.I. 45,520; Inderal) is the second specific adrenergic beta-receptor-blocking drug which has been introduced recently (Black *et al.*, 1964). It succeeds pronethalol, which has limited uses because of its tumour-producing effect in mice (Paget, 1963). Initial work with pronethalol had "shown it to be capable of giving some relief of angina pectoris" (Alleyne *et al.*, 1963). Propranolol exerts a beta-receptor blocking action at about one-tenth the equivalent dose of pronethalol; it does not produce tumours in mice (Black *et al.*, 1964).

Methods

Design of Trial.—The trial was double-blind. Each patient received propranolol for four weeks and placebo for a further four weeks. The order in which drug and placebo were given was randomized. Though the tablets were indistinguishable in appearance, it was possible to identify the drug because of its bitter taste when sucked. Patients were instructed to swallow the tablets; none commented on their taste. The hospital pharmacist held the code. With one exception, this was not broken until the trial was completed and the results assessed. Patients entered the trial as they presented. Each was given cards on which he was asked to mark down daily the number of attacks of angina pectoris and the number of tablets of glyceryl trinitrate used. All patients were seen by me at fortnightly intervals during the trial. At these visits completed cards were collected and the patients were questioned about the severity of angina pectoris. This was assessed on the basis of effort tolerance. Six grades were used: angina occurring on severe exertion only (grade 1), on moderate exertion, on the flat walking more than 100 yards, on the flat walking less than 100 yards, on watching television, and at rest. The resting heart rate and blood-pressure were also recorded at each visit and evidence of cardiac failure was sought. The bodyweight was measured and an electrocardiogram taken. Blood was collected for haemoglobin, total white-cell and differential count, platelet count, and serum glutamic pyruvic transaminase content. The urine was examined for albumin.

Dosage.—The dose used was 30 mg. t.i.d., the morning dose being taken before breakfast, and the others after the midday and evening meals. This dose was chosen because it was the minimum required to block exercise-induced tachycardia in healthy volunteers (S. A. Stephen, personal communication, 1964). No change was made in existing therapy; in particular, patients were instructed to continue using glyceryl trinitrate as before. Though the patients were aware that a new drug was on trial, they did not know in what way this was being done.

Material

The records of over 100 patients with a diagnosis of angina pectoris were examined. About half of these were eliminated as it was obvious that they did not match the criteria of suitability for trial (see below). The remainder were assessed clinically. The criteria of suitability were unequivocal angina pectoris present for at least four months in a reasonably steady state, with a frequency, estimated by the patient, of about 10 or more attacks a week. Patients with valvular disease, anaemia, or thyrotoxicosis were excluded. Twenty-three patients (14 males and 9 females) fulfilled these criteria and entered the trial. Twenty-one of these had experienced angina pectoris for more than one year. All had electrocardiographic evidence of cardiac ischaemia—20 at rest and three on effort.

* Lecturer in Medicine, University College, Dublin. From the Medical Unit, Mater Misericordiae Hospital, Dublin.

Results

Nineteen patients completed the trial and provided the results for analysis. Of the original 23, one defaulted in the third week because his angina improved following unexpected change to a sedentary occupation; another died following a further cardiac infarct (confirmed at necropsy) at the end of the fourth week, having had placebo only; a third was withdrawn in the fifth week of the trial because of dizziness attributed to propranolol. The fourth patient, a 66-year-old woman with a six-year history of angina, was of particular interest. Prior to trial she estimated that she experienced about 12 attacks of angina weekly; some of these came on at rest. During the first four weeks of the trial she had four attacks in each week; these occurred with moderate exertion only. After change-over she returned prematurely, one week later, because of the occurrence of 30 attacks of angina, the majority at rest. On request the pharmacist broke her code. This showed that she had received propranolol in the first half of this trial. On resuming propranolol she improved markedly, the frequency and severity of her attacks reverting to that already observed on the drug. On continued treatment this improvement has been maintained.

The results of the 19 patients who completed the trial are analysed from three aspects (see Table): (1) the number of attacks of pain experienced by each patient when on propranolol and when on placebo, (2) the number of glyceryl trinitrate tablets used by each patient when on propranolol and when on placebo, and (3) alteration in severity of angina pectoris as assessed by effort tolerance when on propranolol and when on placebo. Thirteen patients had fewer attacks on the drug than on placebo, five had more attacks on the drug than on placebo, and one had the same number of attacks in both periods. This result is statistically significant ($P<0.05$). Glyceryl trinitrate tablets were used by 18 patients. Fourteen required fewer tablets while receiving the drug than while on placebo, three

Individual Results of the Trial

Case No.	No. of Attacks of Pain		No. of Glyceryl Trinitrate Tablets Taken		Severity of Angina (Grades 1–6)	
	Propranolol	Placebo	Propranolol	Placebo	Propranolol	Placebo
1	37	68	37	68	3	4
2	121	116	61	56	6	6
3	19	47	19	46	2	3
4	14	26	15	25	2	3
5	16	79	16	79	2	4
6	4	6	4	6	2	2
7	24	24	24	24	4	4
8	118	100	0	0	4	4
9	5	4	5	8	2	2
10	10	27	10	14	3	4
11	31	19	6	5	4	4
12	31	46	41	71	2	3
13	59	64	59	64	3	4
14	86	175	119	203	6	6
15	1	8	3	21	2	4
16	4	8	3	4	2	2
17	103	96	115	92	3	3
18	6	44	19	43	2	2
19	38	75	38	75	4	4

used fewer tablets on placebo than on the drug, and one used equal numbers in both periods. This result is statistically highly significant ($P<0.01$). Seven patients had improved pain-free effort tolerance while on the drug; there was no difference between the two periods in the other 12 patients. This is statistically significant ($P<0.04$).

Slowing of the resting heart rate was often noted while patients were receiving propranolol. The mean heart rate of the 19 patients on the drug was 63; on placebo it was 78. There was some correlation between bradycardia and decrease in frequency of anginal attacks. Slowing of heart rate was noted in 15 patients while on propranolol; this was associated with decreased frequency of angina in 12. No alteration in the heart rate was noted in the other four patients; only one of these (Case 12) showed a reduced frequency of attacks.

Eighteen patients were normotensive. Fall in blood-pressure while taking propranolol was recorded in only one of these. The remaining patient (Case 15) was hypertensive (B.P.200/100). While taking propranolol the tension dropped to 200/80.

No change in blood picture or S.G.P.T. or evidence of albuminuria was found in any of the patients. Similarly, there was no change in the body weight or electrocardiogram. No patient developed evidence of cardiac failure during the trial. Apart from dizziness in one patient there were no side-effects.

Discussion

It was suggested by Black and Stephenson (1962) that specific beta-receptor blockade might be beneficial in angina pectoris, because of reduction in the oxygen requirements of cardiac muscle. This hypothesis is supported by the results of the present trial, which show, in addition to reduction in number of anginal attacks and consumption of glyceryl trinitrate tablets, improvement in pain-free effort tolerance.

There is one other report of a double-blind trial of propranolol in angina of effort (Srivastava *et al.*, 1964) in the literature. A series of 20 patients were given propranolol 20 mg. t.i.d. for three weeks and placebo for a further three weeks. No significant difference between drug and placebo was found. It is possible that the smaller dose of propranolol used may have been subtherapeutic. In this context it is relevant that slowing of the heart rate was not observed in any patient during the trial. This suggests that effective blockade of myocardial adrenergic beta-receptors was not achieved.

Improved exercise tolerance following intravenous injection of propranolol in patients previously limited by angina has been reported recently (Hamer *et al.*, 1964). The same authors found that beta-adrenergic blockade reduced the heart rate at all levels of exercise, but Bishop and Segel (1963) and Chamberlain and Howard (1964) have shown that the cardiac output on exercise in the erect position is maintained.

From preliminary investigation of propranolol it seems likely that intestinal absorption is incomplete and variable (S. A. Stephen, personal communication, 1964). Therefore it may be that some patients will require larger doses than those prescribed in this trial. It is proposed to restudy, using larger doses of propranolol, those patients who did not respond to 30 mg. t.i.d.

Summary

A double-blind trial of propranolol has been carried out on 19 patients suffering from angina of effort. The drug was found to be significantly better than placebo in reducing the frequency of attacks of angina pectoris and the number of glyceryl trinitrate tablets taken, and in improving pain-free effort tolerance.

I thank Dr. S. Blake, Professor T. B. Counihan, and Dr. M. Moriarty for permission to study patients under their care. I am grateful to the sister and staff of the cardiac department, to the pharmacist, Mr. L. A. Ryan, and to the laboratory staff for co-operation. My thanks are also due to Dr. S. A. Stephen and Mr. C. Clarke, of Imperial Chemical Industries Limited, Pharmaceuticals Division.

References

Alleyne, G. A. O., Dickinson, C. J., Dornhorst, A. C., Fulton, R. M., Green, K. G., Hill, I. D., Hurst, P., Laurence, D. R., Pilkington, T., Prichard, B. N. C., Robinson, B., and Rosenheim, M. L. (1963). *Brit. med. J.*, 2, 1226.
Bishop, J. M., and Segel, N. (1963). *J. Physiol. (Lond.)*, **169**, 112P.
Black, J. W., Crowther, A. F., Shanks, R. G., Smith, L. H. and Dornhorst, A. C. (1964). *Lancet*, 1, 1080.
—— and Stephenson, J. S. (1962). Ibid., 2, 311.
Chamberlain, D. A., and Howard, J. (1964). *Brit. Heart J.*, **26**, 213.
Hamer, J., Grandjean, T., Melendez, L., and Sowton, G. E. (1964). *Brit. med. J.*, 2, 720.
Paget, G. E. (1963). Ibid., 2, 1266.
Srivastava, S. C., Dewar, H. A., and Newell, D. J. (1964). Ibid., 2, 724.

Clinical Evaluation of Human Amnion Tissue Culture

E. G. JONAS,* M.B., B.S., F.R.C.S., M.R.C.O.G.; ANNE E. CAUNT,† B.SC., DIP.BACT.

Brit. med. J., 1965, 1, 898–901

Since Zitcer, Fogh, and Dunnebacke (1955) described the use of human amnion culture for growing poliomyelitis virus, this method has become widely used for growing an increasing range of viruses. Most virologists have experienced some failure of amnion to grow, and Duncan and Bell (1961) suggested that the state of viability of the amnion at the time of delivery was more decisive than technical details of its subsequent processing. The experience of this laboratory supports that view, as it proved possible to grow in culture 90% of amnions by discarding obviously damaged—that is, opaque or meconium-stained—membranes.

* Consultant Obstetrician and Gynaecologist, Uxbridge Group of Hospitals; formerly Senior Registrar, Liverpool Maternity Hospital.
† Lecturer in Bacteriology, University of Liverpool.

As amnion is a foetal tissue, and taking Duncan and Bell's suggestion to its logical conclusion, it is possible that the behaviour of amnion in tissue culture mirrors foetal growth and development. To test this hypothesis, and in the hope of finding clear predictors of successful culture of this tissue, results of 314 consecutive amnion culture attempts were correlated with selected clinical data.

Laboratory Materials and Methods

Collection of Placentae.—Only sterile normal saline was used for swabbing patients in the course of vaginal deliveries. Whole placentae were collected in dry, sterile jars. Those from caesarean sections were usually transferred to the laboratory