Trial of Propranolol in Acute Myocardial Infarction

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Propranolol is a β -adrenergic blocking drug which reduces cardiac contractility and myocardial oxygen consumption (Folle and Aviado, 1965) and suppresses cardiac arrhythmias (Besterman and Friedlander, 1965). Snow (1965), in a study in which alternate patients with acute myocardial infarction were given propranolol, reported a mortality of 16% in treated patients and 35% in control cases, the difference in mortality being statistically significant ($P < 0.02$). The reduction in mortality in treated patients could have been due to the antiarrhythmic or the oxygen-sparing effect of propranolol.

The present study was undertaken to test the hypothesis that propranolol lowers mortality or alters morbidity in acute myocardial infarction. A double-blind protocol was used, and over 500 patients were studied. Relevant details of past history, condition on admission to hospital, and subsequent progress were recorded in all cases, so that mortality and morbidity could be studied in detail. As no effect of propranolol on mortality was found, data from trial patients and from patients not admitted to the trial have been combined to form a study on the pattern of hospital mortality in infarction (Norris *et al.*, 1968) and a new "coronary prognostic index," which is in preparation.

Method

The trial was carried out from March 1966 to March 1967 in Auckland, Green Lane, and Middlemore Hospitals, which together admit all patients with myocardial infarction who are treated in public hospitals in Auckland City. All patients who on clinical and electrocardiographic evidence were thought to have had a myocardial infarct within the previous three days, and who were not in shock, heart failure, heart block, or sinus bradycardia were included in the trial. Heart failure was originally considered to be present if there was significant breathlessness at rest or if there was jugular venous congestion over 5 cm. from the sternal angle at 45°. Shock was defined as a blood pressure below 90 mm. Hg, while bradycardia signified a heart rate below 50 per minute. Approximately six months after the start of the trial, conditions for exclusion were re-defined as acute pulmonary oedema or a systolic blood pressure below 80 mm. Hg, as it had been found that mild heart failure and shock were not aggravated by propranolol. It was not thought that this change of protocol had any effect on the validity of the result of the trial. Infarction was subsequently graded as certain, probable, or improbable according to whether three, two, or one of the following criteria were satisfied: (1) characteristic clinical presentation; (2) pathological Q waves, ST elevation, or T-wave inversion with evolutionary changes; (3) rise in serum aspartate aminotransferase to over 40 units/ml.

Patients admitted to the trial were allocated three weeks' supply of propranolol 20 mg. q.i.d. or placebo tablets according to a random code known only by the hospital pharmacy. All patients with suspected infarction, whether admitted to the trial or not, had details of past history, admission status, and

subsequent progress recorded in numerical form; this information was later transferred to I.B.M. punch cards. Progress was recorded three times weekly on ward rounds, heart failure or hypotension as defined above, arrhythmia, or further chest pain being recorded as present or absent. Patients could be removed from the trial at the discretion of the physician in charge, other treatment such as anticoagulation and time of mobilization being carried out according to individual preference. None of the patients had electrocardiographic monitoring.

Results

A total of 536 patients were admitted to the trial, and the initial diagnosis of myocardial infarction was regarded as certain or probable in 454 (Table I); of these, 226 were given propranolol and 228 placebo. There were 303 patients not admitted to the trial. Mortality in trial patients was 12%, in non-trial patients 46%, and in all patients 26%. The reason for the high mortality in non-trial patients is shown in Table II, patients excluded because of heart failure having a 51% mortality and those excluded because of shock having an 81% mortality.

TABLE I.—Selection of Patients and Hospital Mortality

	No.	Mortality
Patients admitted to the trial	536	
Patients admitted in whom diagnosis of myocardial infarction was sustained	454	12%
Patients not admitted to the trial	303	46%
All myocardial infarction patients	757	26%

TABLE II.—Reason for Non-inclusion to the Trial

	No.	Mortality
Heart failure	112	51%
Cardiogenic shock	63	81%
Heart block or bradycardia	32	41%
Infarct more than 3 days old; retrospective diagnosis; patient taking propranolol	139	27%
Total patients not admitted	303	46%

* Some patients had more than one reason for exclusion

Thirty-six patients were removed from the trial, the reasons for removal being shown in Table III. There was no difference between the number of patients removed because of heart failure, shock, or heart block, though all the six patients removed because of sinus bradycardia (heart rate below 50 per minute) were taking propranolol.

Of the 55 trial patients who died, 31 were treated and 24 were controls (Table IV). Some deaths occurred after patients had been removed from the trial because of heart failure or

TABLE III.—Reason for Removal of Patients from Trial

	Treatment	Control	Total
Heart failure	3	5	8
Hypotension	7	4	11
Heart block	2	3	5
Bradycardia	6	0	6
Other	3	3	6
Total	21	15	36

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hypotension, and 20 propranolol-treated patients and 17 controls died while in the trial. These differences were not significant, and the mode of dying in treated and control patients showed no difference in the proportion dying from arrhythmia, heart failure, or shock (Table V).

TABLE IV.—*Mortality in Trial Patients*

	Treatment	Control
Total patients admitted	226	228
Deaths on trial	20	17
Deaths after complications necessitating removal from trial	11	7
Total deaths	31	24

TABLE V.—*Mode of Dying in Trial Patients*

	Treatment	Control	Total
Arrhythmia or sudden death ..	20	17	37
Cardiogenic shock	3	4	7
Heart failure	3	3	6
Pulmonary embolus, cardiac rupture, or other cause ..	5	0	5
Total	31	24	55

Significantly fewer arrhythmias were recorded in treated patients, and this was due entirely to a decrease in the frequency of ectopic beats, there being no difference in the occurrence of atrial or ventricular arrhythmias or heart block (Table VI). Ectopic beats were recorded from feeling the pulse and auscultation on ward rounds, though some were recorded in routine electrocardiographs. Heart failure, hypotension, or further chest pain occurring during the trial showed no significant predilection for treated or control patients.

TABLE VI.—*Morbidity in Trial Patients*

Complication	Treatment (%)	Control (%)	Significance of Difference
All arrhythmias	20	33	P < 0.01
Ectopics	12	22	P < 0.01
Atrial tachycardia and fibrillation ..	7	7	N.S.
Ventricular tachycardia and fibrillation ..	3	4	N.S.
Heart block	3	3	N.S.
Heart failure	17	19	N.S.
Hypotension (B.P. < 90 mm. Hg systolic)	11	8	N.S.
Further chest pain	46	52	N.S.

There was no significant difference between the treated and placebo groups with regard to age, previous ischaemic history, status on admission, administration of anticoagulants, or time of mobilization.

Discussion

The absence of effect of propranolol on mortality found in this double-blind trial confirms the findings of Balcon *et al.* (1966), Clausen *et al.* (1966), and the Multicentre Trial (1966). Our total mortality of 12% in treated and control patients contrasts with a total mortality of 14% in the Multicentre Trial, 24% (Balcon *et al.*), and 32% (Clausen *et al.*). Our low total mortality is explained by the fact that we excluded patients with heart failure and cardiogenic shock, as it was expected that propranolol might prove detrimental for these patients. The patients excluded had a mortality of 46%, and would fall into the "cardiogenic shock" and "severe" group of Goble *et al.* (1966).

Arrhythmia, either proved or assumed, was the mode of dying in two-thirds of the trial fatalities, and there was no difference in mode of dying between treated and control patients (Table V). There was thus no evidence that propranolol in the dose used contributed to death from circulatory failure or prevented arrhythmic death.

There was also no evidence that propranolol caused morbidity from cardiac failure or hypotension (Table VI), nor did it necessitate withdrawal of patients from the trial (Table III). Though Balcon *et al.* (1966) found an increased incidence of heart failure in patients receiving propranolol, this was not statistically significant, and Clausen *et al.* (1966) found no increased incidence of heart failure in patients receiving 40 mg. of propranolol daily compared with placebo-treated patients. These results suggest that the tendency of oral propranolol in a dose up to 80 mg. daily to exacerbate heart failure and hypotension has been overemphasized.

Ectopic beats, as detected clinically on ward rounds or in routine electrocardiographs, occurred in 12% of treated patients and 22% of controls, this difference being significant at the 1% level. There was no difference in the incidence of the more serious arrhythmias, however (Table VI). This finding conflicts with those of other workers, particularly Balcon *et al.* (1966), who found no effect of propranolol in the incidence of ectopic beats in continuously monitored patients. It is now well known from studies involving continuous cardiograph monitoring that ectopics occur in approximately 70% of post-infarct patients (Meltzer and Kitchell, 1966), so that probably less than one patient in four in our trial who had ectopic beats was noticed to have them. Nevertheless, the structure of our trial leads us to the conclusion that ectopic beats, as noticed from palpation of the pulse and auscultation on ward rounds, were suppressed by propranolol. The possibility exists that propranolol blocks ectopic activity due to endogenous catecholamine release stimulated by emotional strain engendered by the approach of the senior physician and his retinue. As sudden death is not prevented by propranolol, however, and as ventricular extrasystoles may herald fatal ventricular fibrillation (Lown *et al.*, 1967), one might infer that these ectopic beats are harmless, and not forerunners of cardiac arrest.

Propranolol in a dose of 80 mg. daily did not affect the incidence of chest pain after infarction, the 52% incidence in control cases being insignificantly different from the 46% incidence in treated patients. This result is disappointing in view of the known ameliorating effect of propranolol in some cases of angina (Hamer *et al.*, 1964). However, neither Balcon *et al.* (1966) using 80 mg. of propranolol daily, nor Clausen *et al.* (1966), who used 40 mg. daily, found any effect of propranolol on chest pain, and this conclusion is confirmed.

It is concluded that oral propranolol has no place in the routine management of myocardial infarction, though this may not deny its usefulness in larger doses or given parenterally in some specific post-infarction arrhythmias (Sloman *et al.*, 1966).

Summary

A total of 536 patients with acute uncomplicated myocardial infarction were given propranolol, 20 mg. four times daily, or placebo tablets for three weeks in a double-blind trial. In 454 patients the diagnosis of infarction was sustained, and of these 226 received propranolol and 228 placebo. No difference was found in mortality between control and treated patients nor in the incidence of major arrhythmias, heart failure, hypotension, or further chest pain. Ectopic beats, as detected in the pulse on ward rounds, were reduced by propranolol, however, and a possible reason for this is discussed.

We are grateful to the visiting physicians at Auckland, Green Lane, and Middlemore Hospitals for permission to study patients under their care; to the medical registrars at all three hospitals for recording information and for including patients in the trial; and to the nursing staff for co-operation in administering treatment. Dr. S. A. Stephen and Dr. Charles Proctor, of I.C.I. Ltd., gave much helpful advice, while we are indebted to I.C.I. Ltd. for supplying the tablets and to the staff of the Auckland Hospital Board pharmacies for handling and distributing them. Staff of the

medical records department, Auckland Hospital Board, prepared the data sheets, while analysis of results was greatly helped by the co-operation of Mr. K. E. Bensley, of the medical statistics unit.

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Too Ill for Cardiac Surgery ?

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Rapid advances in open heart surgery and the achievements of individual surgeons have created new possibilities for patients with advanced valve disease. This paper is written to pay tribute to my surgical colleagues Donald N. Ross and Magdi H. Yacoub at the National Heart Hospital and to draw attention to the dramatic results which can be obtained even in very ill patients.

Four patients are reported, all of whom would have died in a matter of days or weeks without valve replacement. They are now well and have returned to their normal occupations. Three had advanced aortic valve disease, which was probably congenital in two. The fourth had rheumatic heart disease with severe destruction of mitral, aortic, and tricuspid valves. All four were so ill that one was hesitant to advise surgery at such a late stage, but it was evident that medical treatment had nothing further to offer.

The operations reported were carried out at the National Heart Hospital between 17 December 1965 and 5 October 1967 and comprised 4 of the 461 open heart procedures during this 22-month period.

Case 1

The patient, a man aged 42, had severe calcific congenital aortic stenosis. Heart disease had been diagnosed at the age of 12 years, when a murmur was heard at a routine school examination. He was asymptomatic until he was 41, when he developed dizziness on exertion. By June 1965 he was getting effort dyspnoea with severe angina, and in the autumn was having recurrent nocturnal dyspnoea. When admitted to hospital on 3 December 1965 he was in status anginosus and was deteriorating mentally. The physical signs were those of severe calcific aortic stenosis with a very low cardiac output. The limbs were cold and the peripheral pulses almost imperceptible. Blood pressure was 90/75 mm. The venous pressure was raised 8 cm. above the sternal angle with a dominant "a" wave. The heart was grossly enlarged and there was an aortic systolic murmur and thrill, also a soft immediate diastolic murmur of aortic regurgitation. The electrocardiogram (E.C.G.) confirmed sinus rhythm, with extreme left ventricular hypertrophy, and there was a small P mitrale. The chest radiograph showed gross left ventricular enlargement with very heavy calcification of the aortic valve and a dilated ascending aorta. The upper-lobe pulmonary veins were dilated (Fig. 1A). Moderate pulmonary hypertension was demonstrated at cardiac catheterization with a mean pulmonary artery wedge (indirect left atrial) pressure of 25 mm. Hg, pulmonary artery 75/25 mm. Hg, mean 40 mm. Hg. The aortic pressure varied from 95/60 to 105/75

mm. Hg. It was not possible to manoeuvre the catheter across the aortic valve, so left ventricular pressures were not obtained. Arterio-venous oxygen difference was 85 ml./l. with a cardiac output 4 l./min.

The patient's condition deteriorated in spite of full medical therapy, the urinary output fell, and the blood urea rose from normal to 140 mg./100 ml. Mr. Donald Ross operated as an emergency on 17 December and decided to insert a Magovern valve rather than a homograft to minimize the time of the operation. The aorta was opened by a long oblique incision, showing a heavily calcified disorganized bicuspid valve with a central irregular slit-like orifice 1 mm. in width by 2 cm. in length. It was completely excised, and large pieces of calcium which ran down into the anterior cusp of the mitral valve were also removed. A purse-string suture was placed round the bases of the aortic cusps and a size 5 Magovern valve was fixed in position, the claws being positioned to engage with the purse-string suture. After closure of the aortotomy the heart resumed its beat without difficulty. The left atrial pressure fell from a pre-valve replacement mean of 40 mm. Hg to 10 mm. Hg and the aortic pressure was well maintained at 110/80 mm. Hg. The total time on cardiopulmonary bypass was 34 minutes.

There were no postoperative problems; the blood urea returned to normal, the heart diminished in size, and the dilatation of the upper lobe veins disappeared. The left bundle-branch block which developed at operation just before insertion of the Magovern valve resolved spontaneously in the fourth postoperative week. The patient left hospital on 25 January 1966. When first seen as an outpatient after the operation on 17 March he was already going for long walks without symptoms and there had been a considerable reduction in heart size (Fig. 1B). He was last seen on 21 September 1967, when he was asymptomatic and again doing a full-time job as a traveller. The Magovern valve was competent and his systemic pressure was 130/80 mm. His only treatment was anticoagulants, which he has been advised to continue owing to the thromboembolic risk associated with prosthetic valves.

FIG. 1.—Case 1. Chest radiographs. A, Before aortic valve replacement (10 December 1965). B, After surgery (17 March 1966).

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