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Treatment of acute myocardial infarction with propranolol

*Further studies on enzyme appearance and subsequent left ventricular function in treated and control patients with developing infarcts**

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SUMMARY The effect of propranolol 0·1 mg/kg intravenously followed by 320 mg in divided doses given over 27 hours orally was further evaluated in a randomised trial involving 62 patients up to 65 years of age who were seen within four hours of onset of uncomplicated myocardial infarction. Thirty-three patients were given propranolol and 29 served as controls. Two indices of infarct size were used: (a) total creatine kinase appearance and peak activity levels measured during the acute stage of infarction, and (b) subjective analysis of biplane left ventriculograms performed one month later in a subgroup of these patients. Total enzyme appearance was reduced by 25 per cent and peak levels were reduced by 23 per cent in treated patients compared with controls. The subgroup subsequently studied by angiocardiography did not show the reduction in enzyme levels shown by the whole group; likewise, quantitative subjective analysis of the left ventriculograms did not show any significant difference between the two groups. Though it could not be confirmed by this radiological method that reduction in enzyme appearance by beta adrenoceptor blockade was associated with restriction in infarct size, this seems the most likely cause for the lower enzyme levels. The safety of intravenous beta blockade when used in carefully selected patients suggests that large-scale clinical trials can be recommended in which measurements of infarct size as well as morbidity and mortality can be used as end-points.

We have previously shown that patients treated with intravenous and oral propranolol starting within four hours of the onset of uncomplicated myocardial infarction have lower serum creatine kinase (CK) levels than control patients.[1] We also found subsequently that patients with 'threatened' infarction given intravenous and oral propranolol within four hours of the onset of pain had fewer completed infarcts assessed by standard electrocardiogram than did control patients.[2] The present study aimed to carry these trials further by investigation of a new group of treated and control patients at one month after infarction by exercise testing biplane cineangiocardiography as well as with enzyme measurements during the acute phase. In this way we hoped first, to check again that enzyme levels were reduced in treated patients if propranolol was given within four hours of the onset; second, to see if the reduction in enzyme levels (if confirmed) was associated with improved left ventricular contractility assessed by biplane angiocardiograms; third, to establish whether treated patients had greater evidence of myocardial ischaemia assessed by exercise testing one month after treatment than did the control patients. Salvage of ischaemic myocardium from infarction by propranolol might have rendered the myocardium chronically ischaemic, and this might be detected during exercise.

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Patients and methods

As in our previous study,[1] we aimed to select patients who were in the early stages of uncompli-

cated transmural infarction as evidenced by (a) typical history of prolonged chest pain with onset less than four hours previously and (b) ST segment elevation in the electrocardiogram of greater than 2 mm in the anterior chest leads, greater than 1 mm in leads II, III, and aVF, or pathological Q waves. Patients had to be no more than 65 years of age, with no history of bronchial asthma, systolic blood pressure above 100 mmHg, heart rate greater than 60/minute, and without breathlessness or basal râles. Patients who had had DC cardioversion were excluded. An anteroposterior chest *x*-ray film taken immediately after admission to the coronary care unit was examined before entry to the trial and patients with *x*-ray evidence of interstitial oedema or pulmonary oedema were rejected though cases showing pulmonary venous congestion without oedema were accepted. Immediately on entry to the trial patients were randomised by the envelope method for treatment with propranolol or no specific treatment. Treated patients were immediately given propranolol 0·1 mg/kg intravenously over 10 minutes followed by 320 mg orally over the next 27 hours. This was given in divided doses of 40 mg at one, three, seven, 11, 15, 19, 23, and 27 hours after entry to the trial. Before each oral dose the patients were assessed by the nurses; if the systolic blood pressure was below 100 mmHg or the heart rate below 50/minute the next dose was omitted and the patient was assessed again in the same way before the next dose was due. No injections were given intramuscularly during the period of the trial. Lignocaine was used as necessary in both treated and control patients for the control of ventricular arrhythmias and in a few cases intravenous or oral frusemide was given for left ventricular failure. In most patients, however, no other specific treatment was given during the period of the trial.

Blood was taken every four hours from an intravenous catheter (Intracath) inserted percutaneously into an antecubital vein. Blood was used for measurement of creatine kinase activity by Rosalki's method[3] using a Bausch and Lomb system 400. Serum propranolol was measured by a fluorimetric method.[4] Specimens for measurement of CK activity were taken for approximately 72 hours or until the enzyme activity had peaked and returned to near normal levels. For calculation of total CK appearance we used our modification[5] of the method of Sobel *et al.*[6] This modification is based on calculation of an individualised decay rate (KD) for enzyme activity which is used for calculation of the total enzyme appearance. As the peak activity measured four hourly correlates closely with the calculated total enzyme appearance[7] we used both the peak CK levels as well as the calculated total appearance as indices of infarct size.

Dosage of propranolol was discontinued at 27 hours and patients were mobilised and discharged in most cases after seven to 14 days in hospital. As part of another study of long-term prognosis in male patients under 60 years of age surviving a first myocardial infarct,[8] some patients were readmitted for two days for exercise testing and angiocardiography at one month after the infarct. Only male patients up to 60 years of age who had been admitted to one of the two participating hospitals (GLH) during the acute phase were considered for angiocardiography. Thus the subgroup selected for cardiac investigations was smaller than the original group of patients, 13 of 29 control patients and 15 of 33 treated cases being studied angiocardiographically.

At readmission to hospital one month after the infarct patients were clinically reassessed and then exercised on a treadmill at 2½ miles per hour for three minutes on the flat and then three, three, and six minutes at a gradient of 5, 10, and 15 per cent, successively. Exercise was stopped if significant angina or dyspnoea developed and a 12 lead electrocardiogram was recorded immediately after exercise. Left ventriculography and coronary angiography were done using the Judkins technique and recording the left ventriculogram simultaneously in 35° right anterior oblique and 25 to 35° hemiaxial 55° left anterior oblique projections. Left ventricular contractility was assessed by subjective segmental analysis of wall motion[7] both by using the segmental contractility of the cardiac silhouette in the two projections of the left ventriculogram (contractility method) and also the movement of the vessels in the coronary arteriograms together with the thickness of the left ventricular wall where this could be identified (muscle loss method).

Results

Sixty-two patients entered the trial which was in progress between March 1977 and March 1979; of these, 33 were randomly allocated to the treatment group and 29 to the control group. Details of age, sex, and position of infarct are given in Table 1, and mortality and morbidity data in Table 2. Selection of patients who were free from overt cardiac failure, not hypotensive, and had not had cardiac arrest ensured that a relatively low risk group of patients was studied. Only one of the 62 patients died in hospital; he was in the treated group but was given only three doses of propranolol because of the development of mild hypotension.

Table 1 *Patients admitted to trial*

	Treated	*Control*
Total cases	33	29
Age in years (mean and range)	51 (31–64)	51 (37–65)
Sex	31 M 2 F	27 M 2 F
Position of infarct*	17A, 13I, 3S	14A, 14I, 1 AI

*A, anterior; I, inferior; AI, anterior and inferior; S, subendocardial (see text).

Table 2 *Complications in treated and control patients*

	Treated (n=33)	*Control (n=29)*
Death in hospital	1	0
Ventricular fibrillation	1	1
Cardiogenic shock	1	1
Left ventricular failure	3	8
Atrioventricular block 2° or greater	0	2

His clinical condition remained satisfactory until 34 hours after the onset when he died suddenly after a further short episode of chest pain and without any change in cardiac rhythm. The circumstances of death suggested cardiac rupture, but permission for necropsy was refused. One treated and one control patient had ventricular fibrillation and both were successfully resuscitated; blood specimens for enzyme activity were discarded after cardioversion, but in the treated patient sufficient information was available before ventricular fibrillation for calculation of the enzyme appearance. Cardiac failure developed in 11 patients but was relatively mild in all cases and responded to treatment with frusemide. Sinus bradycardia (not shown in Table 2) was more common in patients given propranolol. This did not usually require treatment, but in a few cases responded quickly to atropine 0·3 mg intravenously.

The peak measured CK activity levels and calculated total enzyme appearance for treated and control patients are shown in Fig. 1 and 2. Though the range was wide, peak levels in the treated patients were 23 per cent lower on average than in the controls, and this difference was significant ($t=2·27$, $p<0·05$). Similarly, the calculated total CK appearance was 25 per cent lower in the treated patients than in the controls ($t=2·21$, $p<0·05$). For the subgroup of patients who were subsequently investigated, however, the differences were less and were not statistically significant (treated cases 10% lower for peak enzyme levels; $t=0·65$, $p>0·5$, and 13% lower for total enzyme appearance; $t=0·79$, $p>0·5$). Serum degradation rate (K_D) of CK activity, calculated from the rapid phase of decline in enzyme levels, was not altered by propranolol (K_D in treated patients $=0·00086 \pm 0·00019$/min, and in controls $=0·00087 \pm 0·00019$/min).

Examination of the electrocardiogram on which entry to the trial was based showed that in 12 treated and in 11 control patients pathological Q waves were not yet present at entry so that ST segment elevation (in addition to the history) was the sole criterion for inclusion in the trial. All 11 control cases and nine of the 12 treated patients finally developed pathological Q waves. The other three treated patients all developed T wave changes without Q waves and were considered to have had subendocardial infarcts.

The results of clinical evaluation and exercise testing one month after the infarct are shown in Table 3. The incidence of ischaemic pain between

Table 3 *Clinical evaluation at one month after infarction*

	Treated (n=15)	*Control (n=12)*
Further ischaemic pain	7	6
Angina on exercise testing	2	4
*Ischaemic ST changes after exercise	1	3

*Flat or downsloping ST depression of 1 mm or greater.

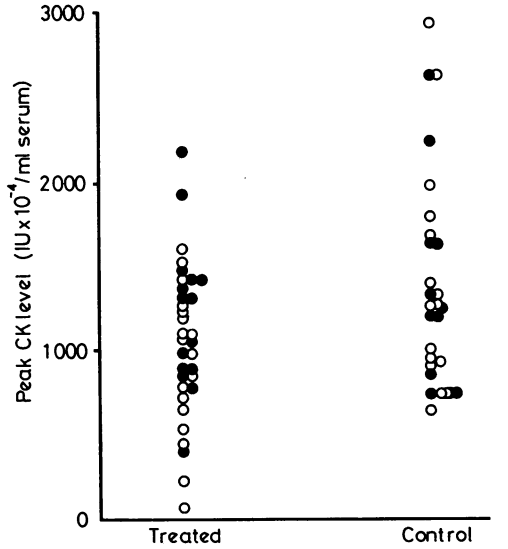

Fig. 1 *Peak CK activity levels in treated and control patients. Levels were 23 per cent in the whole group of treated patients ($p<0·05$), but were not significantly lower in the subgroup* (closed circles) *who were subsequently investigated by left ventriculography. Figures were not available for one control patient who had ventricular fibrillation.*

discharge from hospital and readmission for the exercise test, the incidence of angina during the test and of ischaemic electrocardiographic abnormalities afterwards, were all similar in the treated patients and in the controls. Only two of these patients (one treated and one control) were taking beta blockers at the time of exercise testing.

The angiographic score for left ventricular function calculated by the 'muscle loss' method[7] is plotted against the calculated total CK appearance for treated and control patients in Fig. 3. Similar results were obtained assessing peak enzyme levels and the angiographic score by the 'contractility' method (data not shown). Unexpectedly, the mean figure for the scores shown in Fig. 3 was 23 per cent higher for the treated patients than for the controls, but this difference was not significant ($t=1{\cdot}16$, $p>0{\cdot}3$). The correlation coefficient for all cases (treated and control) shown in Fig. 3 between the contractility score and the integrated enzyme appearance was $r=0{\cdot}54$. Inspection of Fig. 3 shows a possible tendency towards a greater scatter of data for the treated patients when compared with the controls. The possibility that the relation between ventriculographic score and enzyme appearance had been altered by propranolol was tested in two ways (a) by comparing the correlation coefficients of control with treated cases; and (b) by comparing the slopes of the regression lines describing the relation for the two groups separately. Neither comparison showed any significant difference between the two groups, and the same negative result was obtained when the ventriculographic score was calculated by the 'contractility' method and when the peak measured level of CK rather than the calculated total appearance was used as the enzymic index of infarct size.

Discussion

This study has confirmed our previous findings that peak CK levels and total CK appearance are reduced in patients with developing transmural infarction who are given intravenous and oral propranolol within four hours of the onset. However, it has failed to show a corresponding improvement in left ventricular function resulting from the intervention when this was assessed by biplane cineangiocardiograms one month later. Unfortunately, the subgroup selected for angiography did not show the significant reduction in enzyme levels shown by the larger group so that the hypothesis that a reduction in enzyme levels during the acute phase of infarction is associated with better left ventricular function afterwards could not be tested.

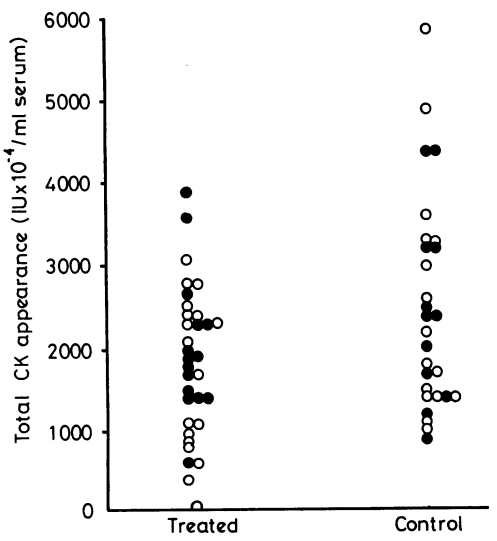

Fig. 2 *Total calculated CK appearance in treated and control patients. Total appearance was 25 per cent lower ($p<0{\cdot}05$) in the whole group of treated patients but was insignificantly lower in the subgroup* (closed circles) *who were subsequently investigated by left ventriculography.*

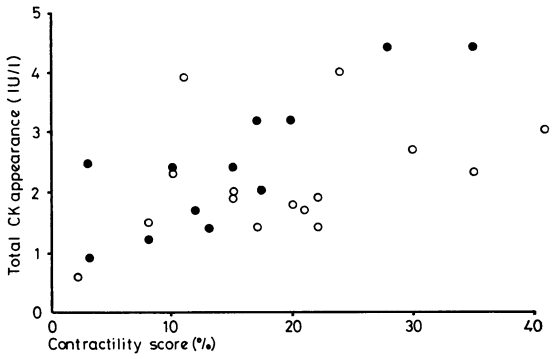

Fig. 3 *Relation between segmental contractility score subjectively assessed from biplane left ventriculograms and total enzyme appearance in control* (closed circles) *and treated* (open circles) *patients. Correlation coefficient (r) for all cases = 0·54. Though the relation between enzyme appearance and contractility score appears to be less close for the treated patients than for the controls, and in some treated patients there appears to be excessive loss in contractility for the amount of enzyme appearance, neither tendency was statistically significant. Use of another index for enzyme appearance (peak levels) and an alternative method for assessment of contractility from the angiocardiograms similarly did not show any difference between treated and control cases.*

There are a number of possibilities which might account for lower enzyme levels with propranolol. First, reduction in collateral blood flow by the beta blocker might reduce enzyme wash-out, causing more enzyme to be degraded locally within the infarct and less to appear in the circulation. Thus a reduction in serum enzyme levels might be seen without any corresponding change in infarct size. Cairns *et al.*[9] have shown experimentally that the serum entry ratio (proportion of CK released into the circulation) is lower in large than in small infarcts, and this is presumably caused by lower collateral blood flow at the centres of large infarcts. Though some workers have shown a reduction in infarct blood flow in anaesthetised animals pretreated with propranolol,[10] we found no change in collateral blood flow,[11] and studies on conscious dogs (which would presumably be more comparable with patients) showed that collateral flow was increased rather than decreased.[12 13] Moreover, animal experiments have shown higher tissue CK levels (compared with controls) at the centres of infarcts in dogs pretreated with propranolol.[14 15] If the effect of propranolol is to increase local degradation of enzyme activity the tissue levels should not be higher in treated animals than in controls.

A second possible reason for lower serum enzyme levels in patients is that propranolol increases the degradation rate of CK in the bloodstream. Though some experimental work suggests that such an effect may operate[16] the measured degradation rate of enzyme activity (KD) in the present study and also in our previous trial[1] was similar in treated and control patients. It is true that dosage with propranolol had stopped while KD was being measured, but blood levels were still in the therapeutic range and haemodynamic effects of beta blockade were still present in many of the treated patients during the period of rapid decline in enzyme activity. Thus it seems unlikely that serum enzyme degradation rates were increased by propranolol.

The most likely explanation for the lower serum levels is that myocardial viability is preserved by the oxygen-sparing action of propranolol, so that fewer myocardial cells became necrotic and less enzyme activity leaked out. In support of this idea is our previous finding[2] suggesting that the electrocardiographic abnormalities of 'threatened' infarction can in some cases be prevented by intravenous propranolol. In this context it is of interest that three out of 12 patients in the present trial who had ST segment elevation but no pathological Q wave in the 12 lead electrocardiogram at entry did not finally develop pathological Q waves. In our first study[1] there were also three patients (out of 10 with no Q waves at entry) who were treated with propranolol within four hours of the onset and did not finally develop Q waves. Combining the results of both trials, six out of 22 treated patients and zero out of 19 control patients who had no Q waves at entry did not finally develop them. This event is not statistically significant ($\chi^2=2{\cdot}94$, $p<0{\cdot}10>0{\cdot}05$). However, in conjunction with the other findings, it does seem to support the possibility that beta blockade protects infarcting myocardium when it is given early.

Reduction of myocardial necrosis by beta blockers, if it occurs, may or may not be beneficial for patients. If some myocardium remains chronically ischaemic rather than infarcted it might cause angina after the infarct or else act as a focus for the development of re-entrant arrhythmias. Exercise testing at one month in the present small group of patients did not suggest that treated patients had more ischaemia, but this point obviously needs to be reassessed in a larger series. Our patient numbers are not sufficient to evaluate the effect of treatment on the subsequent incidence of arrhythmias and sudden death and this, too, would require a large and probably multicentre trial. The present study has failed to show any improvement in left ventricular function in the treated patients compared with the controls. This may be because of the small numbers and the fact that the patients in whom left ventricular function was assessed were not truly representative of the treated and control groups. Even if myocardium were preserved, however, this might not result in improved ventricular function. It is known that though dead muscle results in loss of contractility angiographically, loss of contractility does not necessarily mean dead muscle.[17] Thus, infarcted myocardium might be preserved but still might not show normal contraction subsequently, particularly if it remained chronically ischaemic.

Demonstrations of the safety of intravenous propranolol in the present and previous trials[1 2 18] suggest that large-scale clinical trials can now be recommended if entry is restricted to patients who are not hypotensive and do not show overt cardiac failure. Indeed, some preliminary studies we have made using haemodynamic monitoring in patients with early failure suggest that beta blockade can be given cautiously and in conjunction with a diuretic to patients who are breathless with early interstitial pulmonary oedema. Thus, there seems little risk of exacerbation of cardiac failure if patients have a blood pressure of more than 100 mmHg and do not have breathlessness or basal râles before administration of the beta blocker. Though beta blockade should be used cautiously

in the presence of bradycardia, we have found that severe bradycardia responds readily to atropine. Thus in our experience beta blockers appear to be safer, particularly for prehospital use, than other oxygen-sparing drugs such as glyceryl trinitrate which reduce the afterload to ventricular contraction but may cause a disastrous fall in blood pressure if the dose is not strictly monitored.

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