Reduction of Enzyme Levels by Propranolol
After Acute Myocardial Infarction

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SUMMARY The effect of propranolol (0.1 mg/kg intravenously followed by 320 mg given over 27 hour orally) on serum levels of creatine kinase enzyme was studied in a randomized trial involving 95 patients seen within 12 hours of onset of symptoms of uncomplicated myocardial infarction. In 15 patients who were treated with propranolol within 4 hours of onset, and who eventually developed pathological Q waves, peak measured enzyme levels were 27% (P < 0.0125) lower than in 19 control patients who were also seen within 4 hours of the onset but had no specific treatment. Total calculated enzyme appearance was also lower in the treated patients (reduced 25%, P < 0.05) as was the calculated rate of appearance (33%, P < 0.005). No significant difference was found for treated compared with control patients entering the trial more than 4 hours after the onset of chest pain. This evidence suggests that propranolol may reduce the size of uncomplicated infarctions if it is given intravenously within 4 hours of the onset.

THE WELL-KNOW EFFICACY of beta-adrenergic blocking drugs for the treatment of angina pectoris suggests that these drugs should also be effective for the acute imbalance between oxygen supply and demand which occurs during the early stages of myocardial infarction. Apart from an encouraging report by Snow in 1965, however, a number of carefully randomized early clinical trials of beta blockers showed no effect on hospital mortality from infarction nor on the incidence of arrhythmias in treated patients compared with controls.

A number of recent developments suggest, however, that the use of beta-adrenergic blocking drugs in the acute stage of myocardial infarction should be re-investigated. First, there is the evidence that long-term beta blockade prolongs life after myocardial infarction and that this may be due in part to the prevention of new ischemic events. Second, there is evidence that propranolol given prophylactically to experimental animals reduces myocardial infarct size; this suggests that measurements of infarct size should be used as an end-point for therapeutic trials in man. Third, doses of propranolol used in previous trials (40–80 mg per day) were comparatively low and were administered orally and comparatively late after the onset. Patients given this low dose do not develop blood levels within the therapeutic range for 24–48 hours after first administration of the drug.

The present trial proposed to investigate the effect of high-loading doses of propranolol given within 12 hours of onset of symptoms of infarction on serum creatine phosphokinase (CPK) levels. Results show that CPK levels were reduced by propranolol if the drug was given within four hours of onset of the most severe chest pain.

Patients and Methods

We included in this study those infarctions which were of moderate severity since we postulated they would ultimately cause a moderately high enzyme release for which a reduction would be both easily measurable and clinically meaningful. At the same time it was recognized that early electrocardiographic (ECG) diagnosis of infarction can be difficult in that many patients seen very early after onset do not yet have pathological Q waves. We accordingly selected as our trial group those patients 1) who were seen within 12 hours of onset of typical prolonged chest pain, 2) who had ECG evidence of either epicardial injury (more than 2 mm of ST-segment elevation in the anterior chest leads or more than 1 mm in leads II, III, and aVf) or pathological Q waves, but 3) who had neither potential contraindications to propranolol therapy nor potential interferences with measurement of blood CPK levels. In addition, patients over 65 years of age were excluded from the study. All patients had chest X-rays taken immediately before admission to the trial and they were excluded if the X-ray showed interstitial edema or pulmonary edema; cases showing pulmonary venous congestion but no edema were accepted. Other reasons for exclusion included a heart rate below 60 beats/min, atrioventricular block of more severe than first degree block, ingestion of beta-blocking drugs within the previous 72 hours, or a history of asthma. Patients who had had DC shock for ventricular arrhythmias were also excluded because the cardioversion might have caused a false elevation of blood CPK levels.

On entry to the trial, patients were randomized by the envelope method for treatment with propranolol or no specific treatment, the cases being divided into three groups according to whether the pain started 1) less than 4 hours, 2) 4–8 hours, or 3) 8–12 hours before entry. For the duration of the trial (2–3 days or until the CPK enzyme levels had returned to normal) administration of other cardiac drugs was avoided wherever possible. In a few cases oral furosemide was given; lidocaine was given as necessary for the control of ventricular arrhythmias. Intramuscular injections were avoided during the period of the trial. Patients randomized for treatment with propranolol were given 0.1 mg/kg propranolol intravenously over 10 min followed by 320 mg of propranolol orally over the next 27 hours. This was given in divided doses of 40 mg, at 1, 3, 7, 11, 15, 19, 23, and 27 hours after entry to the trial. Treatment was stopped if cardiac failure or atrioventricular block of greater than first degree developed. If the heart rate fell below 50 beats per minute in sinus rhythm at the time the next dose was
Figure 1. The method for calculation of total enzyme appearance and the rate of appearance is shown. Small filled circles represent the 4-hourly measured levels of CPK activity in one patient who had an uncomplicated anterior transmural infarct. The peak activity at D (approximately 1,300 ml U./ml) occurred about 28 hours after the onset of infarction and the levels subsequently declined to normal. The unfilled circles represent a semilogarithmic replot of the downslope of measured activity from which the disappearance rate (Kd) is calculated using a desk-top computer.19 Using the measured levels and the individually determined Kd, the total cumulative CPK appearance (large closed circles) is plotted. The height of the plateau at A represents total appearance, and the slope of the upstroke (B/C), the rate of appearance. The latter is calculated as 90% of total appearance divided by the time to 90% appearance.

due, it was withheld, but was given at the next scheduled time if the heart rate had risen above 50 beats per minute.

All patients had an intravenous catheter (Intracath) inserted percutaneously into an antecubital vein. This was connected via a 3-way tap to the intravenous drip so that blood could be withdrawn every four hours by the nursing staff for measurement of serum CPK and/or serum propranolol levels. Serum propranolol was measured ten times until 72 hours after entry to the trial, and CPK every four hours until activity had peaked and returned to normal (48–72 hours in most cases). CPK was measured by the Rosalki method18 using a reaction-rate analyzer (Bausch and Lomb system 400); serum propranolol was measured by a fluorometric method.20 CPK activity was considered abnormally high if it was greater than 90 I.U. × 10⁻³/ml serum.

Analysis of the CPK levels follows our previously described18 modification of the method of Shell and Sobel.17 An example from a typical case is shown in figure 1. First, the serial levels were plotted against time on a linear scale. The descending limb of the time-activity curve was then plotted on a semilogarithmic scale so that the terminal rapid fall in enzyme activity could be identified visually and the slope of this line together with its 95% confidence limits could be calculated as a measure of enzyme disappearance rate (Kd). Using the figure for Kd, and the observed levels, the total cumulative CPK appearance was now plotted, being expressed as International Units (IU) of enzyme activity appearing per ml of serum. For each patient total CPK appearance, the rate of appearance, and the highest measured activity level were noted. In a few patients in whom sampling was discontinued inadvertently before activity had returned to normal, or the peak of activity was low, an average figure for Kd of 0.009 min⁻¹ was assumed for calculation of total cumulative appearance.

Differences between control and treated patients were assessed by the unpaired t-test using the one-tailed P value as the measure of significance.

Results

Ninety-five patients were admitted to the trial over an 18 month period. The age and sex distribution of the patients, together with the position of their infarcts, are shown in table 1.

This table also shows that nine patients (five treated cases and four controls) did not ultimately develop pathological Q waves in spite of prolonged chest pain and ST-segment elevation on entry to the trial. All these patients, however, developed late T wave inversions and a rise in serum CPK levels, and we therefore considered that subendocardial infarction had occurred.

The clinical course of these patients in the hospital was remarkably uncomplicated (table 2). No patient died during the trial and none had cardiac arrest; three died in the hospital after the trial had been completed. There was no difference in the incidence of overt cardiac failure or bradyarrhythmia requiring treatment between the treated and control patients. However, in two cases of cardiac failure and two of bradyarrhythmia it was thought that propranolol might have exacerbated the condition. All these

| Table 2. Clinical Course of Patients Admitted to the Trial |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                 | Treated (N = 47)                | Control (N = 48)                |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Death in hospital               | 1                              | 2                              |
| Cardiac failure                 | 5                              | 5                              |
| Bradyarrhythmia                 | 5                              | 3                              |
| Reinfarction during trial       | 1                              | 3                              |
| Ventricular fibrillation        | 0                              | 0                              |

<table>
<thead>
<tr>
<th>Time after onset of chest pain (hours)</th>
<th>Total cases</th>
<th>Age (mean and range)</th>
<th>Position of infarct</th>
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<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Control</td>
<td>Treated</td>
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<tr>
<td>Less than 4</td>
<td>18</td>
<td>19</td>
<td>55 (37–64)</td>
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<tr>
<td></td>
<td>15M, 3F</td>
<td>15M, 4F</td>
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<td>4–8</td>
<td>17</td>
<td>17</td>
<td>56 (45–68)</td>
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<td>53 (37–63)</td>
<td>12M, 5F</td>
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<td>8–12</td>
<td>12</td>
<td>12</td>
<td>51 (39–63)</td>
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<tr>
<td></td>
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<td>54 (41–65)</td>
<td>9M, 3F</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>6A, 4I, 2S</td>
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Abbreviations: M = male; F = female; A = anterior transmural infarct; I = inferior transmural infarct; S = infarct which appeared to be transmural on admission criteria, but subsequently Q waves did not develop, indicating that it was subendocardial.
patients recovered, although it was necessary to treat two with temporary pacemakers and one had intra-aortic balloon counterpulsation following increasing severity of failure immediately after the trial had been completed.

The mean heart rates, blood pressure (measured by the nursing staff using a sphygmomanometer) and serum propranolol levels are shown in figure 2. A modest reduction in heart rate to 60–70 beats per minute was seen in the treated patients and the arterial blood pressure also fell slightly. Serum propranolol levels, although varying widely from patient to patient, were generally within the therapeutic range for this method\textsuperscript{30} for the first 36 hr and then fell to zero after the drug was discontinued.

Data from the serum enzyme measurements are shown in figures 3–6. Preliminary analysis showed no difference between control and treated cases in the 4–8 hour or 8–12 hour groups, so these are combined in the figures. Although the range of results was wide, significant differences were seen for total cumulative enzyme appearance, rate of appearance, and the peak measured levels for patients entering the trial within 4 hours of the onset. For total enzyme appearance the reduction in propranolol-treated patients was 30% (P < 0.025); for the rate of appearance it was 38% (P < 0.005); for the peak levels it was 33% (P < 0.01).

One difficulty in interpretation of these results arises from the fact that three of the treated patients in the under 4 hour group did not have unequivocal evidence of myocardial infarction in that they never developed pathological Q waves. Of these three patients (designated "S" in figures 3, 4 and 5), two had low total enzymes, rates of appearance, and peak activity levels, while these measurements were near the mean for the group in the third patient. Although these patients had been randomized to groups, and met the criteria required for entry to the trial, we believed that cases should be strictly comparable if conclusions were to be drawn concerning the effects of therapy. Accordingly, the data were further analyzed by omitting these cases and comparing 19 control with 15 treated patients who entered the trial within 4 hours of onset of chest pain and who subsequently went on to develop pathological Q waves. When the data were analyzed in this way, the differences between control and treated cases were still apparent. Peak measured enzyme activity was reduced by 27% (P < 0.0125), while the rate of enzyme appearance was reduced by 33% (P < 0.005). Reduction of total calculated CPK appearance was now of borderline significance, however (25% reduction, P < 0.05, 2 P < 0.1). To determine whether propranolol changed the clearance rate (K\textsubscript{D}) of CPK from the serum, K\textsubscript{D} of patients receiving propranolol were compared with those of the control cases. The mean K\textsubscript{D} for treated cases was 0.00085 ± 0.00003 min\textsuperscript{-1} (SEM), while for control cases K\textsubscript{D} was 0.00092 ± 0.00003 min\textsuperscript{-1}. This difference was not statistically significant, showing that propranolol had not changed the disappearance rate of CPK from the blood and suggesting that differences in measured levels were caused by changes in the extent and rate of appearance of enzyme activity.

Discussion

Our study has shown that total cumulative CPK appearance, the rate of appearance, and also the peak levels of CPK activity were reduced in patients treated with
propranolol if this drug was given within 4 hours of onset of uncomplicated myocardial infarction. There is experimental and clinical evidence that total CPK appearance reflects the size of the myocardial infarct,\textsuperscript{17, 18, 21-23} although the subject is controversial and some studies have failed to confirm a relationship between total CPK release and infarct size.\textsuperscript{24, 25} The present results do suggest that enzyme activity was reduced by propranolol in our patients who received treatment early, adding evidence to animal experiments that indicate that propranolol limits infarct size\textsuperscript{15, 14} and favorably affects the course of metabolic changes following acute ischemia.\textsuperscript{15} This study also supports the result of a previous clinical study\textsuperscript{26} which showed that propranolol given intravenously in the same loading dose that was used in the present investigation improved myocardial oxygenation, as judged by extraction ratios of lactate and oxygen across the myocardium.

In the present study we elected to compare CPK appearance in control patients with treated patients in a randomized trial rather than to attempt prediction of total enzyme appearance from the early part of the curve.\textsuperscript{27, 28} Although this latter method has the advantage that each patient can act as his own control, it has the disadvantage that hourly blood specimens must be collected during the first seven hours for prediction before any therapeutic intervention can be made. Our results suggest that such a delay in giving propranolol would have prevented any salutary action of the drug.

Possible difficulties in interpretation of these results arise because of uncertainties over the precise relationship between total CPK appearance and anatomic infarct size. First, it could be argued that reduction of myocardial blood flow by propranolol may have been associated with reduced washout of CPK from the centers of infarcts, causing reduced CPK release in treated patients. We consider this to be unlikely because propranolol given experimentally has not consistently been shown to reduce perfusion of ischemic myocardium;\textsuperscript{29} moreover if reduction of CPK washout by propranolol had been a consistent effect, we would have expected to see it in all treated patients and not just in those who were treated within 4 hours.

Another possible difficulty is that the validity of the one-compartment mathematical model which has been proposed for analysis of the CPK curves\textsuperscript{31} has recently been questioned.\textsuperscript{30} The evidence on which these doubts are based comes mainly from experiments in which the disappearance of CPK injected into dogs was found to conform more closely to a double exponential curve than to a single exponential function.\textsuperscript{31, 32} This in turn suggests that CPK kinetics may approximate more closely a two-compartment system in which CPK diffuses between intravascular and extravascular distribution spaces; one effect of this might be that measured $K_D$ is considerably underestimated, with resultant inaccuracies in the calculation of total CPK appearance.

In our opinion the whole question of circulating CPK kinetics and resultant effect on calculations of total enzyme appearance is far from settled, and the doubts that have been raised make it desirable to examine CPK appearance in a way that does not require use of $K_D$. Accordingly, it was of interest to look at the peak measured CPK activity levels of our patients because this comparison between treated and control cases does not involve assumptions about CPK kinetics. These levels also were lower in patients who were given propranolol within four hours, but there was no difference comparing treated with control patients who entered the trial more than 4 hours after the onset.

It should be emphasized that results from the present study apply only to a highly selected group of patients who were judged to be experiencing acute infarction of moderate severity but who were free from complications. Although hemodynamic measurements with a Swan-Ganz catheter were not made, it is probable that a number of patients who received propranolol had early left ventricular failure; in fact, review of the X-rays after the trial showed that five patients who had been given propranolol had early signs of interstitial edema which were not recognized at the time of entry. These patients did not appear to have been made worse by propranolol and their heart failure responded to a diuretic. However if propranolol were to be given to patients with overt cardiac failure, it is possible that this would be exacerbated, and it is likely that temporary support for the myocardium by such methods as intra-aortic balloon counterpulsation might be necessary. Again, our results are
not necessarily applicable to patients who have a clinical history of myocardial infarction but do not yet have ECG changes.

This study has shown lower CPK levels in patients treated with propranolol less than 4 hours following the onset of symptoms of subsequently proven acute myocardial infarction. In view of continuing controversy about the measurement of myocardial infarct size, similar trials need to be conducted using different methods of infarct size measurement. In addition, the effect of beta blockade on mortality both in the short and in the long term should be re-assessed but this will necessitate a larger trial conducted at several centers.

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