Limitation of myocardial infarct size in patients less than 66 years treated with alprenolol

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SUMMARY Two hundred and eighty-two patients less than 66 years of age admitted with suspected or definite myocardial infarction were allocated in a random fashion to treatment with alprenolol or placebo. Treatment was started immediately upon admission with 5-10 mg alprenolol or placebo intravenously, followed by 200 mg alprenolol or placebo orally twice a day for one year. In 178 patients a definite myocardial infarction was diagnosed. Myocardial infarct size could be estimated from serial determinations of serum total creatine kinase in 42 patients treated with alprenolol and 43 patients receiving placebo. Median infarct size was 20.6 CK g Eq/m² body surface in the alprenolol group, the corresponding figure in the placebo group being 34.4 CK g Eq/m² body surface. Median rate of release of creatine kinase from the ischaemic myocardium was 27.7 U/l per hour and 48.0 U/l per hour after alprenolol and placebo, respectively. Alprenolol limited infarct size significantly provided the treatment was started within 12 hours of the onset of symptoms.

In patients admitted to hospital with an acute myocardial infarction extension of the ischaemic damage to the myocardium is often a dynamic process continuing for hours or days¹⁻³ and is thus susceptible to treatment. Infarct size is related to the occurrence of arrhythmias^{4,5} and the development of pump failure⁶⁻⁸ during the clinical course and also carries prognostic weight^{9,10}; in animal studies it is related to the electrical stability of the myocardium—large infarcts lowering the threshold for ventricular fibrillation.¹¹ Efforts intended to limit infarct size are therefore of major importance. A broad spectrum of measures favourably affects myocardial necrosis after coronary artery occlusion.¹² The use of beta-adrenergic blocking drugs has received special attention in this connection and propranolol in particular has been extensively studied.¹³⁻¹⁵

The aim of the present study was to investigate the effect of the beta-adrenergic blocking agent alprenolol on myocardial infarct size as estimated from serial determinations of serum creatine kinase (CK) in patients less than 66 years of age.

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Patients and methods

From 1 March 1976 until 31 December 1978 all patients admitted to the Coronary Care Unit, Sundby Hospital, Copenhagen, with a suspected or a definite acute myocardial infarct were considered for participation in a double-blind controlled trial of alprenolol. A detailed description of the study design and the mortality data has been given previously.¹⁶ There were 482 patients aged less than 66 years but

Table 1 Criteria for exclusion from trial

Criteria	No. of patients
Cardiogenic shock	16
Pulmonary oedema persisting after 2 hours	33
AV block (Mobitz type 2nd and 3rd degree)	9
Bradycardia < 40 beats/min	11
Chronic obstructive pulmonary disease	25
Labile diabetes mellitus	5
Death immediately after admission	8
Non-resident in area	14
Treatment with a beta-blocker on admission	61
Refusal to participate	10
Terminal or other disease	6
Other	2
Total	200

200 were excluded from entry into the trial mainly because of contraindications to beta-blockade or because they were already receiving this treatment (Table 1). The remaining 282 patients were randomised—140 to treatment with alprenolol and 142 to placebo. Using WHO criteria¹⁷ a definite myocardial infarct was diagnosed in 178 patients. Infarct size as assessed by serial determinations of serum CK was estimated in 85 patients, 42 in the alprenolol group and 43 in the placebo group. The reasons why infarct size was not estimated in the remaining 93 patients are listed in Table 2.

Table 2 *Reasons why infarct size was not estimated*

<i>Causes of exclusion</i>	<i>Alprenolol no. of patients</i>	<i>Placebo no. of patients</i>
Defibrillation	13	17
No increase of CK	4	3
Less than 10 CK values obtained	10	10
Maximum CK values on admission	7	7
Other reasons	10	12
Total	44	49

After arrival in the Coronary Care Unit treatment was started as soon as possible with 5 mg alprenolol or placebo intravenously. This dose was repeated after 10 minutes if the blood pressure or heart rate had not dropped by 10 per cent or more. Three hours later the patients received 200 mg alprenolol or placebo orally and subsequently 200 mg alprenolol/placebo orally twice a day for one year. A sustained release preparation (Aptin Durules) was used.

Blood samples for the analysis of serum total CK were obtained on admission and every four hours for the first two days. Thereafter, blood samples were drawn every morning for the rest of the first week and subsequently once weekly until the end of the study. Serum total CK was assayed as described by Rosalki.¹⁸ Patients received no intramuscular injections.

Infarct size (IS) was estimated from serial determinations of serum CK^{7 19 20} using the formula

$$IS = \frac{BW \times DV}{P_{CK} \times (CK_N - CK_I)} \times E(t) + k_d \int_0^T E(t) dt$$

IS: is stated in CK gram equivalents (CK g Eq), 1 CK g Eq being the quantity of myocardium undergoing necrosis show-

ing total CK depletion equivalent to the depletion in 1 g of tissue undergoing homogeneous necrosis in the centre of the infarct.¹⁹

BW: body weight (kg).

DV: distribution volume unit body weight (ml/kg).

P_{CK} : proportion of CK released into blood compared with CK depleted from the heart.

CK_N : CK activity in a homogeneous section of normal myocardium.

CK_I : CK activity in a homogeneous section of infarcted myocardium.

k_d : fractional rate of disappearance of CK from blood per hour.

$E(t)$: activity of CK in blood at the time (t) of the last observation (U/ml).

The following values were used in calculations²¹:

DV: 50 ml/kg; P_{CK} ; 0.15.

CK_N : 1300 U/g.

CK_I : 195 U/g.

T: 200 hours.

Using a computer program²² CK values were plotted in a serum curve as a function of time. An invasion curve depicting the integrated appearance of CK into the distribution volume as a function of time was also plotted. k_d values were calculated from the descending part of the serum curve for each patient individually.⁷ Calculated k_d values in the interval 0.03 to 0.09 per hour were used directly for estimating infarct size. Calculated k_d values outside this interval were considered inaccurate. Accordingly, values <0.03 and >0.09 per hour were fixed at 0.03 and 0.09 per hour, respectively. In a few patients k_d could not be calculated and in these cases k_d was fixed at 0.06 per hour.⁹ The rate of appearance of CK from the ischaemic myocardium into the blood was defined as 90 per cent of the total CK appearance divided by the time taken to reach this percentage.¹⁵

For tests of significance the Mann-Whitney rank sum test for unpaired data was employed. Infarct size was plotted as a function of delay time assuming linear regression.

Results

Nineteen per cent of the patients treated with alprenolol (8/42) had previously suffered a myocardial infarct as compared with 14 per cent (6/43) of those receiving placebo. Median infarct size in the alprenolol group was 20.6 CK g Eq per m² body surface, the corresponding figure in the placebo

group being $34.4 \text{ CK g Eq per m}^2 \text{ body surface}$ ($p < 0.025$; Fig. 1). Appearance rate of CK from the ischaemic myocardium into the blood was $27.7 \text{ U/l per hour}$ and $48.0 \text{ U/l per hour}$, respectively ($p < 0.025$; Fig. 2). The k_d values in the two treatment groups were $0.45 \pm 0.002 \text{ per hour}$ and $0.39 \pm 0.002 \text{ per hour}$ (mean $\pm$ SEM) (not significant).

Median delay from the onset of symptoms until treatment was 6.0 hours (interquartile range: 3.0–18.0) in the alprenolol group and 5.0 hours (interquartile range: 3.0–12.5) in the placebo group (not significant). The relation between the delay and infarct size in the two treatment groups is displayed in Fig. 3. Provided that treatment was initiated within 12 hours from the start of symptoms a significant limitation of infarct size was obtained in patients receiving alprenolol. Beyond this time limit no significant difference was demonstrable.

Fig. 1 Myocardial infarct size in patients less than 66 years of age treated with alprenolol or placebo. Infarct size related to body surface area is given along the X axis. Total range, quartiles, and median values are also shown. White area: interquartile range.

Discussion

Alprenolol, a non-selective beta-adrenergic blocking agent possessing intrinsic sympathomimetic as well as membrane stabilising properties, has been shown in two prospective randomised controlled studies to reduce long-term mortality in patients suffering an acute myocardial infarction.^{16 23} This study presents evidence that in patients who were less than 66 years, it also limits infarct size as estimated from serial determinations of serum CK.

Our patients were all less than 66 years of age. Older patients were studied but in the end there were insufficient numbers of comparable patients for meaningful analysis. The reasons for this were

Fig. 2 CK appearance rate from ischaemic myocardium to the blood stream in patients less than 66 years of age treated with alprenolol or placebo. Enzyme appearance rate is given along the X axis. Total range, quartiles, and median values are shown. White area: interquartile range.

that, compared with those in the placebo group, more of those treated with alprenolol had had a previous myocardial infarction, more were admitted quickly, and more died in the early days after infarction.¹⁶

Several different methods of estimating infarct size are available.^{10 24-27} The method based upon serial determinations of serum CK was chosen because it is non-invasive and because it is currently used in our Coronary Care Unit. The method

Fig. 3 Myocardial infarct size related to duration of symptoms before treatment in patients less than 66 years of age treated with alprenolol or placebo. Shaded area: observations in patients treated within 12 hours from onset of symptoms.

is supported by extensive animal studies.^{19 28 29} In these the accumulated CK appearing in the blood has been shown to be well correlated with CK depletion from the myocardium and with the extent of necrosis as estimated histologically after a coronary artery occlusion.²⁸ Furthermore, it is well correlated with infarct size judged from epicardial electrocardiographic mapping.³⁰ In man infarct size calculated from serial determinations of serum CK is closely related to the extension of infarction judged pathoanatomically²¹ and also correlates well with the clinical course.^{2 5 7 8} The accuracy of the method, however, has been doubted.³¹ Crucial to this, of course, is that depletion of CK from the myocardium depicts cellular death—and on the other hand that necrosis is regularly followed by release of CK. It is crucial, too, that a change in CK appearance does not merely reflect drug-induced changes in myocardial blood flow³² or other alprenolol effects unrelated to true infarct size. These questions need further elucidation. CK disappearance from blood as expressed by the k_d value is not changed by haemodynamic fluctuations after coronary artery occlusion,²⁰ nor was it influenced in this as in other studies¹⁵ by the beta-blocking agent.

In the present investigation it was possible to calculate infarct size in approximately 50 per cent of the patients having an established acute myocardial infarction. Basing the calculation of infarct size on serial determinations of the specific myocardial CK MB isoenzyme would have increased this percentage by not making it necessary to exclude patients who received direct current shock and those progressing to cardiogenic shock. Apart from this, estimates based upon the CK MB isoenzyme do not seem to be more accurate than those based upon total CK.^{20 33}

Our findings of the limiting effect of beta-adrenergic blockade on infarct size are in good agreement with those published by others.^{13–15 34 35}

The limitation of the extent of necrosis is based upon an improved balance between myocardial oxygen supply and demand. The major determinants of oxygen consumption are heart rate, the contractile state of the myocardium, ventricular wall tension, and shortening of the contractile fibres against a load (Fenn effect).³⁶ Heart rate and contractile state, mainly influenced by catecholamines, which are known to reach high levels in acute myocardial infarction³⁷ and which do increase myocardial oxygen consumption,³⁸ are reduced by beta-adrenergic blockade,^{39 40} but the net effect of this on ventricular wall tension is difficult to assess. Some workers have found that heart size increases after beta-blockade,⁴¹ thus tending to

augment wall tension, while others have reported no increase in ventricular filling pressure.^{13 39 40} Mean arterial blood pressure is somewhat reduced,^{13 14 39} thus tending to decrease wall tension and oxygen consumption because of the Fenn effect.

There are other factors. Oxygen delivery is mainly related to coronary blood flow. The net effect of beta-adrenergic blockade is a reduction of total coronary blood flow.^{39 42 43} Beta-blockers, however, seem to cause an advantageous redistribution of myocardial blood flow, increasing the ratio of endocardial to epicardial perfusion,^{43 44} but conclusions from studies performed in animals with normal coronary vessels should not be extended to human ischaemic heart disease. The oxygen affinity of haemoglobin may be reduced by propranolol, thus augmenting oxygen supply to the myocardial cells,^{45–47} but this finding has not been confirmed⁴⁸ and requires further study. Again, thrombocyte aggregation has been reported to be reduced by propranolol,^{49 50} which might tend to improve the microcirculation in the ischaemic myocardium. The improved balance between oxygen supply and demand accomplished by the beta-adrenergic blockade causes a narrowing of the myocardial arteriovenous oxygen difference³⁹ and, reflecting the improvement of the metabolic state, the ischaemic myocardial cells shift from lactate production to lactate extraction.³⁹

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