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Effect of antilipolytic therapy on ST segment elevation during myocardial ischaemia in man

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SUMMARY Abnormally high circulating free fatty acid (FFA) levels occur in the early hours of acute myocardial infarction in man. Experimentally, reduction of plasma FFA has been shown to reduce myocardial ischaemic injury. The effect of lowering plasma FFA by antilipolytic therapy using a nicotinic acid analogue (NAA) has been studied in man within 6 hours of onset of symptoms of acute myocardial infarction. Myocardial ischaemic injury was assessed by continuous recording and computer analysis of ST segment elevations in 15 treated and 15 untreated patients.

High dose NAA treatment in 9 patients achieved sustained reduction in FFA over 24 hours and a significant fall in ST segment elevation by one and a half hours. Of the 9 patients, 7 developed undesirable side effects of flushing, nausea, or vomiting. Six patients treated with a low dose NAA regimen achieved smaller reductions in FFA with early FFA escape and a transient reduction of ST segment elevation after three-quarters of an hour but without side-effects.

These findings of improved viability of the ischaemic myocardium may be explained on the basis of a change in the proportions of lipid and carbohydrate available for oxidation by the ischaemic myocardium after reduction of revised serum FFA. Further development of antilipolytic agents for this purpose is indicated.

Metabolic intervention has been shown to reduce the extent of myocardial ischaemic injury after experimental coronary artery occlusion in dogs (Opie, 1975; Maroko and Braunwald, 1976; Oliver, 1976). This has been directed principally to decreasing extraction of free fatty acids (Kjekshus and Mjøs, 1973; Miller *et al.*, 1976; Mjøs *et al.*, 1976) or increasing extraction of glucose (Maroko *et al.*, 1972b; Opie *et al.*, 1975; Opie and Owen, 1976) by the myocardium. Such treatment might be expected to reduce infarct size in man and to improve subsequent prognosis.

Plasma free fatty acids are raised immediately after the onset of symptoms suggestive of myocardial infarction (Vetter *et al.*, 1974). An excess of plasma free fatty acids is associated with serious ventricular arrhythmias in patients during impending myocardial infarction (Oliver *et al.*, 1968; Gupta *et al.*, 1969). Experimentally, such an increase is associated with an increase of myocardial oxygen consumption (Mjøs, 1971) and decreased contractility (Kjekshus and Mjøs, 1972). Under conditions of reduced oxygen availability, an energy crisis may result. Raised plasma free fatty acids can be reduced in patients by decreasing adipose tissue lipolysis using a nicotinic acid analogue which has no significant haemodynamic effects (Rowe *et al.*, 1973). This has already been shown to reduce the incidence of ventricular arrhythmias during the first 5 hours of infarction (Rowe *et al.*, 1975) and also the extent of ST segment depression in exercise-induced angina (Luxton *et al.*, 1976).

We describe the effect of this nicotinic acid analogue (5-fluoro-3-hydroxy-methyl pyridine hydrochloride) in patients with myocardial ischaemia using changes in ST segment elevation as an index of changes of myocardial ischaemic injury.

Patients

Thirty patients admitted to the Coronary Care Unit of the Royal Infirmary of Edinburgh with symptoms suggestive of acute myocardial infarction were selected for study. All had severe praecordial pain within 6 hours before admission and the diagnosis of infarction was subsequently confirmed in all cases by the development of Q waves in the electrocardiogram and/or an increase of creatine kinase

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levels. Morphine and diuretics were given when indicated. Patients taking drugs known to affect plasma free fatty acid concentrations such as β-adrenergic blockers, clofibrate and thyroxine, were excluded from the study. Patients with diabetes mellitus, hypertension, and those requiring anti-arrhythmic therapy were also excluded from study.

In the high dose NAA treatment group, studies were limited to cases of acute anterior myocardial infarction and ST segment data obtained by the technique of continuous 35-lead praecordial mapping (Luxton *et al.*, 1977). In the low dose nicotinic acid analogue treatment group cases of both acute anterior and inferior infarction were studied and ST segment data obtained by vector analysis.

Treatment regimens

HIGH DOSE NICOTINIC ACID ANALOGUE

Informed consent was obtained from 9 patients for administration of the nicotinic acid analogue. A further 9 patients were studied without intervention for the purpose of obtaining control ST segment data.

An indwelling venous catheter was inserted for blood sampling. Blood samples were taken at 0, ½, 1 h, 200 mg nicotinic acid analogue was given orally after this 1-hour control period, and further blood samples at 1½, 2, 3, 5, 9, 13, 17, 21, 25, 27, 29, and 33 hours. Blood sampling was not performed in control cases.

In order to prevent the phenomenon of early free fatty acid escape caused by tachyphylaxis, progressively increasing doses of nicotinic acid analogue were given (Fig. 1). Thus 200 mg 2-hourly was given for 8 hours, 400 and 200 mg alternatively for 8 hours, and 400 mg, 2-hourly for 8 hours, the total period of treatment being 24 hours.

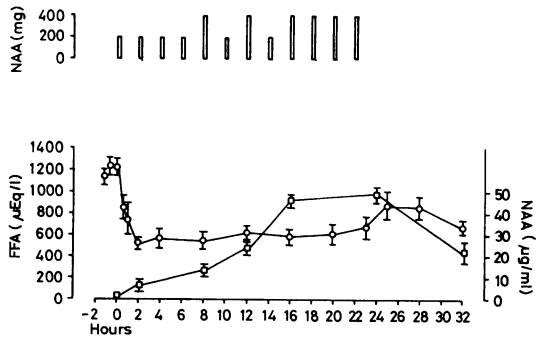

Fig. 1 *Treatment regimen in high dose nicotinic acid analogue (NAA) group. Oral nicotinic acid analogue administered over 24 hours induced a sharp fall of plasma free fatty acid (FFA) and rise in drug levels.*

LOW DOSE NICOTINIC ACID ANALOGUE

A high incidence of side-effects occurred (see below) in the high dose treated patients, and therefore 6 other patients were given a modified low dosage regimen. A further 6 patients were studied without intervention for the purpose of obtaining control ST segment data.

Blood sampling from an indwelling venous catheter was performed as in the high dosage group.

Again, in an attempt to avoid the phenomenon of early free fatty acid escape progressively increasing doses of nicotinic acid analogue were administered, starting with 50 mg orally after the 1-hour control period. Thus 50 mg nicotinic acid analogue were given 2-hourly for 6 hours, 100 mg 2-hourly for 6 hours, 150 mg 2-hourly for 6 hours, and 200 mg 2-hourly for 6 hours, with a total treatment period of 24 hours.

Methods

PRAECORDIAL ST SEGMENT MAPPING

Thirty-five positions were marked out on the praecordium and self-adherent electrodes attached according to the system described by Maroko *et al.* (1972a). Using a purpose-built lead system, signals were passed into a signal averaging device (Luxton *et al.*, 1977). Multiple switches allowed selection to obtain the mean of serial individual leads.

After application of the electrodes, conventional hand mapping was performed in order to identify lead positions showing praecordial ST segment elevation of 0·1 mV or more. These leads alone were selected for averaging. The measured signal was recorded on tape, together with signals from two individual praecordial leads—one from the position of maximum ST segment elevation (central lead) and one from a more peripheral position.

Recordings were carried out during a 30-minute control period and for at least 4 hours during administration of the nicotinic acid analogue. Recordings were again obtained between 23 and 27 hours over the period of cessation of therapy. In the control group of patients, continuous recordings were obtained for between 5 and 8 hours after admission; data were selected according to time after onset of symptoms for matching with treated patients.

During the course of recording, patients were asked to move as little as possible, as even slight movements have been shown to affect ST segment measurement (Luxton *et al.*, 1977).

Data were subsequently replayed from tape at 60 times recording speed through an arrhythmia computer which identified normally conducted

sinus complexes and rejected those with conduction defects, ventricular extrasystoles, or artefacts. A trigger pulse was produced for each normal beat and fed into the ST segment computer: the ST segment computer subtracted the voltage at a reference point on the isoelectric PR segment from the voltage at a selected point at the centre of the flat portion of the ST segment. The output was smoothed by passage through a low pass filter to remove respiratory variations and the resultant time course of ST segment elevation recorded on paper. Continuous monitoring of heart rate, mean ST segment elevation, and ST segment elevation in a central and peripheral lead was obtained.

ST SEGMENT VECTOR ANALYSIS

An alternative approach to the analysis of the ST segment is that of estimation of the magnitude of the ST segment vector (Maroko *et al.*, 1972a). Ten positions were marked out on the body according to the system of McFee and Parungao (1961) using a purpose-designed template and electrodes attached. By means of appropriate amplifiers (McFarlane, 1969) an output was obtained of X, Y, and Z electrograms each of which was recorded continuously on tape for one hour before administration of the nicotinic acid analogue and 4 hours after onset of therapy. Longer periods of recording were obtained in control patients to allow for selection of time-matched changes.

By subsequently passing the output from each tape channel through an ST segment computer a continuous record of ST segment magnitude in each vector was obtained on paper.

Data from X, Y, and Z vectors were extracted at 15-minute intervals and ST segment vector magnitude (ST-VM) calculated by means of the formula

$$\text{ST-VM} = \sqrt{X^2 + Y^2 + Z^2}$$

using an Olivetti bench calculator.

BIOCHEMICAL

Serial measurements were made of plasma free fatty acids (Trout *et al.*, 1960), glycerol (Chernik, 1969), and 5-fluoro-nicotinic acid.

Results

HIGH DOSE NICOTINIC ACID ANALOGUE

Plasma free fatty acid

Plasma free fatty acid levels were raised in all patients during the 1-hour control period (Fig. 2), with mean values of 1054, 1132, 1161 μEq/l at 0, $\frac{1}{2}$, 1 hour respectively. After administration of the nicotinic acid analogue, a sharp fall in free fatty acids occurred in each case over the next 2 hours to around 40 per cent of the initial value (439 μEq/l at 3 hours). Free fatty acid levels were maintained within normal limits during the period of drug treatment. The expected free fatty acid change without treatment is shown in dotted lines (Fig. 2), data being taken from our previous work (Rowe *et al.*, 1973) on 36 untreated patients with acute myocardial infarction.

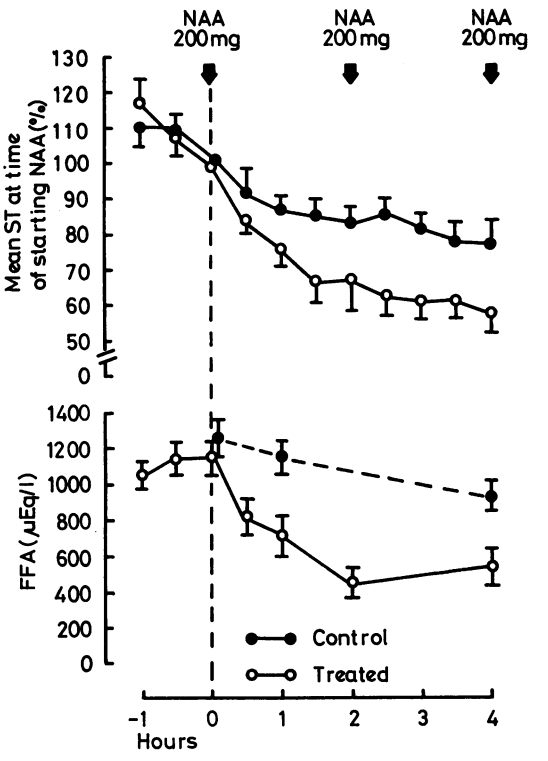

Fig. 2 *Mean praecordial ST segment elevation grouped about time of administration of nicotinic acid analogue (NAA) in 9 treated and 9 untreated patients. Free fatty acid (FFA) data in the treated group are compared with expected free fatty acid change from a previous study (Rowe* et al., 1975).

Glycerol levels

Plasma glycerol levels were also raised during the 1-hour control period, with mean values of 154, 152, 148 μEq/l at 0, $\frac{1}{2}$, 1 hours, respectively. Again, a sharp fall of 64 per cent occurred over 2 hours (53 μEq/l at 3 hours) after administration of the nicotinic acid analogue. Levels remained low until treatment was stopped.

Side-effects

Of the 9 patients studied, 2 patients developed transient flushing after taking the initial capsules of nicotinic acid analogue, 4 patients developed gastric burning, and 1 a small haematemesis. Five patients developed nausea and vomiting during the time of treatment.

Praecordial ST segment elevation

The computer write-out from one patient studied from 2 hours after the onset of symptoms is shown in Fig. 3. During the control period, a slow and gradual decline in mean ST segment elevation was observed. After administration of the nicotinic acid analogue, a distinct increase in rate of fall of ST segment elevation occurred. This change was associated with a reduction in plasma free fatty acids. There was no significant associated change in heart rate or of blood pressure during the period of study.

Grouped data from all 9 cases are shown in Fig. 2. Figures are expressed as percentage ST segment elevation with respect to the value at the time of onset of drug treatment. The time scale refers to the time of onset of drug treatment and not to the actual time after onset of symptoms of infarction. A sharp decline in ST segment elevation occurred after administration of the drug, with values falling to around 55 per cent of the initial levels within 2 hours. There was no significant associated change in heart rate during the period of study.

Q wave analysis

Continuous analysis of Q wave amplitude was performed in addition to measurements of the ST segment. One such recording is depicted in Fig. 3. The time course of Q wave evolution was different from that of ST segment change. There was no increase in rate of development of the Q wave during the period of rapid ST segment decline after administration of the nicotinic acid analogue.

Control data

Praecordial ST segment elevation was continuously measured in 9 patients without intervention. There was no significant difference between the mean ages of the control and treated groups (58·6 and 53·2 years, respectively). There were 6 men and 3 women in the control group compared with 7 men and 2 women in the treated group. Data were analysed from recordings taken at identical time intervals after onset of symptoms to the treated group. There was no significant difference between mean ST segment elevation at the time of administration

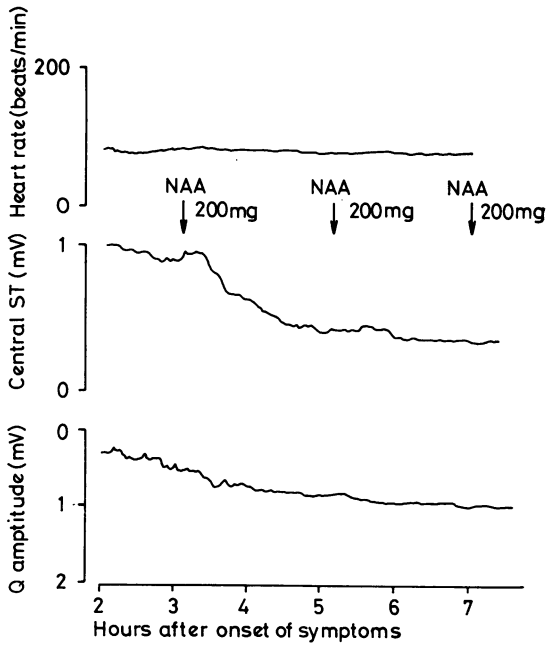

Fig. 3 *Computer recording from patient studied from 2 hours after onset of symptoms of myocardial infarction. Note the increased rate of decline of ST segment elevation 20 minutes after nicotinic acid analogue (NAA) in the absence of any change in heart rate or Q wave evolution.*

of the drug in the treated group and at the comparable time in the control group (0·48 ± 0·06, 0·37 ± 0·09 mV, respectively). Data were again expressed as a percentage of the value one hour after onset of sampling. When expressed in this fashion, a progressive decline in ST segment elevation was seen to occur with time, with a mean fall of 17 per cent in 2 hours. No sharp decline was seen between 1 and 2 hours as in the treated group.

No significant change in heart rate is shown between the two groups. ST segment change was, however, significantly reduced at 1½ hours ($P < 0·05$), 2½ hours ($P < 0·01$), 3 hours ($P < 0·01$), 3½ hours ($P < 0·025$), and 4 hours ($P < 0·025$) after treatment.

LOW DOSE NICOTINIC ACID ANALOGUE

In view of the high incidence of undesirable side effects it was considered that a much smaller dosage of nicotinic acid analogue might produce similar electrophysiological effects in their absence.

Plasma free fatty acids

Plasma free fatty acid levels were up during the 1-hour control period with mean values of 1175,

1134, and 1155 μEq/l at 0, $\frac{1}{2}$, and 1 hour, respectively. These levels were not significantly different from those obtained in the high dose nicotinic acid analogue group. After administration of nicotinic acid analogue a lesser fall in free fatty acid occurred over a period of 2 hours to around 70 per cent of the initial value (718 μEq/l). In addition, in individual cases some degree of FFA escape was observed despite therapy at 4 hours (one case), 8 hours (two cases), 12 hours (one case) or 16 hours (one case) after onset of therapy.

Side-effects

No side-effects were observed in any patients, nor could any evidence of such effects be elicited on direct questioning.

ST vector magnitude

After a latent period of 15 or 20 minutes after nicotinic acid analogue a sharp change in the rate of decline of ST segment amplitude was observed in each case.

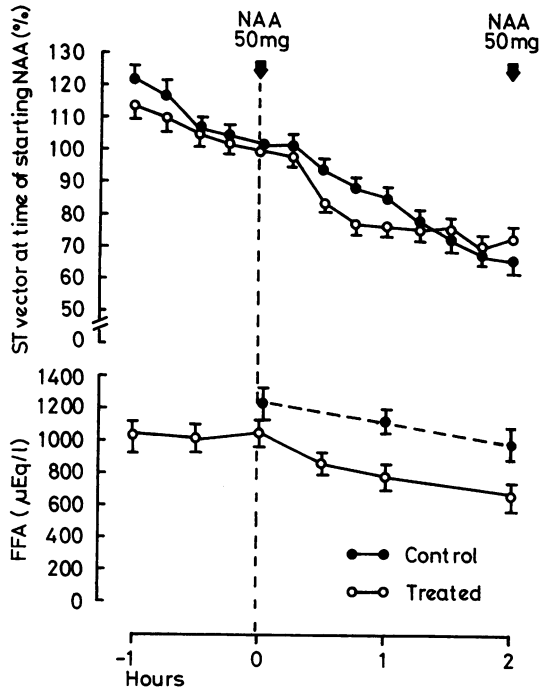

Fig. 4 *ST segment vector magnitude in 6 treated and 6 untreated patients grouped as in the high dose nicotinic acid analogue (NAA). Plasma free fatty acid (FFA) data are contrasted with expected change without treatment. Note the transient effect of treatment and the small fall in free fatty acid compared with the high dose nicotinic acid analogue series.*

Normalised mean values of ST vector magnitude for treated and control patients are shown in Fig. 4. No significant difference was found between treated and control groups of patients over the period before administration of nicotinic acid analogue or its equivalent. Similarly no difference occurred 15 minutes after the drug. At 30 minutes and 45 minutes after nicotinic acid analogue, however, the differences did attain significance ($P < 0.05$, $P < 0.025$, respectively).

The treatment group consisted of 3 male and 3 female patients, initial ST vector magnitude 0·31 ± 0·05 mV. The control group consisted of 4 male and 2 female patients, initial ST vector magnitude at exactly matched times after onset of symptoms 0·226 ± 0·07 mV.

Discussion

This study shows that antilipolytic treatment, using a nicotinic acid analogue without significant haemodynamic effects, increased the rate of regression of praecordial ST segment elevation, and reduced raised free fatty acids to within normal limits in the early hours after onset of symptoms of myocardial infarction. Similar changes were not seen in the control group. The acidic nature of nicotinic acid analogue undoubtedly contributed to the high incidence of gastric side effects occurring in the high dose group. These effects and also the flushing and feelings of nausea were completely abolished by the use of the lower dosage regimen. A smaller reduction in free fatty acids resulted, however, and the effect of reduction on ST vector magnitude was more transient, though significant.

Changes in praecordial ST segment elevation are widely believed to reflect changes in underlying myocardial ischaemic injury (Reid *et al.*, 1971; Maroko *et al.*, 1972; Madias *et al.*, 1975). A close correlation has been shown in the dog between praecordial and epicardial ST segment change (Maroko *et al.*, 1971) and also between epicardial ST segment elevations and changes in local myocardial oxygen tension (Sayen *et al.*, 1961) and blood flow (Kjekshus *et al.*, 1972). It is likely that acute directional changes in praecordial ST segment elevation, as measured objectively by continuous recording and computer analysis, do reflect similar directional changes in underlying myocardial ischaemic injury. The absence of an associated increase in rate of evolution of the Q wave suggests a reduction of myocardial ischaemic injury rather than an increase in cell necrosis in our group of treated patients.

Assessment of the effectiveness of any intervention in man is hampered by the distinct inhomo-

geneities of extent and time course of ischaemic injury. Considerable spontaneous variation in ST segment elevation is common in the early hours after onset of symptoms. Our control groups were similar at least for age and initial ST segment elevation and the temporal relation of significant change to the time of nicotinic acid analogue administration indicates a true effect. Significant reduction in ST segment elevations were observed both from praecordial leads in the high dose nicotinic acid analogue group and from vectorial analysis in the low dose nicotinic acid analogue group after treatment. Though close correlations have been shown between these two systems of recording, vector analysis has the advantage of detecting ST segment change in any plane.

Free fatty acids are preferentially metabolised by the normal and ischaemic myocardium and are the major substrate for cardiac energy production. Uptake is directly related to the molar binding ratio of free fatty acids to albumin. Above a free fatty acid plasma level of 1200 μEq/l, as is common during myocardial infarction, albumin binding sites for free fatty acids become saturated and cell uptake may follow an exponential rather than linear relation (Spector, 1968). In man the systemic metabolic response to infarction with a rise in plasma free fatty acids and catechols and suppression of insulin release may be detrimental to metabolism in the ischaemic cell and reduction of plasma free fatty acid levels may improve survival (Oliver, 1972).

The early free fatty acid escape observed in the low dose nicotinic acid analogue group may explain the more transient effect of treatment on the ST segment. Sustained reduction of free fatty acid was obtained in the high dose nicotinic acid analogue group but at the expense of an unacceptably high incidence of side-effects. Free fatty acid escape occurred in this group when treatment was stopped. The development, in some patients, of pericarditis prevented further ST segment analysis at this time.

Our findings are in keeping with experimental work which has shown a positive correlation between ST segment change and changes in free fatty acid/albumin molar binding ratios after acute coronary occlusions. Reductions of ST segment elevation have been shown after reduction of free fatty acid by p-chloro-phenoxyisobutyrate (clofibrate) (Mjøs *et al.*, 1976), lipid-free albumin infusions (Miller *et al.*, 1976), and β-pyridyl carbinol (Kjekshus and Mjøs, 1973), a substance that is metabolised as nicotinic acid. These changes are the result of alteration in myocardial blood flow. Reduction in plasma-free fatty acid is associated with a fall in myocardial oxygen consumption (Mjøs, 1971) which may lead to less distinct metabolic changes in areas with critical oxygen supply.

Clinical studies with β-pyridyl carbinol after acute myocardial infarction have shown a significant reduction in ST vector magnitude and diminished creatinine kinase release associated with lowering of plasma free fatty acid (Kjekshus, 1976).

The principal effect of nicotinic acid analogue is on the reduction of adipose tissue lipolysis and plasma free fatty acid levels. Some degree of inhibition of myocardial lipolysis may also operate (Christian *et al.*, 1969). In a previous study it has been shown to have no effect on blood glucose or catecholamine levels (Rowe *et al.*, 1975). Heart rate and blood pressure changes, which may influence the degree of ischaemic injury after infarction, were not observed. A direct electrophysiological effect of nicotinic acid analogue should also be considered. The related substance nicotinic acid, however, has no effect on resting membrane potential or action potential in isolated guinea pig ventricular muscle (Beresewicz and Wojtczak, 1976).

To date, available antilipolytic drugs are not safe enough since escape of plasma free fatty acid levels from control could increase the extent of ischaemia and the incidence of arrhythmias, and side effects occur at doses necessary to ensure continued control of free fatty acids. This is a field where new pharmacological agents are needed.

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