citrate (23%). This, together with the improvement in the rate of implantation suggests that prolonged suppression of the pituitary with buserelin may lead to improved quality of oocytes (and therefore of embryos). Further evidence for this is that only eight out of 20 (40%) of women having more than four embryos available after conventional treatment conceived compared with 17 out of 20 (85%) treated with buserelin. Alternatively, buserelin may partly produce its effect by direct action on uterine receptivity, but this factor remains to be investigated.

If the success rate reported in this study is maintained it will facilitate the use of in vitro fertilisation for preimplantation diagnosis to treat couples at risk of having a child suffering from genetic disease. An important advantage of treatment with buserelin is that large numbers of fertilisable eggs are produced during one cycle of treatment. This will allow the simultaneous screening of many zygotes for single gene defects for preimplantation diagnosis, such that women at risk could embark on a healthy pregnancy.¹⁵

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A randomised dose ranging study of recombinant tissue plasminogen activator in acute myocardial infarction

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Abstract

To assess the thrombolytic efficacy and the effect on the systemic fibrinolytic system of recombinant tissue plasminogen activator doses of 20 mg, 50 mg, and 100 mg were compared in a randomised study. Tissue plasminogen activator was infused intravenously over 90 minutes in 50 consecutive patients with acute myocardial infarction of four hours' duration or less; on average the infusion was started 135 minutes (range 20 to 240) after the onset of pain. The affected artery was patent at the end of the 90 minute infusion in 14/17 (82%) of those who received 100 mg, 12/17 (71%) of those who received 50 mg, and 8/16 (50%) of those who received 20 mg. Regardless of dose, reperfusion rates were significantly better for patients treated within two hours of the onset of symptoms (81%) than for those treated in the third and fourth hours (54%). At the end of the infusion serum fibrinogen concentrations fell to 86% of the preinfusion value after 20 mg, 75% after 50 mg, and 63% after 100 mg, and similar dose dependent changes occurred in plasminogen, α_2 anti-

plasmin, and fibrinogen and fibrin degradation products. The mean infarct related regional third ejection fraction was 46% for patients with grade 2 or 3 reperfusion and 35% for those with grade 0 or 1. Ventricular fibrillation occurred in six (12%) patients during the infusion of tissue plasminogen activator, but no late ventricular fibrillation occurred. Bleeding was minimal, reocclusion occurred in three patients, and four patients died from cardiac causes.

Recombinant tissue plasminogen activator is an effective thrombolytic agent which produces better reperfusion rates after a 50 or 100 mg dose than after a 20 mg dose. The effect on the systemic fibrinolytic system is dose dependent. Successful reperfusion results in improvement of left ventricular function.

Introduction

Although streptokinase has been used as a thrombolytic agent for at least 30 years,¹ its use when administered directly into a coronary artery has become feasible only with the emergence of coronary angiography as a safe procedure in acute myocardial infarction. Intravenous administration of streptokinase allows earlier, safer, and more practicable treatment than intracoronary administration.²

Nevertheless, streptokinase has several potential disadvantages. It causes thrombolysis by activating plasminogen to plasmin, which in turn breaks down fibrin to fibrin degradation products. Streptokinase causes a generalised fibrinolytic state by activating plasmin in the circulation as well as at the fibrin surface of the clot. Its antigenic potential results in antibody formation with a risk of anaphylaxis and an anamnestic response on subsequent exposure, possibly during reocclusion, and the long half life makes emergency surgical intervention difficult. These disadvantages have led to the search for

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thrombolytic agents which are clot specific, have no antigenic potential, and have a short half life. Tissue plasminogen activator is the physiological thrombolytic agent with relative clot specificity produced by endothelial cells. Therapeutic quantities are now available, produced initially from melanoma cells¹ and now by recombinant DNA technology.¹

Recombinant tissue plasminogen activator is an effective thrombolytic agent in acute myocardial infarction,² producing reperfusion in the affected artery in 61-62% of patients at 90 minutes^{3,4} compared with reperfusion in 31% of patients after intravenous streptokinase.⁵

A randomised dose ranging study with recombinant tissue plasminogen activator has not, however, been carried out. We therefore assessed the thrombolytic efficacy and the effect on the systemic fibrinolytic system of different doses of tissue plasminogen activator administered intravenously to patients with acute myocardial infarction.

Patients and methods

Study population—Consecutive patients with pain who were suspected clinically of having suffered an acute myocardial infarction were considered for entry into the study. Patients were admitted via the mobile coronary care unit, from the accident and emergency department, and from other hospital wards.

Entry criteria—Patients were entered into the study if they were aged under 75 years and had ST segment elevation of at least 0.2 mV in the electrocardiogram in at least two inferior leads, of 0.3 mV in at least two precordial leads, or of 0.2 mV in leads I and aVL. The time limit between the onset of pain and the start of treatment was up to four hours.

Exclusion criteria—Patients were excluded if they were of childbearing potential; were in cardiogenic shock; had a history of bleeding diathesis or using anticoagulant drugs; had undergone cardiac surgery, recent surgery, or trauma; had severe hypertension or any general medical condition precluding thrombolytic treatment, had had a stroke, or had an electrocardiogram showing left bundle branch block.

Trial design—Patients were randomised to receive 20 mg, 50 mg, or 100 mg recombinant tissue plasminogen activator infused intravenously over 90 minutes. The randomisation was prepared from a random number sequence, and the drug was supplied in numbered packs, which were used in sequence. Reperfusion was assessed by coronary angiography performed at the end of the 90 minute infusion. Although the investigator who performed the coronary arteriography was aware of the dose of tissue plasminogen activator, the angiograms were subsequently viewed and graded by two investigators who were blind to the dose given.

Treatment and administration—The randomised dose of recombinant tissue plasminogen activator (double chain), which was provided by Wellcome Research Laboratories, was supplied as a white lyophilised powder which was dissolved in sterile water and infused intravenously over 90 minutes using a battery powered infusion pump (Graseby MS 2000). Treatment was started in the coronary care unit, accident and emergency department, or ward or outside hospital by mobile coronary care unit staff.

Trial observations—Before tissue plasminogen activator was started the patient's age, sex, medical history, and physical findings were documented and a standard 12 lead electrocardiogram recorded. Blood was drawn for measuring cardiac enzyme activities (total creatine kinase and creatine kinase MB isoenzyme) and clotting factors—serum fibrinogen, plasminogen, α_2 antiplasmin, and fibrin and fibrinogen degradation products. Coronary arteriography by the Judkins technique was performed at the end of the 90 minute infusion, and the reperfusion grade of the affected coronary artery assessed and scored using thrombolysis in myocardial infarction (TIMI) grades 0-3 (grade 0 no perfusion, grade 1 penetration with minimal perfusion, grade 2 partial perfusion, grade 3 complete perfusion). Angiograms were subsequently viewed and scored by two investigators blinded to the dose given. Clotting factors were assayed from blood taken at the end of the 90 minute infusion and four hours and 24 hours after the start of treatment. Blood was drawn into citrate tubes (Sarstedt Monovette) and immediately placed in ice and centrifuged within 30 minutes at 600-1000 g for 10 to 15 minutes. Plasma was then transferred in 500 μ l aliquots to tubes containing antibody to tissue plasminogen activator, thereby preventing continuing in vitro fibrinogenolysis. Tubes were frozen immediately to -20°C and transported in dry ice for analysis. Specimens were analysed for fibrinogen (Clauss method), plasminogen (streptokinase assay), α_2 antiplasmin (functional assay), and fibrin and fibrinogen degradation products (enzyme immunoassays). Cardiac enzyme activities were measured on specimens drawn every four hours after the start of treatment for 28 hours. Total creatine kinase was assayed by an optimised standard method

(Randox Laboratories Ltd) using a parallel analyser (American Monitor). Creatine kinase MB was assayed by an immunoassay method adapted for the Roche Cobas Bio Centrifugal Analyser (Boehringer Mannheim GmbH Diagnostica).

Subsequent management—Management after the 90 minute angiogram was decided on by the senior investigator who performed catheterisation, with the aim of improving patency in a vessel with grade 0 or 1 reperfusion or maintaining patency in a vessel with grade 2 or 3 reperfusion. When possible patients underwent assessment of left ventricular function by gated blood pool scanning during their stay in hospital.

Statistical methods—Univariate methods of statistical analysis were used. Clotting factors were analysed using one way analysis of variance. Reperfusion grades for the different doses were examined using the χ^2 test for association. Cardiac enzyme activities and regional and global ejection fractions were analysed with unpaired *t* tests. The conventional 5% level of statistical significance was adopted as standard.

Results

Study population—Fifty consecutive patients (41 men and nine women) with a mean age of 59 (range 42-71) were studied. Twenty three had anterior infarction and 27 inferior infarction. Treatment was started at a mean of 135 minutes after the onset of pain (range 20-240 minutes). In 20 patients treatment was started outside hospital by the mobile coronary care unit staff.

Reperfusion rates—Coronary artery patency (conventionally taken as TIMI grade 2 or 3) was seen in 14 out of 17 patients (82%) who received 100 mg, in 12 out of 17 (71%) who received 50 mg, and in eight out of 16 (50%) who received 20 mg ($\chi^2=4.04$, $p>0.05$) (table I). There was no statistical difference in patency rates after the 50 mg and 100 mg doses (difference in proportions=11.8%, SE=14.5%, 95% confidence interval -17.2% to 40.8%). The overall reperfusion rate (grades 2 and 3) for patients treated up to 120 minutes after the onset of pain was 81% regardless of dose (10/10 receiving 100 mg, 5/5 receiving 50 mg, and 6/11 receiving 20 mg) and was significantly better than for those treated between 121 and 240 minutes—that is, 54% (4/7 receiving 100 mg, 7/12 receiving 50 mg, and 2/5 receiving 20 mg) ($\chi^2=4.058$, $p<0.05$) (table II).

TABLE I—Reperfusion grades in the affected artery after tissue plasminogen activator according to dose

Reperfusion grade	Dose of tissue plasminogen activator			Total
	20 mg	50 mg	100 mg	
0	4	4	1	9
1	4	1	2	7
2	3	5	4	12
3	5	7	10	22
Total	16	17	17	50

$\chi^2=6.22$; df=6, $p>0.05$.

TABLE II—Patency rate in affected coronary artery by time from onset of symptoms to start of tissue plasminogen activator infusion

Time (min)	Patients with reperfusion grades		Patency rate %
	0 and 1	2 and 3	
0-60	0	5	100
61-120	5	16	76
121-180	6	6	50
181-240	5	7	58
Total	16	34	

* $p<0.05$

Clotting factors—The reduction in serum fibrinogen concentration was dose related (figure, table III). It fell to a mean of 86.3% (SD 14.9) after 20 mg, to 75.1 (14.1) after 50 mg, and to 62.8 (20.6) after 100 mg when assessed at 90 minutes after the start of infusion ($p=0.001$). There were similar dose dependent changes in plasminogen, α_2 antiplasmin, and total fibrinogen and fibrin degradation products (table III).

Subsequent management—After the initial infusion 41 patients received a further 50 mg tissue plasminogen activator over the next five hours followed

by intravenous heparin in an effort to maintain patency of the affected vessel. To improve patency in a vessel with grade 0 or 1 reperfusion seven patients received 50 mg tissue plasminogen activator over one hour followed by intravenous heparin. Three patients underwent mechanical probing of the affected artery, and eight received nitrates infused directly into the narrowed coronary artery. Ten patients underwent acute percutaneous transluminal coronary angioplasty because of residual stenosis of 85% or more in the affected vessel, and a further two underwent elective percutaneous transluminal coronary angioplasty during their stay in hospital. Twelve patients required coronary artery bypass grafting (10 of whom had severe three vessel disease), one as an emergency because of the severity of his coronary artery disease.

Cardiac enzyme activities—All patients had abnormal cardiac enzyme values. Patients undergoing direct current conversion or further acute revascularisation procedures were excluded from enzyme analysis. There was no difference in mean peak creatine kinase or creatine kinase MB values between patients with grade 0 or 1 reperfusion (total creatine kinase 2541 (SEM 278) U/l and MB isoenzyme 290 (32) U/l) and those with grade 2 or 3 reperfusion (2187 (405) U/l and 212 (39) U/l).

Left ventricular function—Gated blood pool scans were carried out a mean of 46 hours after the onset of pain. Global and infarct related regional third ejection fractions were calculated using the left anterior oblique 45° view. Patients undergoing other acute reperfusion treatment—acute percutaneous transluminal coronary angioplasty, coronary artery probing, intracoronary nitrates, or coronary artery grafting—were excluded from the analysis of ejection fraction. There was no difference in mean global left ventricular ejection fraction between patients with grade 2 or 3 reperfusion (48% SEM 3.7%) and those with grade 0 or 1 reperfusion (41% (3.7%)) (table IV). Infarct related regional third ejection fraction for patients with grade 2

TABLE IV—Mean global left ventricular ejection fraction and infarct related regional third ejection fraction for patients with grade 2 or 3 reperfusion compared with those with grade 0 or 1*

	Reperfusion grade	
	2 or 3 (n=20)	0 or 1 (n=8)
No with affected artery:		
Left anterior descending coronary artery	7	5
Right coronary artery	10	2
Circumflex coronary artery	3	1
Mean global left ventricular ejection fraction (%)	48	41
Mean regional third ejection fraction (%)	46	35

*Patients undergoing additional acute reperfusion treatment resulting in change in patency from grade at 90 minutes were excluded.

or 3 reperfusion was 46 (3.6%) compared with 35 (4.7%) for patients with grade 0 or 1 reperfusion ($0.05 < p < 0.1$). This statistical result was based on the assumption that reperfusion may result in either improvement or deterioration of regional ejection fraction. Assuming, as is likely, that regional ejection fraction can only improve after reperfusion then the observed difference can be declared to be statistically significant on the basis of a one tailed *t* test ($p < 0.05$).

Arrhythmias—At the start of recombinant tissue plasminogen activator treatment all patients were in sinus rhythm, although three had had third degree atrioventricular block when first seen. Twenty patients had one or more arrhythmias during the 90 minute infusion. Four patients developed ventricular fibrillation during the infusion (one during cardiac catheterisation): three of the four had grade 1 and one had grade 2 reperfusion. Two patients had idioventricular rhythm, two had self terminating ventricular tachycardia (five or more consecutive ventricular extrasystoles), six had runs of ventricular bigeminy, two had atrial fibrillation (self terminating), one had transient 2:1 atrioventricular block, three had nodal rhythm (two nodal bradycardia, one nodal tachycardia), and two had sinus bradycardia. Among the seven patients who received 50 mg tissue plasminogen activator for a further hour after the initial infusion one patient developed idioventricular rhythm and nodal rhythm during the extra hour. Among the 41 patients who received 50 mg for a further five hours two patients developed ventricular fibrillation (one grade 2 and one grade 3 reperfusion), nine had idioventricular rhythm, and six had self terminating ventricular tachycardia during this extra period. There was no late persistent ventricular tachycardia or late ventricular fibrillation during the stay in hospital.

Complications in hospital—Four patients developed pericarditis during their stay in hospital. One had grade 3, one grade 2, and one who also had exacerbation of renal failure, had grade 1; the fourth patient had grade 2 reperfusion at 90 minutes but suffered reocclusion and then developed pericarditis. Ten patients had clinical or radiological evidence (or both) of left ventricular failure after tissue plasminogen activator during their stay in hospital: the worst Killip class after tissue plasminogen activator was class I in one patient, class 2 in five, and class 4 in four. Throughout their stay in hospital bleeding complications were mild. One patient with unsuspected polycystic renal disease bled into a renal cyst while receiving heparin and required transfusion with one unit of packed cells. One patient with gross pulmonary oedema had haemoptysis, one had bloody diarrhoea, and 15 had cutaneous bruising at the catheterisation or venepuncture sites, or both. Reocclusion was suspected clinically in five patients. All five underwent repeat angiography, which confirmed reocclusion in three. Four patients died, all from cardiac causes: three from cardiogenic shock and one from renal failure complicating cardiogenic shock. Two of these four had had an anterior myocardial infarction and two an inferior myocardial infarction, and three of the four had severe disease with either total occlusion or high grade lesions in both the circumflex and left anterior descending coronary arteries. Two patients had had grade 0 reperfusion at 90 minutes, one grade 2, and one grade 3: the last patient had angiographically proved reocclusion two days after tissue plasminogen activator. Three of the four patients came to necropsy and all had extensive myocardial damage.

Discussion

The primary end points of this dose ranging study were the reperfusion grade of the affected coronary artery and the change in the fibrinolytic system at the end of the 90 minute infusion.

Reperfusion rates were higher after the two larger doses—100 mg and 50 mg. Although the reperfusion rates after these doses were not significantly different from those after the 20 mg dose, the

Percentage fibrinogen remaining after 20, 50, and 100 mg doses of tissue plasminogen activator.

TABLE III—Twenty four hour clotting factor profiles for the three doses of tissue plasminogen activator. Results are means (SD)

	Time (h)	Dose over 90 minutes			p Value
		20 mg	50 mg	100 mg	
% Fibrinogen remaining	1.5	86.3 (14.92)	75.1 (14.12)	62.8 (20.61)	0.001
	4	91.8 (15.30)	73.6 (18.70)	60.4 (18.05)	
	24	107.6 (23.10)	90.3 (27.59)	69.9 (21.37)	
% Plasminogen remaining	1.5	85.4 (6.85)	73.3 (13.35)	72.4 (6.92)	0.001
	4	83.4 (8.37)	75.0 (13.80)	73.1 (6.12)	
	24	87.8 (11.53)	75.1 (12.46)	74.9 (13.42)	
% α_2 Antiplasmin remaining	1.5	65.1 (10.13)	36.9 (15.86)	24.5 (11.28)	0.0001
	4	50.8 (17.51)	30.9 (19.99)	22.4 (15.47)	
	24	72.5 (12.48)	57.5 (13.50)	54.2 (13.14)	
Total degradation products (mg/l)	0	0.71 (0.21)	0.86 (0.48)	0.69 (0.43)	
	1.5	1.90 (1.08)	5.45 (4.55)	8.32 (11.35)	0.046
	4	2.77 (1.67)	7.41 (4.99)	6.81 (4.99)	
	24	1.51 (1.52)	1.86 (1.81)	2.48 (3.69)	
Fibrinogen degradation products (mg/l)	0	0.55 (0.13)	0.56 (0.11)	0.55 (0.14)	
	1.5	0.81 (0.41)	1.93 (1.31)	2.51 (3.10)	0.05
	4	1.13 (0.49)	2.23 (1.25)	2.81 (2.60)	
	24	0.81 (0.62)	0.85 (0.73)	1.13 (1.15)	
Fibrin degradation products (mg/l)	0	0.51 (0.03)	0.59 (0.24)	0.53 (0.12)	
	1.5	1.15 (0.85)	3.49 (3.20)	5.48 (8.40)	0.07
	4	1.93 (1.47)	5.01 (3.71)	3.96 (3.18)	
	24	0.87 (0.73)	1.02 (0.74)	1.43 (2.04)	

difference was clinically important enough for us to discontinue use of the 20 mg dose. For patients receiving 100 mg the patency rate (grade 2 or 3) was 82%. This compares favourably with reported reperfusion grades of 61-62%^{5,6} for tissue plasminogen activator and 31% for streptokinase⁶ when patients had coronary arteriography 90 minutes after the start of the infusion. For patients treated within two hours of the onset of symptoms the overall reperfusion rate (grade 2 or 3) was 81% regardless of dose compared with 54% for those treated in the third and fourth hours after the onset of symptoms.

These results support the view that thrombolytic treatment should be started as soon as possible after the onset of symptoms.⁷ The absence of data on the pretreatment grade of the affected artery may have resulted in our reperfusion rates being falsely high, but acquiring such baseline data would have delayed the start of treatment. As all patients in this dose ranging study had abnormal cardiac enzyme activities, the incidence of subtotal occlusion must have been low.

Blood clotting factor measurements showed that the upset in the fibrinolytic system was dose dependent. The reduction in serum fibrinogen values and rise in fibrinogen derived degradation products indicate the relative but not absolute clot specificity of tissue plasminogen activator. Nevertheless, the maximum reduction in fibrinogen concentration seen after the 100 mg infusion (to 63%) compared favourably with a fall to 7% of the preinfusion values after streptokinase.⁸

Even with the upset in fibrinolysis after the 100 mg infusion over 90 minutes, the incidence of bleeding in hospital was low and confined mainly to vascular access sites. Scrupulous care with these sites after catheterisation and venepuncture and retention of the catheterisation sheath while thrombolytic treatment is being continued produce a low incidence of cutaneous bruising. We also think that the low incidence of haemorrhagic complications was related to the strict application of the exclusion criteria. The one patient who required transfusion had polycystic renal disease, which would have precluded thrombolytic treatment had we known of it before starting treatment.

The lower creatine kinase and creatine kinase MB isoenzyme values in patients with successful reperfusion suggest limitation of myocardial damage with successful reperfusion. The accuracy of this assumption is, however, limited by the change in enzyme profile which occurs after successful reperfusion⁹ and by the absence of complete enzyme data in two of the four patients who died. In this study, where gated blood pool scans were carried out on average 46 hours after the onset of pain, there was no significant difference in global left ventricular ejection fraction between those with grade 2 or 3 reperfusion (48%) and those with grade 0 or 1 reperfusion (41%). The infarct related regional third ejection fraction for patients with grade 2 or 3 reperfusion was 46% compared with 35% for those with grade 0 or 1 reperfusion, and this difference was statistically significant on the basis of a one tailed *t* test. There were more right coronary artery and circumflex lesions among those with grade 2 or 3 reperfusion than among those with grade 0 or 1 reperfusion, but comparisons are difficult because of the small numbers of patients with grade 0 or 1 reperfusion.

The reocclusion rate of 6% in hospital is low and compares favourably with figures of up to 45% quoted in other studies of intravenous tissue plasminogen activator.¹⁰ The short half life of tissue plasminogen activator increases the theoretical risk of reocclusion. The low incidence of reocclusion we reported may have been due to the use of a low dose infusion over five hours after the initial infusion in most of our patients, the rationale for which is based on studies in dogs¹¹ and in humans.¹⁰

Reports on the benefit of percutaneous transluminal angioplasty immediately after thrombolysis are conflicting.^{12,13} Angioplasty was considered to be feasible and necessary in the acute phase in only 10 of these 50 patients, in all of whom either the lesions in their arteries were thought to be at high risk of reocclusion or thrombolytic treatment had failed. The procedure was successful in five (reduction in gradient or improvement in angiographic appearances, or both). The commonest reason for failure of the procedure was inability to cross the residual lesion. Angioplasty in patients with

residual thrombus partially occluding the lumen was associated with a high incidence of complications; two of these patients underwent reocclusion at the time of angioplasty and a further patient reoccluded two days after the procedure. Our results suggest that acute percutaneous transluminal coronary angioplasty in patients with residual thrombus is of limited value. In contrast, both patients who underwent elective angioplasty did so successfully. Thus seven patients underwent successful angioplasty, and this may be an additional factor in our low reocclusion rate.

Six patients developed ventricular fibrillation during either the initial infusion or the subsequent low dose infusion. This incidence is no higher than that occurring in patients seen in the same time period who do not receive thrombolytic treatment. This suggests that reperfusion is gradual rather than sudden. Only four patients developed pericarditis, and no patients developed late sustained ventricular tachycardia or late ventricular fibrillation. This suggests that reperfusion limits the infarct size and therefore the potential for late arrhythmias. All four patients who died had extensive myocardial damage and all died from cardiac causes. No death was attributable to thrombolytic therapy.

Recombinant tissue plasminogen activator is an effective thrombolytic agent when used early in patients with acute myocardial infarction. Reperfusion grades are better when the 50 and 100 mg doses are infused intravenously over 90 minutes, but beginning treatment early allows high reperfusion rates, even when using the 20 mg dose. The effect on the systemic fibrinolytic system is mild and dose dependent but even with the highest doses used bleeding complications are minimal provided scrupulous care is taken with vascular access sites and patients are carefully screened for potential bleeding diatheses. There is improvement in the left ventricular global ejection fraction, particularly in the infarct related regional third ejection fraction, for those with grade 2 or 3 reperfusion when compared with those with grade 0 or 1 reperfusion. The incidence of arrhythmias after treatment is similar to that in patients with acute myocardial infarction who do not receive thrombolytic therapy.

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