A pilot study of the efficacy and safety of bolus administration of alteplase in acute myocardial infarction

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Abstract

Objective—To examine the efficacy, safety, and the pharmacokinetic profile of a bolus dose administration regimen of alteplase in the treatment of acute myocardial infarction.

Design—An open pilot study.

Setting—District general hospital.

Patients—33 suitable consecutive patients presenting within six hours of the onset of symptoms who satisfied the electrocardiographic criteria for acute myocardial infarction.

Interventions—Two intravenous boluses of 35 mg alteplase, 30 minutes apart.

Main outcome measures—Angiographic coronary patency at 90 minutes and 24 hours. Plasma alteplase concentration-time profile and pharmacokinetic analysis.

Results—Coronary patency at 90 minutes: 26 of 30 arteries (87%, 95% confidence interval (CI) 74–99%). Coronary patency at 24 hours: 24 of 29 arteries (83%, CI 69–97%). Mean (SD) plasma tissue plasminogen activator (t-PA) concentration reached 4434.8 (2117.8) and 4233.3 (2217.5) ng/ml within 10 minutes of each bolus and fell to 425.8 (288.3) ng/ml between boluses. The estimated peak concentrations at two minutes after boluses were 12 389 (8580) ng/ml and 10 811 (6802) ng/ml. The derived pharmacokinetic variables were volume of distribution 3.11 (1.89) l, clearance 21.3 (9.3) l/h, half life 5.9 (1.7) minutes.

Conclusions—This simple administration regimen achieved brief, high concentrations of plasma t-PA that were well tolerated. The regimen was associated with a high coronary patency rate at 90 minutes that was well maintained at 24 hours.

Thrombolytic therapy is now accepted as a standard treatment for acute myocardial infarction because studies have shown that it improves left ventricular function and reduces mortality.¹⁻⁴ The benefit of thrombolysis is improved by early treatment^{2,5} and the re-establishment of coronary patency. Therefore, the ideal thrombolytic agent should be easily and rapidly administered by the intravenous route and should effectively and rapidly restore

coronary patency without adverse side effects. The ease of administration of the agent becomes increasingly important with the emphasis on immediate treatment on arrival in hospital and the possibility of starting treatment in the community.

Alteplase (recombinant tissue plasminogen activator) is successful in restoring coronary patency,⁶⁻¹¹ with higher patency rates than a conventional dose of intravenous streptokinase.^{6,7} At present, the recommended dosage regimen for alteplase is a 10 mg bolus, with a tapering dose of 90 mg infused over three hours. This regimen was based on the apparent short half life of alteplase in the circulation,¹² but clearly this regimen is a cumbersome one to apply urgently.

We assessed the efficacy of two boluses of 35 mg alteplase administered intravenously 30 minutes apart in achieving angiographic coronary patency. We also studied the pharmacokinetics of this regimen.

Patients and methods

Thirty three consecutive patients (23 men and 10 women, age range 40–74, mean age 56.3 years) were admitted to Stobhill Hospital coronary care unit and recruited into the study. Patients were eligible for inclusion if they presented with chest pain of at least 30 minutes' duration, could be treated within six hours of the onset of symptoms, and had electrocardiographic evidence of acute myocardial infarction (ST elevation >1 mm in two limb leads or >2 mm in two precordial leads). Patients were excluded if they were over 75 years of age, had a previous infarct in the same anatomical distribution, or had any of the recognised contraindications to thrombolytic therapy⁶ or coronary angiography. The study protocol was approved by the local research and ethics committee.

Table 1 shows the baseline characteristics of the patients recruited. After the patients had given their written informed consent and the protocol had been discussed with accompanying relatives, the patients were given 35 mg alteplase intravenously over 30 seconds. This dose was repeated 30 minutes later. All patients received 150 mg aspirin orally immediately on entry to the study and daily thereafter. All patients were given an intravenous infusion of glyceryl trinitrate

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Table 1 Details of study population

Data	Result
Total	33
Sex:	
Male	23
Female	10
Mean age (yr)	56.3 (10.5)
Infarct related artery:	
LAD	12
RCA	15
LMCA	1
Cx	2
Angiography not performed	3
Mean (SD) time to therapy	208 (75) min
Mean (SD) time to first angiographic injection	49.4 (13.3) min
Mean weight	73.2 (12.8) kg
Dose of alteplase administered	70 mg
Mean dose of alteplase administered	0.984 (0.173) mg/kg

Cx, circumflex; LAD, left anterior descending; LMCA, left main coronary artery; RCA, right coronary artery.

starting at 0.25 mg/h unless there was a specific contraindication.

Coronary angiography was performed in the coronary care unit with an image intensifier (Siremobil 2N/2H) linked to a video tape recorder (JVC CR8200E). Details of this system have been described elsewhere.¹³ The Seldinger percutaneous approach was used and a femoral sheath was left in situ. The coronary angiogram was started immediately after the second bolus of alteplase (30 minutes after the first bolus), and the infarct related coronary artery (as indicated by the admission electrocardiogram) was visualised as soon as possible after 30 minutes, then by selective injections at 60 and 90 minutes. The degree of perfusion was scored according to the Thrombolysis in Myocardial Infarction (TIMI) scale and reviewed by an independent experienced cardiologist: a score of 0–1 indicated non-patency and one of 2–3 indicated a patent artery.⁶

If the artery was occluded at 90 minutes, the study protocol allowed additional treatment to be given up to the total dose of 100 mg alteplase, as recommended by the product licence. The other coronary arteries were visualised in standard angiographic projections. The femoral sheath was left in situ and coronary angiography was repeated at 24 (8) hours after treatment to assess patency and reocclusion.

An intravenous heparin infusion was started in all patients 3–4 hours after onset of treatment, and the dose was titrated against the thrombin time to a therapeutic ratio of 2:3. No bolus of heparin was given at the start of alteplase treatment. In all patients heparin was stopped for a short period at the time of the second angiogram to allow removal of the

femoral sheath. Venous blood samples were collected via an indwelling venous catheter from the first 24 patients before treatment, and then 10, 20, 30, 40, 50, 60 minutes and 2, 4, 8, 12, 24 hours after the first bolus of alteplase, into sodium citrate. The samples were centrifuged immediately at 0°C, separated, and frozen at –40°C. Subsequent analysis for antigen was performed by an enzyme linked immunosorbent assay (ELISA).

Results

ANGIOGRAPHIC PATENCY

The infarct related artery was first visualised at 49.4 (13.3) minutes after the first bolus of alteplase. The artery was visualised within 55 minutes in 26 of 30 (86%) patients. In three patients an acute angiogram was not obtained: in one because of haemodynamic instability, in one because of death before 90 minutes, and in one it was not possible to inject the right coronary artery.

In three patients, although the entry criteria were satisfied, the serial electrocardiographic changes of acute myocardial infarction did not occur and cardiac enzymes were normal. In one of these patients the right coronary artery could not be visualised and this patient is not included in the angiographic data. In all other patients angiographic data were obtained within 90 minutes of start of treatment and the results presented are the patency rates of all patients in whom coronary visualisation was achieved at each time point. At the first injection of the infarct-related artery (49.4 (13.3) mins) 23 of 30 (77%, 95% confidence interval (CI) 61 to 92%) arteries were patent. At 90 minutes this had increased to 26 of 30 (87%, 95% CI 74 to 99%) arteries (table 2).

Two patients were given a further intra-coronary dose of 30 mg alteplase after the 90 minute angiogram. In one there was intermittent reperfusion of the index artery during the period of angiographic observation. In the other, after occlusion of the left main coronary artery, there was penetration only of the circumflex at 90 minutes. In both patients, the arteries were patent at the 24 hour angiogram.

One patient did not undergo the 24 hour angiogram because of haematoma formation after splitting of the femoral sheath. At 24 hours, 24 of 29 arteries (83%, 95% CI 69 to 97%) were patent. Seven patients improved their angiographic appearance by at least one grade, with three achieving reperfusion. However, five deteriorated at least one grade with three arteries becoming reoccluded (10%, 95% CI 0 to 22%).

ADVERSE EVENTS

The only adverse events documented in our study group were bleeding complications. In five patients significant haematomata developed at the site of arterial access for coronary angiography. Two patients suffered minor coffee-ground haematemesis and one other bled from the gums. No patient required a blood transfusion or specific intervention.

One patient died during the study. This

Table 2 Angiographic details

	Number of patients			
	TIMI grade	First injection 49.4 (13.3) min	90 min	24-h
Non-patent	0	5	3	2
	1	2	1	3
Patent	2	15	18	10
	3	8	8	14
Reoccluded	—	—	0	0
Angiography not performed	—	3	3	4

Figure Plasma t-PA concentrations (mean (SD)) after two intravenous boluses of 35 mg alteplase.

patient had severe triple vessel disease and a previous myocardial infarction. Shortly after admission and treatment cardiogenic shock developed and he died despite inotropic support.

PLASMA t-PA CONCENTRATIONS

The mean (SD) pretreatment plasma t-PA concentration (20.1 (4.3) ng/ml) was significantly higher than our laboratory normal (3.6 (1.3) ng/ml). It rose to 4434.8 (2117.8) ng/ml within ten minutes of the first bolus of alteplase, fell to 425.8 (288.3) ng/ml before the second bolus, and rose again to a peak of 4233.3 (2217.5) ng/ml within 10 minutes of the second bolus (figure). Mean concentrations then fell rapidly and at four hours were about twice the pretreatment values (40.6 (28.6) ng/ml). After this t-PA concentrations were low, variable, and at approximately physiological values. This introduced considerable random variation in the pharmacokinetic fitting; therefore the data fitted were the baseline-subtracted concentrations confined to the four hour period after the administration of alteplase. This approach was adopted by others.^{12,14}

The individual declines in t-PA concentration were fitted to one, two, and three compartment pharmacokinetic models, but a satisfactory fit was obtained only with the one compartment model. The pharmacokinetic results derived from this model were volume of distribution 3.11 (1.89) l (coefficient of variation (CV) 35.6 (26.7)%), clearance 21.3 (9.3) l/h (CV 14.1 (11.7)%) and half life 5.9 (1.7) min. The coefficients of variation are means (SD) of the coefficients of variation of the individual fitted data and express the quality of fit of the model (table 3). Using this model we estimated the plasma t-PA concentrations two minutes after the beginning of the intravenous boluses of alteplase, as a measure of the peak concentra-

tions achieved with this administration regimen. The peak concentration was 12 389 (8580) ng/ml two minutes after the first bolus and 10 811 (6802) ng/ml after the second bolus of alteplase.

Discussion

Our results show that a regimen of alteplase administered intravenously as two boluses of 35 mg at an interval of 30 minutes is effective in restoring coronary artery patency in acute myocardial infarction. To allow comparison with other patency studies, our primary end point of efficacy was patency at 90 minutes after treatment, but in addition we have angiograms earlier in the course of treatment to assess the time to reperfusion. At the time of first injection, at a mean of 49 minutes after treatment, 77% of our patients had patent index coronary arteries; this improved to 87% within 90 minutes, showing that patency is achieved rapidly and effectively.

Direct comparison with other studies of recombinant tissue-type plasminogen activator (r-tPA) is difficult because of several confounding factors. Other studies used different administration regimens with widely varying doses of two different preparations of r-tPA, with different specific activities.^{15,16} In addition, whereas some workers studied patency others studied reperfusion, with a difference owing to sub-total coronary occlusion at presentation and spontaneous reperfusion.¹⁷

Verstraete and coworkers showed patency rates of 61% at 75–90 minutes after treatment using 0.75 mg/kg of double chain rt-PA over 90 minutes.¹¹ The same group using a 40 mg infusion of double chain rt-PA over 90 minutes achieved a coronary patency rate of 66% at 90 minutes.¹⁸ Topol and the TAMI group achieved a patency rate of 68% with 70 mg of rt-PA over 90 minutes and one of 79% with a high dose (1.5 mg/kg) of alteplase over four hours in conjunction with a high dose of heparin.^{19–21} In TIMI I workers used 80 mg of double chain rt-PA over three hours and found a reperfusion rate of 56%.^{6,7} Williams *et al* used the same dose of 80 mg over three hours and found a similar reperfusion rate of 68%.⁸

Published reports of studies of bolus doses of alteplase are limited. Verstraete *et al* using single boluses of alteplase found that doses of 60 mg and 50 mg were associated with reperfusion rates at 90 minutes of 32% and 45% respectively, although a maximum dose of 70 mg achieved reperfusion in 72%.²² Khan *et al* evaluated four boluses of double-chain t-PA of 25 mg given over 60 minutes and showed recanalisation in 11 of 14 patients; they suggested that this regimen achieves coronary patency more rapidly.²³ In our study, 70 mg divided into two boluses also achieved a high patency rate, and would be expected to be associated with fewer bleeding complications.²⁴

In a recent small study Smalling *et al*, used rapid intravenous infusion of a weight adjusted dose of alteplase, and a median dose of 145 mg. They reported a 90 minute patency rate of 84%, which was significantly higher than the

Table 3 Pharmacokinetic variables

Variable	Mean	SD
Clearance (l/h)	21.4	9.3
Coefficient of variation of estimates of clearance (%)	14.1	11.7
Volume of distribution (l)	3.11	1.89
Coefficient of variation of estimates of volume (%)	35.6	26.7
Half life (min)	5.9	1.7

control group who received a conventional three hour infusion of 100 mg.²⁵ These results suggest that rapid administration of the thrombolytic agent achieves higher patency, and that it is the peak concentration of agent achieved that is important—an inference supported by our data.

The reported higher patency rates were achieved with higher weight adjusted doses of rt-PA. In our study the total dose of 70 mg alteplase represents a mean dose of 0.98 mg/kg. This contrasts with 1.5 mg/kg administered by Topol *et al*²⁰ and the fixed doses of 150 mg used in the TIMI II study²⁴ or 100 mg used in the Australian National Heart Foundation Study.²⁶ The 100 mg dose is recommended by the manufacturers²⁷ and is now in regular use. Despite the lower dose we used, our patency rate of 87% at 90 minutes compares favourably with the published data.

Pharmacokinetic analysis of the plasma t-PA concentration-time profile after this bolus administration regimen of alteplase shows that very high, short lived concentrations of t-PA are achieved shortly after injection of the drug. The concentration of t-PA achieved at 10 minutes (4434.8 (2117.8) ng/ml) is 34% higher than the peak concentration attained by Seifried *et al*, with 100 mg of single chain rt-PA delivered as a 10 mg bolus and 90 minute tapered infusion.¹⁴ We found t-PA concentrations in excess of 2 300 ng/ml in all our patients and predicted concentrations two minutes after the boluses of alteplase in excess of 10 000 ng/ml. As would be expected, the period during which t-PA concentration was in excess of 1000 ng/ml is shorter with bolus administration than with prolonged infusion.

Despite the short duration of high plasma t-PA concentrations the reocclusion rate to 24 hours of three of 29 patients (10%) resembles previous experience.¹⁸

Our patients' pretreatment t-PA concentrations were raised, but 4–8 hours after alteplase concentrations fell to physiological values. After four hours in all patients, t-PA concentrations were low and variable, making fitting to pharmacokinetic models difficult. To eradicate this variable, we fitted the data for the first four hours only and used baseline-subtracted values. Despite taking frequent blood samples we were unable to define multiple phases of elimination, unlike others. Our data fitted our chosen model satisfactorily, as reflected in low standard deviations for each individually fitted variable. These individual standard deviations were expressed as coefficients of variation (CV) of their respective estimated variable and the CVs expressed as the mean. The mean CV of the estimate of mean clearance was 14% and that of the estimate of mean volume of distribution 36%, which indicates that the estimate of these mean variables was reliable. Previous studies have not reported details of the quality of fit of their models and therefore of the reliance that can be placed on their estimations.^{12,14}

Our findings confirm the rapid clearance of t-PA from the circulation, with a half life of 5.9 (1.7) minutes and modest inter-patient

variability. These closely correlate with previous reports in patients, although they are somewhat slower than findings in normal volunteers with a lower total dose—possibly reflecting diminished cardiac output and hepatic blood flow in our patients with myocardial infarction. Our estimate of volume of distribution of 3.1 (1.9) l is very similar to previous estimates in both patients and volunteers.

Some workers have found a dose related rise in bleeding complications, in particular intracranial bleeding.²⁴ In our study, using a relatively small dose of alteplase, we saw bleeding complications in eight (24%) of 33, with five of these being related to arterial access for coronary angiography; there were three episodes of minor gastrointestinal bleeding (9%). No patients required transfusion or specific intervention. These results are similar to previously published data,^{6,9,10} but our small study numbers do not allow firm conclusions to be drawn.

Our findings show that alteplase administered as two intravenous boluses of 35 mg 30 minutes apart reliably produced very high concentrations of t-PA in the plasma, which was rapidly cleared from the circulation and allowed a high coronary patency rate in acute myocardial infarction. The total dose administered was less than that used in many studies reporting high patency, yet reocclusion rates were similar to those reported before. The greater simplicity of administration and higher efficacy of this regimen may allow alteplase treatment to be safely started before admission to hospital with the advantages that such earlier administration would give.

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