Safety and efficacy of repeat thrombolytic treatment after acute myocardial infarction

Harvey D White, David B Cross, Barbara F Williams, Robin M Norris

Abstract
Thrombolytic treatment for acute myocardial infarction increases the risk of subsequent reocclusion of the infarct related artery. The efficacy and safety of repeat thrombolytic treatment was assessed in 31 patients treated with streptokinase (n = 13) or tissue plasminogen activator (n = 18) a median of five days (1-716) after the first infusion. The indication for readministration was prolonged chest pain with new ST segment elevation. Efficacy was assessed by infarct artery patency at angiography at a median of eight days after readministration in 22 patients and by non-invasive criteria in 23 patients (reperfusion was deemed to be likely if serum creatine kinase was not increased or reached a peak <12 hours after infarction). Angiography showed patency of 70% of the infarct arteries after readministration of streptokinase and of 75% after tissue plasminogen activator. The corresponding patency rates assessed non-invasively were 73% and 75%. Reinfarction was prevented in nine (29%) patients. Allergic reactions occurred in four of eight patients who received streptokinase twice (plasmacytosis and acute reversible renal failure developed in one patient). Two patients had major bleeding and two minor bleeding, all after tissue plasminogen activator, and one of them died of cerebral haemorrhage.

Repeat thrombolytic treatment results in late patency rates similar to the rates after the initial administration. Allergic reactions were common in those treated twice with streptokinase.

Thrombolysis is now used widely in acute myocardial infarction to reduce mortality and to preserve left ventricular function. Results of a coronary thrombus, however, results in an infarct related coronary artery with an unstable endothelial lesion and often residual thrombus. Angiographic studies showed a rate of about 20% for early reocclusion after thrombolysis. Reinfarction is associated with further myocardial damage and mortality. Though angioplasty seemed to be an attractive approach to preventing reocclusion, four studies showed no reduction of reinfarction. Aspirin treatment has been clearly shown to reduce reinfarction but even so reinfarction occurs in approximately 2% of patients. Another approach is to repeat thrombolytic treatment, either with the same or a different agent, if acute coronary thrombosis recurs.

The benefits of repeat thrombolytic treatment for threatened reinfarction may resemble those of the initial administration, but the risks and benefits have not been well described. We report the results of repeat thrombolytic treatment in 31 patients with threatened reinfarction.

Patients and methods
We studied 31 patients (22 men and nine women, mean (SD) age 58 (9) years) who had all been treated with intravenous thrombolysis for acute myocardial infarction. Indications for initial thrombolysis included ischaemic chest pain lasting more than 30 minutes with onset less than six hours before thrombolytic treatment and associated ST segment elevation of >1 mm in two limb leads or V4–V6 or >2 mm in leads V1–V3. The initial thrombolytic treatment was an infusion of streptokinase 1-5 million units intravenously over 30 minutes in 23 patients and of recombinant tissue plasminogen activator 100 mg intravenously over three hours in eight patients. In all four patients with aspirin (50–300 mg per day) was started on admission to the coronary care unit and 12 patients were also given dipyridamole (400 mg daily). Heparin was given intravenously for at least 48 hours in 19 patients, with dose adjustment to maintain the activated partial thromboplastin time between 90 and 110 seconds. Treatment with oral β blockers was started within three days of admission in patients without contraindications. One patient underwent angioplasty of a severe stenosis of the left anterior descending coronary artery seven days after initial thrombolysis and three days before readministration.

STUDY PROTOCOL
Thrombolysis was repeated in patients in whom recurrent ischaemic pain lasting >30 minutes developed despite nitrate treatment and who fulfilled the criteria for ST segment elevation described above. Patients were given the same dose of either streptokinase or tissue plasminogen activator as was used for the initial treatment. All patients were treated by thrombolysis within six hours of the onset of the second episode of pain. The physician chose the thrombolytic agent; though strep-
tokinase was generally avoided between seven
days and three months after initial streptokinase
treatment and in patients with allergic
reactions to their first dose of streptokinase.
Steroids or antihistamines were not routinely
administered before repeat streptokinase
treatment, but one patient did receive intra-
venous hydrocortisone before readministra-
tion. Concomitant treatment was similar to
that during the initial administration; all
patients were given aspirin and most were
given intravenous heparin.

All patients were observed closely for
evidence of allergic reactions or hypotension,
and any bleeding was noted. Serum concen-
trations of creatine kinase were measured at
least every four hours for the first 24 hours.
Coronary arteriography was performed in
survivors unless the coronary anatomy had
already been defined. Coronary arteriography
and left ventriculography were performed by
the Judkins technique. The infarct related
artery was identified by correlation of the
coronary arteriogram with the electrocar-
diogram and wall motion abnormalities on
biplane left ventriculography. The coronary
arteries were viewed in multiple projections.
The patency of the infarct related artery was
coded according to the TIMI criteria.11

The time course of creatine kinase release
from the onset of thrombolytic treatment was
used as a non-invasive marker of early reper-
fusion. Patients with either no increase in
serum creatine kinase or with an early peak of
creatine kinase after thrombolytic treatment
(<9 or <12 hours) were considered likely to
have achieved reperfusion,12 though we have
no independent validation of the specificity or
sensitivity of these indices.

We excluded from the enzyme analysis
patients in whom sampling was inadequate for
reliable timing of the enzyme peak. We also
excluded patients in whom persistence of
raised creatine kinase concentrations after the
index infarction made it difficult to time a
“hump” on the washout curve.

Results
Table 1 shows the baseline characteristics of
the study group. The threatened reinfarctions
occurred at a median of 5 (range 1–716) days
after the initial infarction. Table 2 shows the
drug treatment that patients were receiving
immediately before threatened reinfarction.
All but two patients were taking aspirin and six
patients were still receiving intravenous heparin
after the initial thrombolytic treat-
ment. The electrocardiographic changes as-
associated with the threatened reinfarction were
in the same coronary artery distribution as
initial infarction in all but one patient.

The thrombolytic agent chosen for the
repeat treatment was streptokinase in 13
patients and tissue plasminogen activator in 18.
The mean (SD) delay from the onset of pain to
readministration was 107 (63) minutes. Eight
patients received streptokinase on both
occasions. Table 3 outlines the treatment given
to each patient, the delay between initial
thrombolytic treatment and readministration,
and the results of enzyme analysis and cardiac
catheterisation.

Sampling for creatine kinase was adequate in
23 patients. One patient underwent an emer-
gency operation for stenosis of the left main
coronary artery and another underwent “res-
cue” angioplasty 2.5 hours after repeat throm-
bolysis. In five patients not enough samples
were taken between six and 18 hours after
readministration to determine the time of peak
creatine kinase, and in one patient (case 9) in
whom thrombolysis was repeated two days
after the initial treatment, creatine kinase was
still increased by the initial infarct.

Cardiac catheterisation was performed in 22
patients at a median of eight (0–63) days after
repeat thrombolysis. Four patients had died, in
four the coronary anatomy was already known,
and in one elderly patient without inducible
angina at exercise testing the physician wanted
to avoid catheterisation.

Efficacy
Table 4 summarises the results of non-invasive
assessment of reperfusion and the angiographic
assessment of infarct artery patency for the four
possible combinations of thrombolytic treat-
ment. Streptokinase achieved late angiographic
patency in 70% of patients and tissue plasmin-
gen activator achieved it in 75%. In patients
previously treated with streptokinase, re-
administration with either streptokinase or
tissue plasminogen activator resulted in similar
rates of reperfusion assessed non-invasively or
angiographically. In nine (29%) patients no
rise in cardiac enzymes ensued, implying
prevention of further myocardial necrosis.

Reperfusion assessed non-invasively and
patency at late angiography were not always
concordant. Both angiographic and enzyme
data were available in 18 patients. Three (23%)

<table>
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<th>No (%)</th>
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<td>Aspirin</td>
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<tr>
<td>Dipyridamole</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Intravenous heparin</td>
<td>6 (19)</td>
</tr>
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<td>Subcutaneous heparin</td>
<td>3 (10)</td>
</tr>
<tr>
<td>5 Blockers</td>
<td>18 (58)</td>
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<tr>
<td>Calcium antagonists</td>
<td>5 (16)</td>
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<tr>
<td>Nitrates*</td>
<td>8 (26)</td>
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*Regular oral, sublingual or transdermal, or intravenous infusion.
### Table 3: Treatment and outcome of individual patients

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<th>Patient</th>
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<th>Agent 2</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Interval (days)</th>
<th>Antithrombotic treatment</th>
<th>Peak CK on readmission (U/l)</th>
<th>Hours to peak</th>
<th>Angiographic patency of infarct artery</th>
<th>Comments</th>
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<td>SK</td>
<td>59</td>
<td>M</td>
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<td></td>
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<td></td>
</tr>
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<td>SK</td>
<td>SK</td>
<td>52</td>
<td>F</td>
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<td>M</td>
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<td>ASP</td>
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<td>ASP</td>
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<td>60</td>
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<td>4</td>
<td>ASP</td>
<td>No rise</td>
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<td>No</td>
<td></td>
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<td>rt-PA</td>
<td>63</td>
<td>M</td>
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<td>ASP, DP</td>
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<td>12</td>
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<td>72</td>
<td>F</td>
<td>23</td>
<td>ASP, HEP</td>
<td>674</td>
<td>17</td>
<td>No angiogram</td>
<td>Died early—cardiogenic shock</td>
</tr>
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</table>

*Inadequate sampling.
SK, streptokinase; rt-PA, recombinant tissue plasminogen activator (alteplase); CK, creatine kinase (normal < 300 U/l); ASP, aspirin; DP, dipyridamole; HEP, heparin.

Of 13 patients in whom enzyme analysis suggested reperfusion subsequently had an occluded infarct artery, and three of the five patients in whom enzyme analysis did not support early reperfusion subsequently had a patent infarct artery.

**ADVERSE REACTIONS**

Allergic reactions were seen in four of the eight patients who received streptokinase on two occasions. The interval between the initial and second administrations was three days in two, five days in one, and seven days in another. The four patients who did not have an allergic reaction were retreated on days 2, 8, 190, and 268. Allergic reactions were characterised by transient fever and rigors. No patients suffered bronchospasm, angio-oedema, or anaphylactic shock with readministration of streptokinase. In one patient placsmotysis and transient renal impairment subsequently developed.

No allergic reactions were seen with tissue plasminogen activator.

Transient hypotension and bradycardia were seen during thrombolytic infusion in five patients—two receiving streptokinase and three tissue plasminogen activator. All patients with significant hypotension had a threatened inferior infarction.

All important haemorrhagic complications were associated with treatment with tissue plasminogen activator. A 62 year old woman died after receiving tissue plasminogen activator for threatened reinfarction seven days after initial treatment with streptokinase. Neurological signs developed six hours after the start of treatment and necropsy showed a recent cerebellar haemorrhage. In a second patient a large groin haematoma developed at the site of arterial puncture after angioplasty three days earlier and required transfusion of 1-5 litres of blood. One patient had a single

### Table 4: Patency and reperfusion rates after repeat thrombolytic treatment

<table>
<thead>
<tr>
<th>Agent 1</th>
<th>Agent 2</th>
<th>No</th>
<th>Angiographic patency*</th>
<th>No CK rise</th>
<th>Peak CK &lt;9 h or no CK rise†</th>
<th>Peak CK &lt;12 h or no CK rise†</th>
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<tr>
<td>SK</td>
<td>SK</td>
<td>8</td>
<td>5/6</td>
<td>2/6</td>
<td>4/6</td>
<td>4/6</td>
</tr>
<tr>
<td>SK</td>
<td>rt-PA</td>
<td>15</td>
<td>5/12</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
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<td>rt-PA</td>
<td>rt-PA</td>
<td>3</td>
<td>1/2</td>
<td>1/2</td>
<td>2/3</td>
<td>2/3</td>
</tr>
<tr>
<td>rt-PA</td>
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<td>2/4</td>
<td>1/2</td>
<td>2/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>31</td>
<td>16/22 (73%)</td>
<td>9/23 (39%)</td>
<td>14/23 (61%)</td>
<td>17/23 (74%)</td>
</tr>
</tbody>
</table>

*Angiographic patency = TIMI 2 or 3 flow.
†Time from start of thrombolytic treatment.
SK, streptokinase; rt-PA, recombinant tissue plasminogen activator (alteplase); CK, creatine kinase.
Discussion

Reinfarction occurs in approximately 9% of patients during the first 12 months after thrombolytic treatment for acute infarction. It is attractive to extrapolate the substantial evidence for benefit seen with initial use of thrombolytic treatment to readministration in the event of subsequent threatened infarction, but the risks and benefits of this approach are not well defined.

Streptokinase is a foreign protein and is antigenic in humans. Possible allergic reactions were reported in 4.4% of patients treated with streptokinase in ISIS-2 and 3.4% of patients receiving streptokinase in GISSI-1.1 Anaphylactic shock occurred in 0.1% of patients treated with streptokinase in GISSI-1 and did not occur in ISIS-2.2 The use of prophylactic steroids is theoretically unlikely to be helpful.15 In ISIS-2 22% of patients received prophylactic steroids, with no reduction in the reported rate of allergic reaction.

Because most patients already have antibodies to streptokinase from previous streptococcal infections the dose needs to be greater than 1.25 million units to ensure that these antibodies are overcome.16 Neutralising antibodies sufficient to inhibit conventional doses of streptokinase develop as early as four days after administration. This titre of antibody persists in most patients tested at six months and one year17 (and D Massell, JB Gill, AGG Turpie, JA Cairns, personal communication). The relation between lytic efficacy and antibody titres is not clear. Moran et al found a discrepancy between streptokinase specific IgG measured by a radioimmunounassay technique and the functional streptokinase resistance titre in some patients.18 Even so, it seems prudent to avoid readministration of streptokinase when antibody titres are likely to be high. The presence of IgE antibodies is likely to increase the risk of immediate allergic reactions, and high IgG titres (in addition to compromising efficacy) may increase the risk of late complications such as serum sickness and Guillain-Barré syndrome, which are occasionally seen after initial treatment.19-22 It has been suggested that streptokinase resistance titres should be measured before streptokinase is readministered, and the dose increased appropriately.22 We think that such an approach is untenable because it would delay thrombolytic treatment.

Because anistreplase contains streptokinase a similar incidence of hypersensitivity reactions might be expected. In the German multicentre trial 2.5% of patients receiving anistreplase had allergic reactions24 and two of 502 patients receiving anistreplase in the AIMS Study suffered anaphylactic reactions.4 Vascularisis has also been reported after treatment with anistreplase.25

Readministration of plasminogen activators such as tissue plasminogen activator and urokinase, which are non-allergenic, is less likely to reduce efficacy and cause allergic reactions. Little is known of the risks of readministration of these agents, however, particularly of haemorrhage during the first few days after initial treatment. These agents are also more expensive than streptokinase.

This study shows that repeat thrombolysis was feasible and was as effective in restoring vessel patency and probably in limiting myocardial necrosis as the initial treatment. Efficacy was assessed by two methods. Patency of a coronary artery late after thrombolytic treatment does not necessarily indicate early patency. We found a similar high frequency of early reperfusion assessed by enzyme analysis and late arteriographic patency, but as expected there were some discrepancies. In nearly a third of patients receiving repeat thrombolytic treatment for prolonged chest pain with ST segment elevation there was no elevation of cardiac enzymes. We believe that reinfarction was prevented in these patients.

Allergic reactions were frequent when streptokinase was given twice, but these reactions were not associated with a lack of lytic efficacy. Transient hypotension was equally common during the initial and repeat infusions and was not confined to streptokinase treatment.

The role of angioplasty and coronary surgery after readministration of thrombolysis is uncertain. Trials of early angioplasty after initial thrombolysis25-26 and comparison of conservative and invasive management strategies20-26 suggest that watchful waiting is better than immediate intervention in most patients. These results clearly cannot be extrapolated to patients with threatened reinfarction. We have often offered such patients a revascularisation procedure on the assumption that a patient suffering two acute coronary events is more likely to have a third. There is no firm evidence for this approach and prospective clinical trials are required.

We believe that prompt readministration of thrombolytic treatment is appropriate in patients with threatened reinfarction and is likely to be as safe and effective as the initial treatment. In view of concerns about efficacy
and the occurrence of allergic reactions, we think that streptokinase or anistreplase should not be readministered within a year. We need more information on how common high anti-streptokinase titres are more than one year after the initial treatment.

We thank the nurses and physicians who treated the patients in this study.

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