Reports on Therapy

Improved Thrombolysis With a Modified Dose Regimen of Recombinant Tissue-Type Plasminogen Activator

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To improve further the patency rate of infarct-related coronary arteries, the following accelerated dosage regimen of recombinant tissue-type plasminogen activator (rt-PA) was administered to 80 patients with acute myocardial infarction of ≤6 h duration: 15 mg intravenous bolus, 50 mg infusion over 30 min and 35 mg infusion over the following 60 min. After coronary angiography at 90 min coronary angioplasty was performed in 16 patients and additional thrombolysis in 3 patients. Six patients were not included in the final angiographic analysis, mostly because of borderline ST segment elevations, in order to avoid overestimation of the efficacy of this dose regimen. Four of these had a patent infarct artery; no early angiogram was performed on two.

Sixty minutes after the start of infusion, 54 (74%) of 73 patients had a patent infarct-related artery (Thrombolysis in Myocardial Infarction [TIMI] grade 2 or 3) as did 67 (91%) of 74 patients at 90 min. At 24 h, 61 (92.4%) of 66 patients showed a patent infarct artery. Recurrent myocardial ischemia was noted in 12 patients, 7 (9.4%) of whom experienced reinfarction during the hospital stay. Minor local bleeding complications were observed in 14 patients (17.5%). There were four in-hospital cardiac deaths; one patient who underwent additional thrombolysis for recurrent ischemia died from bleeding complications.

These results show that a rapid infusion of 100 mg of rt-PA over 90 min yields a high early patency rate of the infarct-related artery without an increase in reocclusion rate and adverse reactions.

Methods

Study patients. Between June 1987 and June 1988, 80 patients with acute myocardial infarction diagnosed ≤6 h after symptom onset by ST elevation in at least two electrocardiographic (ECG) leads (≥1 mm in standard leads or ≥2 mm in precordial leads) and between the ages of 25 and 75 (57 ± 10) years were included in the trial. Sixty-seven were men and 13 women. The myocardial infarction was anterior in 39 and inferior in 41 patients. The mean time between onset of symptoms and the start of rt-PA infusion was 150 ± 26 min.

All patients received 5000 IU of heparin as an intravenous bolus before entering the trial. After informed consent had been obtained, a 15 mg rt-PA (Actilyse, Dr. Karl Thomae, GmbH) intravenous bolus injection was given followed by an intravenous infusion of 50 mg of rt-PA over 30 min and a further 35 mg over the following 60 min. During the infusion period the patient was transferred to the catheterization laboratory and the first angiogram of the infarct-related vessel was performed. Thereafter a second and third angiogram was performed at 90 and 180 min. After coronary angiography at 90 min coronary angioplasty was performed in 16 patients and additional thrombolysis in 3 patients. Six patients were not included in the final angiographic analysis, mostly because of borderline ST segment elevations, in order to avoid overestimation of the efficacy of this dose regimen. Four of these had a patent infarct artery; no early angiogram was performed on two.

Within the last few years a number of large, controlled clinical trials (1-4) have shown that thrombolytic therapy reduces mortality after acute myocardial infarction. This result is generally accepted to be a consequence of the recanalization of the infarct-related coronary artery. Patency rates between 55% and 75% have been reported, the higher values being obtained with recombinant tissue-type plasminogen activator (rt-PA) (5-10).

Because of the positive correlation between thrombolytic efficacy and infusion rate of rt-PA (11,12), we hypothesized that the recanalization rate of initially occluded coronary arteries could be increased and the time to reperfusion shortened by administering the recommended dose of 100 mg within 90 min rather than 3 h.

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Table 1. Angiography and Interventions in 80 Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>No.</th>
<th>%</th>
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<tbody>
<tr>
<td>Total no. of patients</td>
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<td></td>
</tr>
<tr>
<td>60 min angiogram</td>
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<td></td>
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<tr>
<td>90 min angiogram</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>No. of finally included patients</td>
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<td></td>
</tr>
<tr>
<td>60 min angiogram</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>90 min angiogram</td>
<td>74</td>
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</tr>
<tr>
<td>Interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
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<td></td>
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<tr>
<td>12 to 36 h angiogram</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>14 to 21 days angiogram</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
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<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>2</td>
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</tbody>
</table>

PTCA = percutaneous transluminal coronary angioplasty.

Coronary artery was performed 60 min after the start of infusion. After angiography of the other coronary arteries the angiogram of the infarct-related artery was repeated at 90 min. After the 90 min coronary angiogram, the possibility of further interventions was left to the discretion of the investigator.

Angiographic evaluation of the infarct-related artery was repeated between 12 and 36 h after rt-PA infusion; coronary angiography and ventriculography were again repeated between 14 and 21 days after therapy with rt-PA. The patency of the infarct-related artery was assessed centrally from the coronary arteriograms according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) Study Group (13).

Serum creatine kinase-MB was analyzed at 4 h intervals until 48 h. Hemostatic variables were analyzed in plasma samples taken at baseline and at 90 min, 24 h and 48 h after treatment. Intravenous heparin at therapeutic levels was given at least until day 4, followed by subcutaneous heparin or oral anticoagulation.

Results

Coronary angiographic findings. Among the 80 patients included in the study, a 60 min angiogram was available in 77 and a 90 min angiogram in 78 (Table 1). To avoid overestimation of the efficacy of treatment in this uncontrolled study, six patients were excluded from the final angiographic evaluation for the following reasons: four patients had only borderline ST elevation as judged by the central evaluation of the ECG at entry; one of these died before angiography and the other three had patent coronary arteries. In another patient with patent coronary arteries, the infarct-related artery could not be identified. One patient aged 24 years did not undergo early angiography because of acute left ventricular failure and resuscitation. Because no significant coronary artery lesion was detected in the 3 week coronary angiogram, a severe myopericarditis was suspected, although the initial ST segment elevation of 47 mm in the anterior leads resolved almost completely within 24 h.

In 73 of the finally included 74 patients the first angiogram was performed 60 min after the start of the infusion. Forty-three (59%) had an open infarct-related coronary artery with prompt distal filling (TIMI grade 3), 11 (15%) had an open vessel with delayed peripheral perfusion (TIMI grade 2) and 19 (26%) had no or only minimal perfusion (TIMI grade 0 or 1). After 90 min, angiography was performed in all of the 74 included patients. The infarct-related artery was fully perfused (TIMI grade 3) in 58 patients (78%), and there was delayed perfusion (TIMI grade 2) in 9 patients (12%); only 7 patients showed an occluded artery (TIMI grade 0 or 1).

Coronary angioplasty was performed in five of the seven patients with an occluded infarct-related artery; it was successful in four cases. Eight patients with an open infarct-related artery at 90 min also underwent coronary angioplasty.

In the third angiographic study, performed in 66 patients between 12 and 36 h after the start of the therapy, an open infarct-related coronary artery (TIMI grade 2 or 3) was found in 61 patients (92%) (Fig. 1, Table 2).

Reocclusion, reinfarction and mortality. A total of 12 patients demonstrated clinical signs of recurrent ischemia. Five of these did not develop reinfarction (symptoms and
After 24 h was not confirmed because neither computed tomography nor an autopsy was performed. One patient had epistaxis after nasal intubation. Fourteen patients (18%) had prolonged bleeding or hematoma at the arterial puncture site.

Hemostatic findings. Degradation of circulating fibrinogen was comparable to that found in the German Activator Urokinase Study (GAUS) (6); our study shows no significantly increased fibrinogen degradation despite the increase of dosage from 70 to 100 mg within 90 min (Table 3). The fibrinogen level at 90 min was below 1 g/liter in 17 (23%) of the 74 patients. In the GAUS study (6), the fibrinogen level after 90 min was below 1 g/liter in 15% of the patients treated with 70 mg of rt-PA. In the urokinase-treated group, 70% of the patients had a fibrinogen level of <1 g/liter at 90 min.

Discussion

Patency of infarct-related artery. The increased infusion rate of rt-PA evidently resulted in faster thrombolysis and a higher rate of early reperfusion of thrombotic coronary occlusion in myocardial infarction. In this study, the patency rate of infarct-related coronary arteries was 91% (95% confidence interval, 82% to 96%) 90 min after the start of infusion (5-11,12). Because this was an uncontrolled clinical study, the patency rates have to be interpreted with caution. In an attempt to avoid overestimation of the efficacy of this dose regimen. 6 of the 80 patients were excluded from the final angiographic analysis, mostly because of borderline ST segment elevations in the qualifying ECG. Data analysis on the basis of intention to treat leads to even higher patency rates (75% at 60 min and 91% at 90 min).

In some previous studies, the total administered dose of rt-PA was higher, but the dose infused within 90 min was lower than in this study. The higher efficacy of the increased infusion rate with a larger initial bolus (15 mg) can be explained by the direct relation between dose and thrombolytically effective plasma levels (12). The high initial plasma levels resulted in the high patency rate of 74% as early as 60 min after the start of infusion, with 59% of vessels showing complete reperfusion (TIMI grade 3).

The comparison of patency rates of different studies requires a comparable study design, especially with respect to the time of angiography. In the GAUS study (6), with an identical angiographic protocol at 90 min, the patency rate was only 69%. In that study rt-PA was given in a dose of 70 mg over 90 min, which corresponds to the 90 min dose of the currently recommended 100 mg of rt-PA over 3 h. The 90 min patency rate of 75% in the Treatment of Acute Myocardial Infarction (TAMI) study (8,11) with a cumulative dose between 70 and 85 mg over 90 min was also lower than reported here. Patency rates after 3 h or even later may be similar for all these dose regimens; however, this question cannot be answered from available data.

The fact that no angiography was performed before the initiation of thrombolysis is of little importance if the patency rate is high. Assuming a 20% rate of vessels not totally occluded initially, the reperfusion rate has to be as high as 87.5% to lead to a patency rate of 90%.

The primary goal of fibrinolytic therapy in acute myocardial infarction, namely, lysis of the occluding coronary
thrombus, can be achieved with intravenous administration of rt-PA at the dose schedule described here in the same percentage of patients as with intracoronary thrombolysis in combination with mechanical recanalization (14). A further significant increase of patency rate achieved with thrombolysis is unlikely, since in the remaining cases the occlusion of the infarct-related coronary artery may not be of thrombotic origin (15).

Reocclusion and reinfarction. The total dose of rt-PA was limited to 100 mg to minimize the risk of bleeding. Therefore, a higher infusion rate was only attainable by reducing the infusion time. However, this short infusion time did not lead to a higher rate of reocclusion and reinfarction as far as could be concluded from the number of patients in the trial, although the increased patency rate theoretically increased the number of patients at risk for reocclusion. The number of angiographically documented early reocclusions, namely, 7 (11%) in 76 patients with an open vessel at 90 min, is not higher than that in comparable earlier investigations (6,7). The number of reinfarctions, 7 (9%) in 74 patients during the hospital stay, is also within the range reported previously. Despite its high initial efficacy, the short duration of the infusion did not lead to a major increase of the reocclusion and reinfarction rate.

Risk of bleeding. In principle, a higher fibrinolytic efficacy may be associated with an increased risk of bleeding. On the other hand, the reduction of duration of the infusion may lead to a decreased bleeding risk. Fibrinogen degradation with this dose did not markedly exceed the fibrinogen degradation found in the GAUS study (6) and was therefore lower than with nonfibrin-specific fibrinolytic agents (5).

The number of angiography-related episodes of local bleeding (at the arterial puncture site), however, is in the same range as that previously reported (6). All three major bleeding complications in this study could be attributed to predisposing factors as detailed earlier. Therefore, it cannot be estimated from our data whether weight adjustment of the dosage of rt-PA might further reduce the risk of bleeding, as has been suggested by Topol et al. (11). Also, the number of patients in this trial is too low to estimate conclusively the risk of rare events such as intracranial bleeding.

Conclusion. The increased infusion rate of rt-PA with a 15 mg intravenous bolus injection, 50 mg infusion over 30 min, and further infusion of 35 mg over the following 60 min (cumulative dose 100 mg over 90 min) leads to improved coronary thrombolysis with a patency rate of 91% at 90 min. This high efficacy does not appear to be associated with an increased risk of reocclusion, reinfarction or bleeding complications. These results have to be confirmed by a larger randomized study comparing this regimen with other more widely used regimens of thrombolytic treatment.

References


