Alteplase (r-TPA) *vs* streptokinase

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Abstract
The GUSTO trial and an Australian consensus meeting in 1993 led to the recommendation that recombinant tissue plasminogen activator (r-TPA) was the preferred thrombolytic in patients with acute myocardial infarction (AMI) and ST segment elevation under the age of 75, whose infarction was anterior, who could be treated within four hours of the onset of symptoms and who did not have a contraindication to thrombolysis. Available data suggest that streptokinase (SK) should not be administered in a patient who has received this drug three days or more previously.

New data on the risks of stroke confirm that the use of r-TPA is associated with a higher risk of intracranial haemorrhage than SK, and those with a high risk profile for intracranial haemorrhage (hypertension and advanced age) should receive SK rather than r-TPA.

It may be justified to give r-TPA to any patient with a large infarct regardless of location, within four hours of the onset of infarction in an attempt to achieve TIMI flow grade 3 (complete) reperfusion, reduce mortality and improve left ventricular function and clinical outcomes. The focus for the future will be on how to treat more patients earlier with thrombolytic agents, rather than the choice of agent. (Aust NZ J Med 1998; 28: 514-517.)

Key words: *Streptokinase, alteplase (r-TPA), acute myocardial infarction.*

BACKGROUND

Current opinions on the place of recombinant tissue plasminogen activator (r-TPA) in patients with acute myocardial infarction (AMI) crystallised after the GUSTO 1 study.[1] This landmark study showed the benefit of an accelerated r-TPA regimen combined with aggressive heparin therapy over streptokinase (SK) with either intravenous or subcutaneous heparin. GUSTO also clearly showed the relationship between TIMI flow grade 3 reperfusion, left ventricular ejection fraction and 35 day mortality.[2] The cost of r-TPA and its increased risk of intracerebral haemorrhage compared to SK have been major problems limiting its widespread use. Following GUSTO, it was widely accepted that r-TPA was the preferred thrombolytic agent in patients with AMI and ST segment elevation under the age of 75 years, with anterior infarction and treated within four hours of the onset of symptoms, provided no contraindication to thrombolysis existed.[3]

The results and implications of GUSTO for practice in Australia and New Zealand were discussed at a meeting of cardiologists and emergency medical physicians in Canberra in July 1993 and a consensus was established endorsing the above recommendations.[4]

CURRENT RECOMMENDATIONS

To illustrate the place of r-TPA *vs* SK, a possible management plan for patients being considered for reperfusion is shown in Table 1. The place of primary or emergency PTCA is being addressed elsewhere in this issue and will not be considered here. Suffice it to say that the effectiveness of PTCA in providing rapid TIMI flow grade 3 appears clear and that it has been shown to be at least as good as thrombolytic regimens in terms of clinical benefit, without the accompanying risk of intracranial haemorrhage and that its use will remain limited by rapid availability and cost. Primary PTCA should be of special benefit in patients in whom contraindications preclude the use of thrombolytic drugs.

TABLE 1
Myocardial Infarction with ST Elevation within 12 Hours of Onset

Consider revascularisation Anterior infarct in shock	------→	? PTCA
↓ Contraindications to TL	------→	? PTCA anterior infarct within 4 hours
↓ Previous SK therapy	------→	r-TPA
↓ Age less than 75 Anterior infarct within 4 hours	------→	r-TPA
↓ High risk of IC haemorrhage	------→	SK (no heparin)
↓ Large infarct Any age within 4 hours	------→	r-TPA
↓ Moderate infarct <6 hours	------→	SK
Large infarct 6-12 hours		

SK=streptokinase.
TL=thrombolysis.
PTCA=percutaneous transluminal coronary angioplasty.
r-TPA=recombinant tissue plasminogen activator.

PREVIOUS SK THERAPY

The next point to consider is whether the patient has had previous SK therapy; if a person is treated with SK, it is very important indeed that they be told about this therapy. On current data, if a patient has had previous SK therapy at any stage, then this drug should probably not be used again. SK antibody levels rise after two to three days, to levels that could be expected to neutralise over 1.5 million u of SK. Various studies have documented the time course of such antibody levels; thus Elliott *et al.* showed that antibody levels peaked at two weeks and slowly fell over 12 months but that 50% of patients still had antibody levels sufficient to neutralise a standard dose of SK up to four years after initial SK administration.[5]

A study of 104 patients receiving SK at The Royal Melbourne Hospital showed, on the other hand, that neutralising antibody levels had returned to control levels by two years.[6] Other studies have also showed variable results.[6] It is by no means certain that the *in vitro* documentation of neutralising antibody capacity to block SK does in fact block a clinically useful thrombolytic effect. White *et al.*[7] showed a patent infarct related artery in five of six patients who were retreated with SK, whereas Brugeman showed a close association between the achieving of infarct related artery patency after anistreplase and the presence or absence of SK antibodies.[8] Similarly for allergic reactions, Lee found allergic reactions to SK only in patients with pre-existing anti-streptokinase antibodies[9] and White[7] found allergic reactions in 50% of patients receiving a repeat dose of SK. Fears' *et al.* showed, in a group of patients with no known previous SK administration, no correlation between antibody levels and allergy or infarct related artery patency with subsequent SK doses, although antibody levels were low and in the community range.[10] At the moment, therefore, it would seem prudent not to use SK again in a patient who has received a dose of this agent three days or more previously.

WHEN IS r-TPA PREFERRED OVER SK?

Having excluded the patients who are to have angioplasty and who, because of previous SK administration, should certainly receive r-TPA, the next group of patients to consider is that for whom r-TPA would seem appropriate at the beginning of therapy. For patients less than 75 years of age, within four hours of onset and with anterior infarction, GUSTO has shown a significant decrease in mortality with the use of the accelerated r-TPA and heparin regimen compared with SK.[1] The data also show a strong trend to benefit in patients whose myocardial infarction (MI) is at other than anterior sites; overall, the only group for whom r-TPA lacked even a trend to benefit was in patients over six hours. GUSTO clearly showed an increased incidence of haemorrhage strokes in the r-TPA group, especially over the age of 75 years. Thus the incidence in patients treated with SK and with r-TPA was 0.42% and 0.52% under the age of 75 years, and 1.23% and 2.08% in those over the age of 75 years respectively.[1] Similar excess intracranial haemorrhage rates have been reported in previous comparisons of SK and r-TPA including the GISSI 2 and ISIS 3 studies. In 1993, Simoons *et al.* reviewed 150 patients with documented intracranial haemorrhage, looking for risk factors for such bleeding.[11] Multivariate analysis identified four independent predictors of intracranial haemorrhage.

Age >65 years (OR 2.2 95% CI 1.4-3.5)
Body weight <70 kg (OR 2.1 95% CI 1.3-3.2)
Hypertension on hospital admission (OR 2.0 95% CI 1.2-3.2)
Administration of alteplase (OR 1.6 95% CI 1.0-2.5).

Hypertension was defined as a systolic pressure over 165 or a diastolic pressure of over 95 or both. It must be noted that many of the studies reviewed by Simoons did not use weight adjusted doses of r-TPA. However, there was no increased risk with low body weight with SK. Simoon showed that the incidence of intracranial haemorrhage depended on the number of risk factors and quantified these in four age groups: in patients under 65 years, aged 66-75 years, 76-85 years and over 85 years. Thus, in those age groups for patients with no risk factors, there were incidences of intracranial haemorrhage of 0.3, 1.0, 1.5 and 2.3% respectively; for patients with one risk factor, 1.0, 1.3, 2.0 and 2.9% respectively; and for patients who had two risk factors, 1.3, 2.2, 3.3 and 5.0% respectively. There was also an excess of intracranial haemorrhage in females and this has been confirmed elsewhere.[12] Some assessment can be made therefore of the clinical risk of intracranial haemorrhage and perhaps those at higher risk should be treated with SK rather than r-TPA in view of the increased bleeding risks of the latter.

With regard to the remaining patients being evaluated for thrombolytic therapy, consideration should perhaps be given to the use of r-TPA in any patients with a large infarct within four hours of the onset of infarction. One of the major findings of GUSTO was the correlation of reduced mortality with the achievement of TIMI flow grade 3 reperfusion; thus 30 day mortality was 8.9% for TIMI 0-1, 7.4% for TIMI flow grade 2 and 4.4% for TIMI flow grade 3 reperfusion (the difference between mortality rates of TIMI 0-1 and TIMI 3 was significant p=.009). Recently Gibson *et al.*, using a qualitative method of assessment of coronary flow at coronary angiography, have raised doubts as to the reliability of TIMI flow assessments as indicators of coronary flow.[13] Nonetheless, the GUSTO investigators did show that TIMI flow grades do correlate with mortality, LV function and clinical outcomes. Other groups, such as Ito *et al.*, using myocardial contrast echocardiography have shown that all patients with TIMI flow grade 2 showed evidence of the no reflow phenomenon, whereas only 16% of TIMI flow grade 3 patients showed no reflow.[14] Thus TIMI flow grade 3 does appear to provide evidence of adequate reperfusion and tissue flow. Recent data show that SK has a time dependence in its ability to achieve TIMI flow grade 3 (it is less effective when given after three hours from onset of pain), whereas r-TPA does not.[15]

It might be extrapolated from such data that the achievement of TIMI flow grade 3 reperfusion could be beneficial in patients with high mortality rates, especially those of any age with haemodynamically important infarcts within four hours of the onset.

Remaining patients requiring pharmacological reperfusion should be treated with SK. These would include patients with moderate sized infarcts within six hours or with large infarcts to be treated within 12 hours of onset.

The real dilemma of thrombolysis is not whether to use r-TPA or SK, but rather how to treat patients earlier and how to treat more of the patients who deserve thrombolysis and who currently do not receive such therapy. The question of 'r-TPA *vs* SK' will probably become even less relevant in the future, as better thrombolytics and anti-thrombotic drugs and regimens are developed. ■

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