Can we improve on front-loaded alteplase (r-TPA)?

Philip Aylward
Director of Cardiovascular Medicine, Flinders Medical Centre, Adelaide, SA.

Abstract
The method of administration of alteplase has evolved since its introduction to clinical practice in the late 1980s. The initial dosage regimen of a graded administration of 100 mg was replaced by the front-loaded weight adjusted regimen, the efficacy of which was demonstrated in the GUSTO 1 trial.

Double bolus administration was shown to achieve superior TIMI 3 patency of the infarct related artery in a small angiographic study, but the COBALT trial failed to show equivalence and indeed showed a slightly higher mortality and incidence of stroke, so cannot be recommended.

Reteplase, a deletion mutant of alteplase, also showed superior efficacy in achieving coronary patency but no clinical superiority in outcomes in the 15,000 patient GUSTO 3 trial. The case of administration of reteplase, however, has some attraction as an alternative to alteplase. Trials of newer agents based on further modifications of alteplase are ongoing, but at present the front-loaded alteplase regimen remains the standard for clinical practice. (Aust NZ J Med 1998; 28: 511-513.)
Key words: *Front-loaded alteplase, double bolus administration, reteplase, the COBALT trial.*

BACKGROUND

The method of administration of recombinant tissue plasminogen activator (r-TPA, Actylise, Boehringer Ingelheim) has evolved since its initial use in clinical practice. The initial dosage regimen used in the early r-TPA trials, e.g. National Heart Foundation of Australia,[1] was a 100 mg infusion over three hours. Following work by Neuhaus *et al.*,[2] which showed improved patency of coronary vessels with a more accelerated weight related infusion of r-TPA over 90 minutes, this accelerated regimen was chosen for the Global Utilisation of Streptokinase and for Occluded Arteries (GUSTO) trial.[3]

In the GUSTO trial, coronary patency was shown to correlate with mortality, Thrombolysis in Myocardial Infarction (TIMI) 3 flow being associated with the lowest mortality of 4.2% compared to TIMI 1 flow which was associated with a mortality of nearly 10%. Coronary patency at 90 minutes post thrombolytic therapy has now been accepted as a surrogate for mortality benefit produced by a thrombolytic agent.

The administration of r-TPA as two boluses 30 minutes apart has many practical advantages, in particular the ability to commence thrombolytic therapy out of hospital. A small pilot study was conducted in Belfast by Purvis *et al.*[4] This demonstrated a very high TIMI 3 patency of 90%.

Based on this apparent benefit on patency, the COBALT trial was designed to test the efficacy and safety of the double bolus regimen compared to the front-loaded weight-related continuous infusion used in the GUSTO trial.

COBALT TRIAL DESIGN: FRONT-LOADED *vs* DOUBLE BOLUS r-TPA

The trial design was unusual but the aim of the study was to determine whether double bolus administration and front-loaded accelerated infusion of r-TPA were clinically equivalent. Strict statistical definition of the equivalence was utilised such that the mortality with the double bolus must be ≤to the 30 day mortality of front-loaded plus 0.4%. The plus 0.4% was chosen because this was the lower

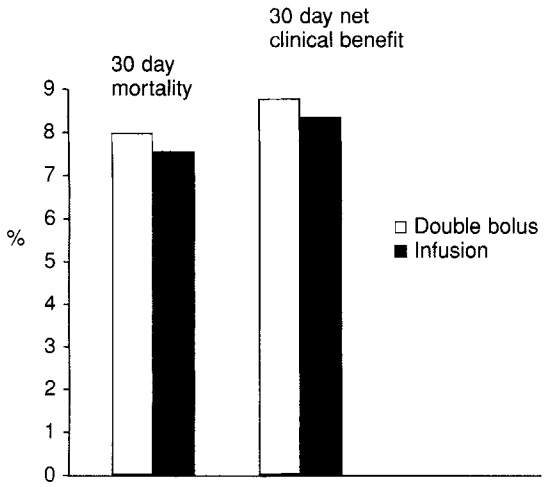

Figure 1: COBALT trial – mortality and net clinical benefit.

95% confidence limit of the 1% difference in 30 day mortality between front-loaded r-TPA and streptokinase in GUSTO 1. As the overall 30 day mortality was expected to be similar to that in GUSTO 1 the sample size was calculated to be 4029 patients per arm giving an 80% power with a significant level of 5%.

The inclusion/exclusion criteria were chosen similarly to GUSTO, in particular the time window for entry was onset of chest pain within six hours. Patients were required to have symptoms of ischaemic pain with ST elevation. The trial was an international multicentre trial in Europe, Middle East, South America, Australia and New Zealand. There were no United States or Canadian centres.

COBALT TRIAL RESULTS

A total of 7169 patients were randomised between January 1995 and January 1996. There were 398 centres in 24 countries.

The trial was terminated early by the Data and Safety Monitoring Committee because it was felt that the differences between the two arms were such that it would be impossible for the two regimens to be shown to be equivalent.

Presenting Characteristics

As expected in a study of this size, there were no significant differences between the baseline demographic characteristics, baseline risk factors, or presenting characteristics. The average age of the patients was 63 years and 23% were female. The average time to treatment was 180 minutes.

Endpoints

The primary endpoint of the trial was 30 days mortality and this was 8.0% in the double bolus regimen and 7.5% in the front-loaded regimen (p=0.55) (Figure 1). There was a higher incidence of strokes – 1.92% in the double bolus compared to 1.53% in the infusion (compared to 1.59% in the non-US arm of GUSTO 1 with the front-loaded regimen).

As many of the stroke patients died, the endpoint of net clinical benefit, death or non-fatal stroke was compared and was 8.8% in the double bolus regimen and 8.3% in the front-loaded regimen (p=0.40) (Figure 1).

There appeared to be no major differences in other bleeding between the two arms. Interestingly, in view of the current data on heparin, the activated partial thromboplastin time at six hours was markedly higher in the double bolus arm than the front-loaded infusion, 101 seconds *vs* 84, but thereafter they were at similar levels.

Although the groups did not differ when judged by the standard statistical tests, they were not equivalent by the standards of the precise criteria initially applied in the trial.

Subgroup analysis as always should be treated with caution but interestingly, in patients under the age of 75 years, there was no difference between the two arms.

CONCLUSION: FRONT-LOADED *vs* DOUBLE BOLUS r-TPA

Based on this trial, double bolus r-TPA was not as effective as front-loaded r-TPA in terms of mortality and was associated with an excess of stroke. Although the detrimental effects may be confined to those over the age of 75, it is not safe to reach that conclusion. At this time the double bolus regimen could not be recommended as a standard method of giving r-TPA.

THE GUSTO 3 TRIAL: FRONT-LOADED r-TPA (ALTEPLASE) *vs* r-PA (RETEPLASE)

Reteplase r-PA is a new thrombolytic agent, a deletion mutant of wild-type tissue plasminogen activator. Reteplase has the advantage of being rapid acting and suitable for bolus dosing, suggesting it may be suitable for simple and effective administration in clinical practice.[5] Two angiographic studies, RAPID 1 (the Reteplase Angiographic Phase 2

International Dose-finding study) in 606 patients, and RAPID 2 (the Reteplase *vs* Alteplase Patency Investigation During Acute Myocardial Infarction) in 324 patients, have shown that double bolus dosing of reteplase is superior to front-loaded r-TPA in achieving TIMI flow grade 2 or 3 coronary patency, at 90 minutes. A randomised trial against streptokinase, the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial showed no apparent differences between reteplase and streptokinase.[6] The apparent superiority of double bolus reteplase and alteplase in achieving early coronary patency led to the GUSTO 3 trial in over 15,000 patients. The primary hypothesis was that reteplase would be superior to alteplase in reducing mortality at 30 days. The results have been reported but not published.[7] The 30 day mortality rate in the reteplase group was 7.43%, compared with 7.22% in the alteplase group. The rate of haemorrhagic stroke was 0.91% for reteplase and 0.88% for alteplase. The overall stroke rate was 1.67% for reteplase and 1.83% for alteplase.

Although equivalences of effect cannot be concluded with certainty from a trial in which the primary hypothesis was to demonstrate superiority of reteplase over alteplase, the absence of any significant differences in the major endpoints in a trial of 15,000 patients strongly suggests that the two agents are equivalent in effect. Why reteplase does not reduce mortality while apparently achieving better coronary patency remains unexplained.

THE ASSENT TRIAL

A further mutation of TPA is being trialled, using the hybrid plasminogen activator, t-NK. This has the advantage of a longer half life and is more resistant to inactivation from alteplase. Following a dose ranging study in 113 patients,[8] a mortality study is about to commence internationally with participation by Australian and New Zealand centres. ■

References

1. Thompson PL, Aylward P, Federman J *et al.*, in association with the National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. Lancet 1988; ??: 203-8.
2. Neuhaus KL, Feuerer W, Jeep-Tebbe S, Niederer W, Vogt A, Tebbe U. Improved thrombolysis with a modified dose regimen of recombinant tissue-type plasminogen activator. J Am Coll Cardiol 1989; 14: 1566-9.
3. The GUSTO Investigators. An international randomised trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673-82.
4. Purvis JA, McNeill AJ, Siddiqui RA *et al.* Efficacy of 100 mg of double-bolus alteplase in achieving complete perfusion in the treatment of acute myocardial infarction. J Am Coll Cardiol 1994; 23: 6-10.
5. Noble S, McTavish D. Reteplase. A review of its pharmacological properties and clinical efficacy in the management of acute myocardial infarction. Drugs 1996; 52: 579-605.
6. Weaver WD. The role of thrombolytic drugs in the management of myocardial infarction comparative clinical trials. Eur Heart J 1996; 17 (Suppl.): 9-15.
7. Cody RA. Results from late-breaking clinical trials sessions at ACC 97. J Am Coll Cardiol 1997; 30: 1-7.
8. Cannon CP, McCabe CH, Gibson GM *et al.* tNK – tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 10A dose-ranging trial. Circulation 1997; 95:351-6.