

THROMBOLYTIC TREATMENT FOR ACUTE MYOCARDIAL INFARCTION

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Thrombolytic treatment is the greatest advance in the management of acute myocardial infarction since the introduction of the defibrillator over 25 years ago. The purpose of this article is to give a balanced view of the evidence for the value of thrombolytics in acute myocardial infarction, and to weigh up the advantages and disadvantages of the different agents which are available. We need to decide which drug to use, who should administer the treatment and which patients should receive thrombolytic therapy. We also need to consider the value of adjuncts such as treatment with aspirin, heparin and the use of coronary angioplasty.

WHY HAS THROMBOLYSIS TAKEN SO LONG TO BECOME ESTABLISHED?

First descriptions of coronary thrombolysis date from 1958 when streptokinase was tried. The drug was pyrogenic and was often given some days after the onset of infarction. Also pathologists tended to believe that thrombosis was a secondary rather than a primary event, and selective coronary arteriography and non-invasive assessment of left ventricular function were not available. It was not surprising therefore that these initial trials failed to show sufficient benefit to recommend the technique. Two factors stimulated enthusiasm for further investigation of thrombolysis in acute infarction. First was the demonstration of clot lysis angiographically following the administration of fibrinolytic agents into the coronary arteries. Second was the proof that intracoronary thrombi occurred early in the onset of acute myocardial infarction.

CURRENTLY AVAILABLE THROMBOLYTIC AGENTS

All the drugs work by activating plasminogen either directly or indirectly to form plasmin. The differences between them include time of action and half life, persistence within clots, affinity for fibrin bound compared with circulating plasminogen, the amount of inhibition and inactivation in the circulation, immunogenicity and haemodynamic effects. Bleeding problems are similar with all the drugs but have proved acceptable and less of a problem than originally anticipated. Strokes overall are not increased possibly because an increase in haemorrhage is counterbalanced by a reduction in cerebral thrombosis.

Streptokinase was the first agent which was available and is a streptococcal protein which combines with circulating plasminogen producing a complex that converts the plasminogen to plasmin. It has been widely used and is effective and cheap.

Urokinase which was isolated from human urine activates plasminogen directly and is non immunogenic in contrast to streptokinase. Its precursor, single chain urokinase plasminogen activator (scu-PA), is inactive itself but readily converts to urokinase by reaction of plasmin.

Tissue Type Plasminogen Activator (rt-PA) was initially isolated from melanoma cells and subsequently produced by recombinant DNA technology. Various forms are available in the laboratory, but clinically available preparations of rt-PA have a circulating half life of five minutes, persist for prolonged periods within clots and have a high affinity for fibrin so activate fibrin bound plasminogen in preference to the circulating variety. No immune reactions have been reported so far.

The commercial name for rt-PA is Actilyse (alteplase).

Anisoylated Plasminogen Streptokinase Activator Complex (APSAC) has effects the same as those with streptokinase and acts like a sustained-release form of streptokinase. It was developed initially as a clot selective agent but its main advantage clinically is that it is active for several hours after a single bolus injection.

The commercial name for APSAC is Eminase (anistreplase).

Both rt-PA and APSAC are possibly more effective than streptokinase but are much more expensive.

THE EFFICACY OF THROMBOLYTIC AGENTS

Different types of study have been used to show that thrombolytic therapy works. They include:-

1. Recanalisation Studies

This requires angiography to show the site of obstruction and then further angiography to assess the effect of the drug on patency. The disadvantage of such trials is that there must be a delay in giving the drug while the initial coronary arteriograms are performed, hence this type of trial has mainly been of importance in establishing the fact that thrombolytics can clear obstructed arteries.

2. Patency Trials

Here the initial angiography is omitted so that there is less delay in using the drugs. The snag with this approach is the estimated frequency with which the patent vessels are found after myocardial infarction without the benefits of active treatment is almost 50% after a few days. Evaluation therefore must be made 90 minutes after an intravenous agent and only two trials have done this so far.

3. Studies Based on Mortality or Clinical Criteria such as Left Ventricular Function

These require large numbers of patients based on an 'intention to treat' principle.

Patency studies suggest that the initial recanalisation with intracoronary drugs is constantly about 75%. Intravenously, however, streptokinase is significantly less efficient with patency rates of approximately 50%. Intravenous APSAC is more effective at around 60-70% and rt-PA appears to be equally effective when given intravenously or by intracoronary routes with patency rates of around 70%.

Practically speaking intravenous therapy is the only method of treatment which is likely to be beneficial for everyday use and mortality studies give the best evidence of benefit from such treatment. The literature is full of trials with clever acronyms most of which have inadequate numbers and hence lack the power to show clear benefit from the treatment. The most important trials are:-

1. **GISSI**, the Italian trial, in which 11,806 patients with acute myocardial infarction were randomised. Patients were treated within 12 hours of the onset of infarction and hospital mortality was reduced from 13% to 10.7% and improved mortality was sustained over the subsequent 12 months. Reduction of mortality was most dramatic (47%) amongst patients treated within one hour of the onset of symptoms.
2. **ISIS-2 (International study of Infarct Survival)**, in which 17,187 patients with suspected acute infarction were randomised into four treatment groups: streptokinase, oral aspirin, streptokinase plus aspirin and placebo control. Streptokinase and aspirin reduced mortality almost to the same extent. Use of both agents produced a higher rate of survival.

These are the only two trials with sufficient numbers to be able to prove that intravenous thrombolytic agents benefit mortality. So far there are no trials which give convincing evidence that left ventricular performance has been improved and there are no adequate trials which compare the three available drugs.

UNRESOLVED CLINICAL PROBLEMS

a) The Use of Adjuvant Pharmacological Agents

ISIS-2 gave conclusive evidence of the value of immediate aspirin and all patients with suspected AMI should be asked to crush 150 mg of aspirin in the mouth immediately. Heparin has been widely used in the reported trials in an attempt to maintain patency of vessels after successful thrombolysis, but there is no adequate evidence which suggests that heparin is successful. The ISIS-3 trial will be addressing this problem. Various other agents are being studied such as antithrombins and combined antiplatelet and fibrinolytic agents but at the moment none of these has been shown to have clinical value.

b) Coronary Angioplasty

Early coronary reocclusion is a persistent problem after thrombolysis. It occurs in approximately 20% of patients, particularly those with severe residual stenosis. Thus percutaneous transluminal coronary angioplasty (PTCA) may help. The Thrombolysis in Myocardial Infarction study phase 2 (TIMI-2) addressed this problem. Rt-PA was used intravenously. Routine coronary arteriography in 18 to 48

hours after rt-PA, with angioplasty if it was felt suitable, was compared with conventional PTCA during the six weeks after thrombolysis only if the clinical condition suggested that it was necessary. One subgroup compared immediate catheterisation and PTCA, ie within two hours, with the other two groups. The results of the studies were reassuring for the finances of the National Health Service. The mortality and morbidity associated with immediate arteriography and PTCA were unacceptably high and the results of PTCA in those with arteriography in the 18 to 48 hours after thrombolysis were no better than with conservative therapy which resulted from reassessment within six weeks from the initial incident.

c) Which Drug?

The simple approach to this would be to accept the claims of the drug firms and agree that their initial aims have been achieved with the drugs available. In other words the advantages of rt-PA would be greater efficacy than streptokinase when given intravenously and that it targets the fibrin bound plasminogen rather than circulating plasminogen so reducing the risk of bleeding. Unfortunately the latter has not been achieved clinically and there seems little difference between the two drugs as regards bleeding complications although this is dependent on dosage. There does seem to be improved efficacy with rt-PA over streptokinase although this has been questioned, but the one major drawback of the recombinant plasminogen activator is its price which is approximately ten times that of streptokinase. APSAC or anistreplase as it is now called has the great advantage of being effective when given as a single bolus but is as antigenic as streptokinase and has again proved disappointing as far as reduced general bleeding is concerned. It is cheaper than rt-PA but is still four times as expensive as streptokinase. Most answers to these questions should come from GISSI II which compares streptokinase and rt-PA and from ISIS-3 which is a comparison of all three drugs.

Currently streptokinase is widely used because it has been available longest, has proven efficacy and is relatively cheap. Most units in hospital keep some rt-PA for use in patients who require further thrombolytic treatment within three months of having received streptokinase to avoid allergic reactions. The possibility that APSAC, because of its use in bolus form, could become the most useful drug for giving in the home or ambulance again should await results of trials. So far trials of intravenous thrombolytic agents have restricted the patients treated to about 10% of patients with chest pain query infarct because of strict exclusion criteria. The safety of treating patients with chest pain who may have a whole series of pathologies other than acute myocardial infarction remains to be shown.

d) The Role of the General Practitioner

A recent report of a working group of the British Heart Foundation emphasises the importance of prompt care of acute myocardial infarction. The role of the general practitioner is crucial but health authorities, hospital physicians, ambulance services and GPs are exhorted to co-ordinate their efforts so that early treatment, preferably well within six hours, is available for patients with acute infarction. They suggest that the dangers of giving thrombolytic therapy to conditions other than myocardial infarction mean that treatment should be given only when the diagnosis is likely and when close observation over the next few hours can be maintained. At the moment

therefore the recommendation is that thrombolytic therapy should not be given out of hospital except when trained and equipped personnel are in attendance.

IN LANCASTER NOW

We are starting with the ISIS-3 trial. All patients with possible acute infarction seen within 24 hours will be considered for randomised treatment. Those patients with clear evidence of AMI will have either streptokinase or APSAC or rt-PA and those with less clear cut features will be randomised to either active drug or placebo. There is no upper limit for consideration on the grounds of age and the exclusion criteria generally are at the discretion of the admitting doctor's guidelines which have been circulated among local general practitioners. A further aspect of the trial will seek to clarify the role of subcutaneous heparin.

SUMMARY

The value of intravenous thrombolytic therapy for AMI is proven. Early reperfusion, especially within three hours of onset, reduces the incidence of sudden death and some benefit seems possible up to 24 hours after the onset of symptoms. All patients with suspected acute infarction should receive aspirin immediately and be considered for a thrombolytic drug which should be administered in hospital until evidence on the safety of treatment in the community by general practitioners, nurses or ambulancemen is available. The choice of drug, streptokinase, APSAC or rt-PA should be reserved until the results of the current large trials are available and price will dictate the use of streptokinase in most centres in the meantime. The use of adjuncts such as heparin should also become clearer soon and angioplasty

should be considered on clinical grounds, possibly supplemented by stress testing or ECG ambulatory monitoring, in the weeks following the acute infarction.

The conclusions which will be reached over the next year or so about the use of thrombolytic drugs will have major implications for all health care personnel involved in the management of patients with coronary heart disease. Political decisions will be crucial to deal with the financial aspects and careful local audit will be essential if we are to reap optimal benefits for our patients.

Suggestions for Further Reading:

1. Gruppo Italiano per lo Studio della Streptokinase nell'Infarto Miocardico (GISSI). Lancet 1986; 1:397-401
2. ISIS-2 (Second International Study of Infarct Survival). Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. Lancet 1988; 2:349-60.
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4. The AIMS trials study group. Effect of intravenous APSAC on mortality after acute myocardial infarction. Lancet 1988; 1:545-9.
5. TIMI study group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI 2) trial. N Engl J Med 1989; 320:618-27.
6. Role of the general practitioner in managing patients with myocardial infarction; impact of thrombolytic treatment. BMJ 1989; 299:555-7.



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