Streptokinase

As long ago as 1933 streptococci were found to produce a substance which can lyse fibrin.1 Nearly 20 years ago this material, streptokinase, was shown, quite convincingly, to lyse clots in the human circulation.2 Yet today the place of streptokinase in treatment is still controversial; and the lack of generally accepted indications for its use argues that it is likely to remain of very restricted value in therapeutics.

Streptokinase acts by converting plasminogen to the active proteolytic enzyme, plasmin. The complex formed by the interaction of streptokinase with plasminogen has its greatest activity when the two substances are present in a one-to-one molar ratio. Formation of the complex changes the plasminogen molecule by exposing an active catalytic site, giving activator activity to the whole complex.3 The plasminogen in the complex is converted to plasmin, and this streptokinase-plasmin complex also has activator activity.3

Plasmin is formed principally from non-complexed plasminogen by proteolytic cleavage of a single arginyl-valine bond.4 The streptokinase in the complex is degraded with progressive loss of activity.5 Two proactivators in human and bovine plasma may also be activated by streptokinase to produce plasmin from plasminogen,6 but it is not clear whether this pathway is important in therapeutic thrombolysis.

Dissolution of thrombus probably results from endogenous lysis caused by the formation of plasmin by the activator complex from plasminogen7 or by action of the activator; both are incorporated into the thrombus during clotting. The alternative concept of exogenous lysis proposes that plasmin is released from a complex with antiplasmin near the thrombus owing to the strong affinity of plasmin for fibrin.8 Experimentally, however, exogenous lysis is feeble, thrombus lysing only slowly in solutions of pure plasmin.9 So the rationale behind streptokinase treatment is to produce activator activity with only limited release of free plasmin into the circulation. The methods used to achieve this balance and to monitor streptokinase treatment have been reviewed recently.10

Streptokinase has been tried in many clinical conditions with convincing evidence of benefit in few. The clearest indications are in the venous circulation—perhaps not surprisingly, since the venous thrombus most closely resembles the test tube clot. Controlled clinical trials have shown that streptokinase dissolves extensive deep venous thrombi more often and much more completely than other drugs.12-15 While this may be irrelevant to the subsequent incidence of pulmonary embolism, it is the form of treatment most likely to preserve the function of the deep venous valves.16 Destruction of the valves is probably the main cause of the postphlebitic syndrome—a chronically bloated limb prone to stasis ulceration. Long-term follow-up of patients with deep venous thrombosis suggests that streptokinase treatment reduces the number of patients with residual swelling and aching of the limb.17 A strong case can therefore be advanced for this treatment in younger patients in whom massive deep venous thrombosis extends above the knee.

The case for giving streptokinase after pulmonary embolism has occurred is less clear. Effective treatment must achieve one of three objectives: a reduction in mortality, a reduction in the period of incapacity, or an improvement in the long-term functional result. There is no clear evidence that treatment with streptokinase attains any of these objectives. Its use in patients with acute massive pulmonary embolism accelerates clearance of emboli from the pulmonary circulation and improves right heart function more rapidly than when heparin is given,18 though some patients may still require embolectomy.19 But most patients who are going to die will do so before any treatment can be given. The National Heart and Lung Institute Pulmonary Embolism Study showed that thrombolytic treatment had no real advantage over heparin in clearance of the lung scan six months after the acute event.20 Streptokinase treatment should therefore be reserved for the few patients who have acute massive pulmonary embolism with obstructed right-heart outflow but who do not appear to require surgical embolectomy to prevent impending death. Should a pregnant patient near term fall into this category streptokinase may be used successfully.21

A recent controlled clinical trial showed that prognosis in central retinal vein occlusion may be marginally improved by streptokinase treatment.22 Unfortunately, 15% of treated patients went blind in the affected eye as a result of vitreous haemorrhage, and the improvement in vision in the remainder, though statistically significant, was not impressive. Use of streptokinase should be restricted to the patient with healthy eyes and a transient thrombolytic tendency—for example, a young woman taking an oral contraceptive—or to the patient already blind in one eye, in whom the hope of saving some sight may justify the risk.

The great hope for thrombolytic treatment has been that it might be possible to reduce morbidity and mortality from myocardial infarction by limiting the size of the infarct as a result of improved blood flow to areas of injury near the infarct. Streptokinase might achieve this by lysing incompletely obstructing thrombus, preventing further distal propagation...
of thrombus, and reducing blood viscosity. Many trials of variable quality have been completed, but, disappointingly, the three studies in coronary artery occlusion for incomplete coronary occlusion of therapy in myocardial infarction are large logistic problems in completing a trial large enough to show convincingly even a 25% reduction in mortality from myocardial infarction. The story of anti-coagulant therapy in myocardial infarction indicates the need for great caution until, if ever, the place of streptokinase is validated by large-scale trials of irrefutable experimental design.

Similarly, results with streptokinase have been disappointing in occlusion of peripheral arteries. In acute arterial obstruction surgery is likely to be more successful and more reliable and, again, the results of treatment with streptokinase of chronically occluded vessels have been generally unsatisfactory. Hence probably streptokinase has only a small part to play—in treating patients unfit for surgery in whom arterial obstruction is incomplete. A few patients with occlusion of the retinal artery may attain improved vision from thrombolysis, but properly controlled studies have not been carried out.

There is a mass of uncontrolled evidence from compilations of case reports, recently reviewed, in which streptokinase has been used successfully to treat occluded arteriovenous shunts, pseudoaneurysms, disseminated intravascular coagulation, and thrombosed valve prostheses. There are no reports of its use in cerebrovascular disease, but experience with urokinase in treating established stroke was not encouraging. Miscellaneous uses coupled to diagoses of deep venous thrombosis by streptokinase coupled to 99-technetium, but this method has no obvious advantage over standard isotope diagnostic methods.

Haemorrhage is the only serious complication of treatment with streptokinase, but it may be massive and difficult to control—a compelling reason for restriction of streptokinase to conditions where benefit has been clearly established. At the moment these are few. Further developments, such as combining streptokinase with plasminogen, may improve results, but it seems more likely that streptokinase will remain a valuable drug for use in only a few carefully selected patients.

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