Thrombolytic therapy: with streptokinase and urokinase

Streptokinase therapy for deep vein thrombosis

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Streptokinase can dissolve thrombi in the deep veins more effectively than the anticoagulants, heparin or anicrod (Kakkar *et al*, 1969). However, there are still unexpected failures; there are still complications of the treatment. Which patients, therefore, should be treated?

Three questions require an answer for each individual under consideration. Are his symptoms due to thrombosis? Will removal of the intravascular fibrin by thrombolytic therapy give a worthwhile benefit? Do the risks of streptokinase prevent its use?

Are the Clinical Symptoms due to Thrombosis?

Objective diagnostic methods of use during life—phlebography, labelled-fibrinogen uptake, and ultrasound—unite with retrospective necropsy studies to show that many thrombi give no clinical sign of their presence. The reverse is also true; clinical signs may suggest the existence of a thrombus when the veins are shown to be clear by phlebography and there is no uptake of labelled fibrinogen. In our recent study (Kakkar *et al*, 1969) a confident clinical diagnosis of major thrombosis was shown to be wrong in 30% of the patients.

The major factor now preventing the widespread application of streptokinase therapy for deep vein thrombosis is the restricted availability of the modern methods of diagnosis and localization of thrombosis. Without them it is arguable that the risks of systemic streptokinase are seldom justified.

Will Removing the Fibrin Give Benefit?

There is a high rate of spontaneous thrombolysis, particularly in patients treated with anticoagulants. In the study quoted, 21% of major thrombi dissolved completely, within a week, even without streptokinase. Accumulating evidence shows that thrombi which are distal to the popliteal vein in the legs

usually resolve completely, even without anticoagulant therapy.

Studies of the natural history of thrombosis show, however, that thrombi in the popliteal or more proximal veins are associated with a great risk of pulmonary embolism. If these thrombi can be accurately identified there is a clear reason for treatment with streptokinase.

Yet more extensive thrombi threaten the viability of the limb. The massive interference with blood flow means that the fibrinolytic enzymes will have only limited access to the affected area. Though it seems likely that the fibrin could ultimately be dissolved there would be little gain from restoring the patency of veins in a gangrenous leg. Surgical thrombectomy is indicated in these patients, perhaps combined with local streptokinase therapy.

Do the Risks Outweigh the Benefits?

The major risk is of bleeding from already damaged vessels. Minor allergic reactions are not uncommon but they can be controlled with antihistamines and corticosteroids and no fatal case of anaphylaxis has been reported. There is an impression that bacterial infections may spread more widely but this aspect has been little studied.

Any patient treated with anticoagulants or with streptokinase is liable to bleed. In the hours following a loading dose of 500 000 units of streptokinase bleeding from injection sites and leakage around any catheters left in vessels is often obvious. The tendency continues to a lesser degree throughout a maintenance infusion of 100 000 units hourly. The bleeding could perhaps be related to the drop in plasma fibrinogen or other coagulation factors or to the antihaemostatic effects of the fibrin or fibrin degradation products (FDP) which antagonize the action of thrombin, the polymerization of fibrin, and the aggregation of platelets. Alternatively, it could be due to the digestion of fibrin in haemostatic plugs.

Clinical experience suggests that the major risk of bleeding is determined by the presence of damaged vessels, with the necessity to form haemostatic plugs. Search for any possible vascular damage is, therefore, more important than any change in the haematological findings when predicting the risk. Surgical wounds older than 72 hours and healing by first intention do not appear to create a hazard but bleeding may come from granulating areas or from around drainage tubes in wounds much older than this.

Conclusions

The real need for treatment with streptokinase is confined to those patients with thrombi in the popliteal or more proximal deep veins, where there is a great risk of pulmonary embolism. Early treatment is more likely to preserve the function of venous valves. Treatment may be contraindicated by vessel damage which requires the continued formation of haemostatic plugs. The selection of these patients is, unfortunately, impossible on clinical grounds alone. It requires phlebography or scanning to detect the uptake of radioactive labelled-fibrinogen.

This communication has so far ignored the other important question, the occasional failures of treatment. Clinical impressions suggest that these are often related to the age of the thrombus or to the continuation of a recognizable stimulus to thrombosis. There is no absolute rule but thrombi present for longer than five days often fail to dissolve. Rethrombosis has been an important problem in patients with pelvic sepsis. The majority of reported studies have used a high loading dose of streptokinase with a profound fall in plasminogen; further work is needed to compare these results with those of other dose regimes.

Abstract

Thrombolytic Treatment of Recent Arterial Occlusion

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It has been shown conclusively that during the administration of streptokinase (SK) in patients with a recent thromboembolic occlusion of a limb artery, patency of the main artery can be restored (Verstraete, Amery, and Vermeylen, 1963; Winckelmann, Hiemeyer, Weissleder, and Schoop, 1963).

The results of 15 European centres which are using purified streptokinase administered intravenously for the thrombolytic treatment of recent and acute occlusions in limb arteries have been collected by Hess (1967). The dose of streptokinase infused was usually the titrated initial dose followed by a maintenance dose of 100 000 units streptokinase per hour. This study was not planned ahead but the results of the various centres were collected, assuming that the patient's condition, the dosage scheme, and the criteria of evaluation were similar.

In total 252 arterial emboli and 206 thrombi or unclassified arterial occlusions were treated. A return of arterial pulsations at all levels was obtained in 43%, partial clearing (ie, return of arterial pulsations at least at one level but not at all levels) was obtained in 16%, and there were 41% failures.

A higher success rate was obtained for arterial occlusions at the popliteal level (61%) compared to aortic occlusion (12%); this difference is statistically significant ($P = 0.002$). The thrombolytic success rate was greater in patients with arterial emboli (55%) compared with arterial thrombosis (34%). Also this difference is statistically significant ($P < 0.001$) and persists in comparing groups of arterial thrombi or emboli of different duration (between 24 and 120 hours). The sooner an arterial occlusion is treated with streptokinase, the shorter the infusion period required to obtain thrombolysis: emboli of less than 19 hours' duration had an average lysis time of 39 hours, emboli older than 19 hours' duration required an average of 62 hours' treatment; a parallel relationship was found for arterial thrombosis. When therapy was started within 30 hours, lysis occurred on the average in seven hours; when therapy was started after 30 hours, lysis occurred in about 99 hours (Schmutzler, 1968).

Two important side effects should be mentioned: the first is the risk of emboli during thrombolytic therapy: 3.1% of all patients developed a non-fatal embolus and 2.3% developed a fatal embolus.