Effects of fibrinolytic agents on experimental and clinical thrombosis

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Experiments were designed to test the effectiveness of fibrinolytic substances in dissolving thrombi induced in the femoral arteries of dogs. The safety and the laboratory control of the dosage of these agents were also studied and the techniques, after modification, were applied to the treatment of arterial thrombosis in man.

Experimental thrombi were formed in 50 dogs by the method described by Tsapogas, Flute, Cotton, and Milroy (1962). Forty-eight hours later the wounds were re-opened, and, if satisfactory thrombi were formed, an infusion was given for three hours through a catheter placed locally into the occluded artery or intravenously, by means of a micropump. Another catheter was inserted into the femoral vein to take blood samples for frequent measurements of the dilute blood clot lysis time, the fibrinolytic activity on a fibrin plate, as well as plasminogen, fibrinogen, and other clotting factors.

The critical dose of activator in units per millilitre of plasma was measured by methods which are discussed by my colleague Dr. Flute on page 337. It is then multiplied by the plasma volume to obtain the dose needed to produce general lysis.

When the local intra-arterial route is employed, an infusion of saline containing the critical dose of activator in units per millilitre is administered. No loading dose is given for a local infusion. The lysis of the thrombus is detected by inspection, palpation, and arteriography. If activator is to be given intravenously an initial dose estimated to produce general lysis is given and a sustained infusion continues over a period of three hours. Our recent practice is to give such an amount of fibrinolytic agent as to equal half of the loading dose hourly.

The methods of administration to patients are essentially similar to those described above. When the closed method is employed, a Seldinger needle is inserted above the thrombosed segment of the artery and a catheter introduced through it (Cotton, Flute, and Tsapogas, 1962).

In these experiments, two substances have proved to be equally effective in dissolving thrombi, namely, streptokinase and urokinase. Heparin, normal saline, and a heparin-trypsin complex given under the same plan failed to dissolve thrombi.

Streptokinase has not caused any significant side-effects; however, it is antigenic and produces a considerable increase of neutralizing antibodies.

After infusion with urokinase two main complications occurred in some of the dogs, bleeding and delayed healing. The cause of bleeding has not yet been determined. It could be due to the fibrinolytic action of urokinase but it occurred even when clotting factors were normal and fibrinogen breakdown products could not be demonstrated. It is suggested that an increase in capillary permeability may be at least partly responsible for this complication. In the dogs in which healing of wounds was delayed, histological examination did not reveal any significant decrease in fibrin or collagen. Local infection might have been an important contributory factor.

No evidence of pathological change in any of the organs was detected in the post-mortem examination, either macroscopically or microscopically. No sensitization or increase of inhibitors has been found in dogs after infusion with urokinase.

Fibrinolytic therapy was applied to a small number of patients with acute arterial thrombosis of embolism in the lower limbs. The extent of thrombosis and the progress of the therapy can be demonstrated in these conditions by repeated arteriography.

No definite conclusions can be drawn from the small series of patients studied. It has been shown that streptokinase and urokinase can dissolve recent thrombi in patients. Nevertheless, in extensive thrombosis the limb is not necessarily saved because of the slow dissolution of the thrombus. This coincides with our experimental findings; arterial thrombus 4 cm. long requires about two hours of infusion before it can be dissolved.

If the thrombotic episode is secondary to occlusive atheromatous process, fibrinolytic therapy obviously will not have any effect on the organized lesion.

When dealing with extensive peripheral arterial
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thrombosis, we perform an arteriogram, followed by thrombectomy. If after this procedure the back-flow is not satisfactory and arteriography confirms occlusion of the distal vessels, then we proceed with fibrinolytic therapy.

The experience gained from this study may be applied to the treatment of arterial and venous thrombosis in other sites of the body, but it is important at present to obtain an objective assessment of the effects of therapy.

REFERENCES

DR. MNICOL had noted the development of a woody oedema1 in patients who had had prolonged infusions. This might be due to capillary damage from anoxia during the period of vascular occlusion; to damage to the vascular endothelium following removal of fibrin by intense fibrinolysis; or possibly to a toxic effect of streptokinase.

MR. TSAPOGAS had noted this complication occasionally with by-pass grafts but not with fibrinolytic therapy and felt that it was due to restoration of circulation through a limb which had been subjected to gross ischaemia.

MR. PARRY agreed, and said that he regarded the oedema after an arterial graft as a sign of success. He asked whether fibrinolytic therapy should be followed by anticoagulant therapy to prevent further thrombosis in the smaller vessels.

MR. TSAPOGAS felt that the question of anticoagulant therapy should be seriously considered.

MR. TRITHIE asked whether Mr. Tsapogas’s two cases were aetologically different, since one responded to treatment better than the other. He ventured the hypothesis that a vascular occlusion of embolic origin might be expected to respond to fibrinolytic therapy better than one of thrombotic origin, the reason being that in the first the arterial tree was more likely to be healthy than in the second.

MR. TSAPOGAS replied that in one case the occlusion was thrombosis secondary to atheroma, while in the other the thrombosis was not secondary to atheroma.