

Thrombolytic Treatment of Pulmonary Embolism

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Theoretically, major pulmonary embolism offers an excellent and attractive model for the investigation of thrombolytic agents: perfusion to the area is high, the embolus is usually composed of a fresh fibrin, and the underlying vessel is most often normal. Furthermore, the effects of therapy can be assessed objectively by serial angiography, haemodynamic data, and lung scanning studies. Moreover, thrombolytic therapy can simultaneously lyse a fresh deep-vein thrombus and so reduce the incidence of recurrent embolism. Furthermore, measurements as serial angiography, lung scanning, and haemodynamic data can be applied for evaluating the direct effects of the thrombolytic treatment.

However, one has to recognize that the majority of patients who die of major pulmonary embolism do so within a few hours of the embolic episode and therefore before they can be adequately investigated by pulmonary angiography. Therefore clinical trials are performed on a selected group of patients with a relative favourable prognosis. An additional problem is that spontaneous resolution of pulmonary embolism occasionally occurs, but its speed is unknown (Sautter, Fletcher, Emanuel, Lawton, and Olsen, 1964; Fred, Axelrad, Lewis, and Alexander, 1966; Chait, Summers, Krasnow, and Wechsler, 1967).

Sautter and his group have administered urokinase to 10 patients and all did improve clinically, although angiography revealed a clearing in only six of the 10 patients. There was no simultaneous control group but the same authors performed an embolectomy in 14 other patients with acute pulmonary infarction of whom 10 died. In another objective study seven out of eight patients improved after urokinase administration. Angiography, scintillography, and haemodynamic data confirmed the favourable clinical impression (Sasahara, Cannilla, Belko, Morse, and Criss, 1967). Tow, Wagner, and Holmes (1967) have administered urokinase in 13 patients with acute pulmonary embolism of 6 to 8 hours' duration. Responses judged clinically and by lung scans were dramatic in seven of the 13 patients within 24 hours of the thrombolytic therapy. However, there was no simultaneous control group. In two other clinical trials streptokinase was used. Hirsh, Hale, McDonald, McCarthy, and Pitt (1968) have treated 18 patients with recent pulmonary infarction with

streptokinase (24-hr treatment) and 11 patients with heparin (24-hr treatment). In the streptokinase group 14 out of 18 patients had a good clinical response confirmed in 12 cases by angiography. There were four failures; two patients died and two were subsequently subjected to embolectomy and survived. In the heparin group there were only three angiographic controls with no radiological improvement.

In the trial conducted by Miller, Gibson, Honey, and Sutton (1969) nine patients with arteriographically proved pulmonary embolism were treated by a 36-hr infusion of streptokinase. Four of the nine patients had an acute massive pulmonary embolism and in all satisfactory haemodynamic and arteriographic resolution was obtained. Three of the nine patients suffered from pulmonary embolic disease of longer duration, and little or no improvement was obtained with streptokinase treatment. In two patients with minor recent emboli, rapid dissolution was obtained.

Encouraged by this limited but promising clinical study on the use of urokinase or streptokinase in pulmonary infarction, a controlled randomized trial was organized in 16 participating hospitals and sponsored by the National Heart and Lung Institute of the NIH (Bethesda). In a two-year period 160 patients were studied. In this trial, urokinase and subsequent heparin therapy, when compared to heparin therapy alone, significantly accelerated embolus dissolution as shown by pulmonary arteriograms, lung scans, and right-sided pressure measurements. Differences in lung scan resolution between two treatment groups disappeared by the fifth posttreatment day while an average of the original scan defects persisted at one year in both treatment groups. No significant differences in recurrence rate of pulmonary embolism or in a two-week mortality were observed, a finding that was not unexpected in view of the relative small sample of patients. On the basis of radiographic and haemodynamic evidence, patients in shock with 'massive' embolism appeared to show the most favourable response to urokinase treatment (UK Pulmonary Embolism Trial Study Group, 1970).

Phase two of this trial will further evaluate if longer regimens of treatment with urokinase or streptokinase can more readily achieve maximum pulmonary and venous thrombolysis without further increasing the risk of haemorrhage. This further evaluation is required before it can be recommended as a proven clinical therapy.