VALUE OF STREPTOKINASE AND HEPARIN IN TREATMENT OF ACUTE DEEP VEIN THROMBOSIS

B. ROBERTSON, INGA MARIE NILSSON, AND G. NYLANDER (*Department of Surgery, Coagulation Laboratory, and the Department of Roentgenology, University of Lund, Malmö, Sweden* Three coded series of patients, 50 in all, with acute deep venous leg thrombosis of at most 96 hours' duration were treated with streptokinase (Kabikinase(R), Kabi) or heparin by intravenous drip (Table I) followed by subcutaneous heparin (150 to 250 mg/24 hr) for a period of six to seven days. In all three series the trial was carried out by the double-blind method. The diagnosis was made by phlebography in the acute stage with the exception of the first nine patients in series I. The results of treatment were followed by phlebography on the first and fifth days after the infusion. The effect of treatment was judged by a panel of five to eight doctors before the code was broken and classified as good (++), fair (+), or poor (-) (Table II).

TABLE I

DOSES OF STREPTOKINASE AND HEPARIN GIVEN INTRAVENOUSLY IN THE THREE SERIES

	Streptokinase-treated Patients			*Heparin-treated Patients*		
Series	*Initial Dose*	*Maintenance Dose (units streptokinase/hr)*	*Infusion Time (hr)*	*Initial Dose (mg)*	*Maintenance Dose (mg heparin/hr)*	*Infusion Time (hr)*
I	2 × TID (90 min)	50,000	12	75 (90 min)	20	12
II	2 × TID (90 min)	100,000	24	75 (90 min)	20	24
III	2 × TID (90 min)	100,000	72	75 (90 min)	20	72

TABLE II

EFFECT OF TREATMENT OF VENOUS THROMBOSIS

	Good	*Fair*	*Poor*
Series I (50,000 units/hr—12 hr)			
Streptokinase (12 cases)	4	7	1
Heparin (8 cases)	4	2	2
Series II (100,000 units/hr—24 hr)			
Streptokinase (8 cases)	5	2	1
Heparin (8 cases)	1	2	5
Series III (100,000 units/hr—72 hr)			
Streptokinase (7 cases)	3	1	3
Heparin (7 cases)	1	1	5

In series I no difference was found between the effect of streptokinase and heparin; in series II streptokinase was three times, and in series III, twice as good as heparin. Even those cases that responded well to treatment with streptokinase still showed small residual thrombi. In a few of the streptokinase-treated patients in series II and III phlebography showed that the previously involved valves were intact after treatment. The results of treatment with heparin appear much poorer in series II and III than in series I. This is probably because several of the patients in the heparin group in series I were not examined phlebographically and because good clinical regression was not always accompanied by improvement of the phlebograms. Administration of streptokinase was regularly followed by a high blood fibrinolytic activity. The plasminogen fell to 1 to 4% and the fibrinogen to 64% of the initial value. No split products could be demonstrated 24 hours after the infusion. In several of the streptokinase-treated patients bleeding complications occurred after the infusion during the treatment with subcutaneous heparin.

Our findings show that streptokinase is superior to heparin in the treatment of acute venous thrombosis provided a sufficiently large maintenance dose (100,000 units/hour) is given and that treatment is continued for at least 24 hours. The fact that it proved possible to save venous valves in veins containing thrombus, something we have never observed after treatment with heparin alone, is a further strong indication for streptokinase therapy.

THE TREATMENT OF DEEP VEIN THROMBOSIS

P. T. FLUTE, V. V. KAKKAR, C. FLANC, M. J. O'SHEA, C. F. HOWE, AND M. B. CLARKE (*Departments of Haematology, Surgery, and Medical Physics, King's College Hospital and Medical School, London*) Clinical signs alone are unreliable criteria by which to judge the progress of deep vein thrombosis. More objective studies, the local accumulation of radioactivity following the injection of ^{125}I-labelled human fibrinogen (Flanc, Kakkar, and Clarke, 1968), and functional ascending phlebography (Kakkar and Flanc, 1968) were also used in this study.

Twenty-six patients with extensive thrombosis but whose symptoms were of less than three days' duration were allocated, by a random method, to one of three treatment groups. All received a continuous intravenous infusion of physiological saline containing either streptokinase (Kabikinase, Kabi Pharmaceuticals Ltd), a plasminogen activator, 150,000 units hourly; Arvin (Twyford Laboratories Ltd), an enzyme which specifically destroys fibrinogen (Reid and Chan, 1968), 1 unit/kg body weight every 12 hours; or the anticoagulant heparin, 20,000 units every 12 hours. The loading doses given at the start of the treatment were 500,000 units of streptokinase in 30 minutes, 160 units of Arvin in six hours, or 10,000 units of heparin in five minutes.

The infusion was stopped after seven days or earlier if the disappearance of radioactivity suggested, and phlebography confirmed, the complete dissolution of all thrombi from the limb. This occurred in six of 10

patients treated with streptokinase, one of seven treated with Arvin, and two of seven given heparin.

Streptokinase was shown to cause extensive dissolution of thrombi in all but two of the 12 patients studied, sometimes within 12 hours but in one patient not until after six days of continuous infusion.

Methods and aims of laboratory control were discussed (Kakkar *et al*, 1969) and the side effects of each treatment described. Two fatal cases of retroperitoneal haemorrhage occurred in the heparin-treated group. There was only one other case of severe bleeding, an increased menstrual flow in a patient receiving streptokinase, and this was easily controlled. Most of the patients given streptokinase, but not those in the other groups, developed a pyrexia sometimes with rigors. One patient suffered a serious allergic reaction after a small part of the loading dose of streptokinase had been given; this responded to an antihistamine and hydrocortisone and the infusion was continued with ultimately complete dissolution of the thrombus.

Full results of the trial will be reported elsewhere.

REFERENCES

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Reid, H. A., and Chan, K. E. (1968). *Lancet*, 1, 485.

Two further papers relating to 10 patients each were read by Drs Browse and Olow.

HAEMODYNAMIC AND ANGIOGRAPHIC FINDINGS IN PATIENTS WITH PULMONARY EMBOLISM TREATED WITH STREPTOKINASE

G. A. H. MILLER (*Cardiac Department, Brompton Hospital, London*) Nine patients with arteriographically proven pulmonary emboli have been treated by a 36-hour infusion of streptokinase (Kabikinase(R), AB Kabi, Stockholm) into the pulmonary artery (eight patients) or right atrium (one patient). In all patients single-plane (anteroposterior) serial pulmonary arteriograms were obtained before treatment and repeated, sometimes on two occasions, at times varying from 24 hours to a month after starting treatment. In all but one patient an indwelling pulmonary artery catheter permitted repeated haemodynamic measurements during treatment and was used for the infusion of streptokinase, generally a dose of 600,000 IU for the first half hour followed by 100,000 IU/hour thereafter. The results were as follows:

1 *Acute massive pulmonary embolism.* Four patients studied within 48 hours of the acute episode were shown arteriographically to have emboli involving at least half of the major pulmonary artery branches. All exhibited the characteristic haemodynamic disturbance of massive pulmonary embolism with moderate elevation of pulmonary artery pressure, wide arteriovenous oxygen difference and (in three of the four patients) mild arterial oxygen desaturation. Haemodynamic improvement was evident in all at 12 to 15 hours after starting streptokinase and, in three of the cases without preexisting cardiorespiratory disease, was complete at the final study 48 hours, six days, and 28 days later respectively. The fourth patient had evidence of preexisting thromboembolic disease and had mild residual pulmonary hypertension (33 mm Hg systolic) at the final study 34 days after starting treatment. Arteriographic improvement was seen as early as 24 hours and was complete in two patients when studied at 48 hours and six days respectively. In the remaining two patients considerable arteriographic improvement was present at 48 and 65 hours respectively. One of the patients, who was not critically ill, was initially treated with heparin alone for six days. No haemodynamic or angiographic improvement had taken place by this time but was complete 48 hours after starting a 36-hour infusion of streptokinase.

2 *Chronic pulmonary thromboembolism.* Three patients with a history of longer duration were treated with streptokinase. In one, embolism had occurred six weeks previously, in another repeated emboli had probably occurred over weeks or months, and the third patient had a left pulmonary artery thrombosis at the site of an attempted delayed embolectomy for massive embolism occurring three months previously. In none was there any haemodynamic improvement when studied shortly after completing treatment and angiographic improvement was at the most slight in two and absent in the third patient.

3 *Minor recent pulmonary embol.* In two such patients streptokinase infusion was followed by complete disappearance of the filling defects seen on the pulmonary arteriograms when these were repeated at two and three days respectively.

Complications of treatment included bleeding from skin incisions, haematoma formation, haematuria, and vaginal bleeding.

The indications for streptokinase in treating pulmonary embolism are not yet clear. Encouraging results were obtained in acute massive pulmonary embolism and these patients were spared embolectomy. Nonetheless there will be patients in whom the delay in response associated with streptokinase therapy is unacceptable and in whom embolectomy may be life-saving. Little benefit was obtained in three patients with thromboembolism of longer duration but resolution of minor recent emboli was demonstrated within three days in two patients. There is an urgent need for a controlled trial of streptokinase and of heparin therapy in such patients.

THROMBOLYTIC THERAPY IN CORONARY THROMBOSIS

H. A. DEWAR AND I. S. MENON (*Royal Victoria Infirmary, Newcastle-upon-Tyne*) The use of thrombolytic agents in coronary thrombosis has been based on the experimental work of Ruegsegger, Nydick, Hutter, Freiman, Bang, Cliffton, and LaDue (1959). They described the lysis by streptokinase of thrombi artificially produced in the coronary arteries of dogs and showed that this lytic agent also substantially modified the histological appearances of the infarcts which followed the thrombosis. The lytic treatment had, however, to be given within three hours. A few controlled clinical trials have been