PRELIMINARY COMMUNICATION

Diagnosis of Deep Vein Thrombosis with ^{99m}Tc-streptokinase: A Clinical Comparison with Phlebography

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British Medical Journal, 1974, 4, 748-749

Summary

Nineteen patients with signs of deep vein thrombosis in the legs were investigated with a new technique using ^{99m}Tc-streptokinase. This compound is probably superior to iodine-labelled fibrinogen in detecting established thrombi. The ratio between the activity in the leg with suspected thrombosis and the other leg was calculated. The results were compared with those obtained with phlebography. A pathologically high activity ratio was found in 11 out of 13 patients in whom phlebography showed a thrombus, while the ratio was normal in the remaining six patients who showed no thrombus on phlebography. No negative correlation was found between the activity ratio and the titrated initial dose of streptokinase. The activity ratio as well as diagnosing the presence of a thrombus may also provide a guide for therapy.

Introduction

Deep vein thrombosis in the legs is difficult to detect. Since a reliable diagnosis is often most important a number of diagnostic techniques have been developed. We report here a study of the use of ^{99m}Tc-streptokinase. This has advantages over iodine-labelled fibrinogen in that it is efficiently detected by the 1·25-cm crystal of the Anger camera, streptokinase is probably superior to fibrinogen in locating established thrombi, and there is no risk of transmitting serum hepatitis.

Patients and Methods

Nineteen patients (seven men and 12 women) whose ages ranged from 27 to 86 years were investigated. All had clinical signs of postoperative acute thrombosis in the legs, but no patient whose thrombosis occurred before the 11th postoperative day was included in the study. The titrated initial dose (T.I.D.) of streptokinase was determined in seven consecutive cases.

Stocks of streptokinase were prepared by dissolving 600,000 IU streptokinase with 4·5 mg $Na_2HPO_4\ 2H_2O$ and 23mg $NaH_2PO_4\ H_2O$ in 6 ml physiological saline. The solution was then divided into 12 portions and stored in phials in a deep freeze. Streptokinase can be stored in this way for at least three months (Strindberg, 1974).

When required for use a stock phial of streptokinase was thawed and 4 ml of $NaTcO_4$ solution with an activity of 1-3mCi was added. For use as a complexing/reducing agent 5 mg $SnCl_2 2H_2O$ was dissolved in 1 ml of 1-M HCl and 9 ml physiological saline solution was then added. After a few minutes 1 ml of this solution was added to the streptokinase preparation. The pH was then 2. After passage through a 0·22-μm filter the preparation was ready for use, the whole procedure having been performed under strictly sterile conditions. The quality of the preparation was tested by the gel chromatography column-scanning method (Kempi and Persson, 1974). It showed two peaks representing reduced/hydrolysed Tc and ^{99m}Tc-streptokinase in a proportion of about 1:1. The amounts of labelled phosphate complex were negligible.

Intravenous injection of the final solution resulted in the administration of 50,000 IU streptokinase with an activity of 1-3 mCi. One hour after injection the patient was placed supine under an Anger camera (Nuclear-Chicago high performance gamma camera with a 15,000 parallel-hole high resolution collimator interfaced to a computer system, Cine 200). Exposures of five to ten minutes were made over the thighs and calves of both legs. After correcting for background activity the activity ratio between the two legs was calculated by dividing the activity in the leg with suspected thrombosis by that in the other leg. Values exceeding 1·05 were considered pathological.

Intravenous phlebography was performed either before or after the isotope method, the order alternating randomly. The interval between each investigation was one to four days. The technique used for intravenous phlebography was that described by Greitz (1954). The T.I.D. of streptokinase was calculated according to the method of Nilsson and Olow (1962). The results of phlebography were compared with those obtained with the isotope method. The correlation between the T.I.D. of streptokinase and the activity ratio described above was also studied.

Results

The activity ratios fell mostly into two clear groups. In one the ratios were distinctly over 1·05, ranging from 1·30-2·90. In the other they were close to 1. In two cases the activity ratios were 1·10 and 1·15, but even so their difference from the normal value was statistically significant.

Comparison of the results of isotope examination with those of phlebography (see table) showed that 11 patients who had a pathological activity ratio also had phlebographic evidence of thrombosis while six patients who had a normal activity ratio had no phlebographic evidence of thrombosis. There were no false positive results with the isotope method but in two patients the activity ratio was normal while the phlebographic findings suggested thrombosis. The probability that these results could be due to chance was less than 1%.

Correlation of Activity Ratio with Phlebography. Results are Numbers of Patients

Activity Ratio	Phlebography		Total
	Positive	Negative	
>1·05	11	0	11
⩽1·05	2	6	8
Total	13	6	19

The scan, 60 minutes after the administration of ^{99m}Tc-streptokinase, of a thrombus in the left tibial vein is shown in fig. 1. The activity ratio in this case was 2·2. Phlebography confirmed the presence of a thrombus. The values for the

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T.I.D. of streptokinase and the activity ratios in seven patients are shown in fig. 2. There was no indication of the expected negative correlation between these two values—for example, in our two false negative cases the T.I.D. values were low. Since clearly there was no negative correlation this part of the study was then discontinued.

In none of the 19 patients examined were there any signs of adverse reaction to ^{99m}Tc-streptokinase.

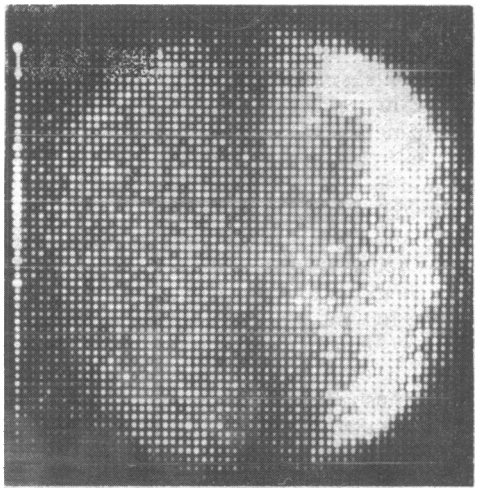

FIG. 1—Scan of both calves in patient with thrombus in left calf. Activity ratio = 2·2.

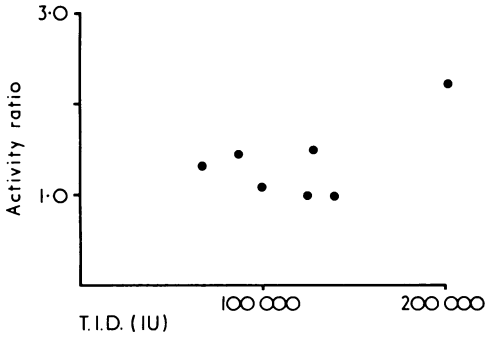

FIG. 2—Values for titrated initial dose (T.I.D.) and activity ratio in seven patients. No negative correlation.

Discussion

The use of isotopes in the diagnosis of venous thrombosis has been mostly limited to radioactive iodine-labelled fibrinogen. Since fibrin deposition is minimal once a thrombus is formed the effectiveness of iodine-labelled fibrinogen in detecting established thrombi is correspondingly diminished. Streptokinase has been shown to induce thrombolysis by means of internal or external lysis or both and ^{99m}Tc-streptokinase should therefore delineate an established thrombus better than iodine-labelled fibrinogen.

Dugan *et al.* (1973) were the first to label streptokinase with ^{99m}Tc. This allows for increased photon flux at the thrombus site and thus better resolution. Their labelling procedure included the use of phosphate buffer and of stannous chloride as the reducing/complexing agent, with a risk that not only ^{99m}Tc-streptokinase but also a ^{99m}Tc-phosphate complex might be formed. Recently ^{99m}Tc-polyphosphate was found to have a strong affinity for infarcted cerebral tissue (Wenzel and Heasty, 1974). It may well have a similar affinity for infarcted or otherwise injured tissue elsewhere. Thus the addition of phosphate buffer in the labelling procedure introduces a risk of loss of specificity. That is why we modified the procedure.

Until now ^{99m}Tc-streptokinase has not been used in a series of patients nor has its diagnostic value been compared with that of an established method for diagnosing deep vein thrombosis. In only two of our patients did it fail to show a thrombus detected by phlebography. There were no false positive results. The two false negative results were perhaps at least partly due to the use in these cases of a rather small dose of streptokinase. When a gamma camera is used the low accumulation of radioactivity in the thrombi necessitates the use of digital systems.

No side effects were observed in any of our patients, but no patient was investigated during the early postoperative period and the risk of haemorrhage was thus avoided. Also we selected for investigation only patients who showed clinical signs of acute thrombosis. Therefore there were no "silent" cases and probably none in which the thrombus was very fresh (Borgström *et al.*, 1965).

The absence of a negative correlation between the T.I.D. of streptokinase and the activity ratio in our cases is interesting. In-vitro determination of the T.I.D. is supposed to indicate the dose of streptokinase needed to induce thrombolysis in vivo. This used often to be taken as the starting dose for treatment but nowadays this cumbersome method is seldom employed. The activity ratio, on the other hand, shows the penetration of streptokinase into the thrombus. Since there is no negative correlation between the T.I.D. and the activity ratio the determination of the T.I.D. is not only rather laborious but also the results are probably misleading. In contrast, the activity ratio of ^{99m}Tc-streptokinase, as described in the present study, may give a better indication of the therapeutic effect of streptokinase, and thus, apart from providing a simple and rapid way of diagnosing deep vein thrombosis, may also provide a guideline for therapy.

We thank A. B. Kabi, Stockholm, for providing the streptokinase used in this study.

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