PRELIMINARY COMMUNICATIONS

New Radioisotope Test for Detection of Deep Venous Thrombosis in the Legs

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Summary

A radiopharmaceutical product, labelled macroaggregates of albumin (M.A.A.), which is in use as a lung scintiscanning agent has been noted to have an affinity for venous thrombi. With this material and an inexpensive portable scintillation detector we have attempted to diagnose and localize thrombi in leg veins. The procedure is performed at the bedside and the result is available in 30 minutes. Thirty-one patients with clinical evidence suggestive of deep venous thrombosis in the legs were studied by the radioisotope method and by phlebography. There was agreement in 18 of 21 legs shown to contain thrombus on phlebography and in 9 of 10 legs shown to be free of thrombosis on phlebography. There was, however, lesser agreement on the site of thrombosis between the two methods. The ease of performing the test combined with the rapidity of obtaining results and accuracy in diagnosis suggests that the test has a clinical application.

Introduction

Pulmonary embolism is responsible for 9% of all hospital deaths (Coon and Coller, 1959). In Ireland pulmonary embolism was the reported cause of death of 223 patients in 1970 (Central Statistical Office, 1970). In the United Kingdom the figure is about 2,500 deaths yearly (Registrar General, 1971). Most of these deaths are due to embolization of thrombi from pelvic or leg veins (*British Medical Journal*, 1966). As the clinical signs of deep vein thrombosis in the legs are notoriously unreliable (Flanc *et al.*, 1968; Kakkar *et al.*, 1969) a number of techniques have been developed to aid diagnosis. These include x-ray phlebography, the ^{125}I -fibrinogen uptake test, and the Doppler ultrasound technique. These tests have a number of limitations and there is scope for a rapid, accurate procedure for the diagnosis of deep vein thrombosis in the legs.

It was noted by a number of workers that occasionally during lung scanning a portion of the injected radiopharmaceutical, radioactive labelled macroaggregates of albumin (M.A.A.),

remained somewhere in the course of the veins towards the right side of the heart. In a few of these patients there was clinical evidence of phlebitis in the veins used for the injection. In the remainder there was the possibility of phlebitis, as all had indwelling venous catheters. This suggested that M.A.A. had adhered to inflamed veins or to thrombi within them. In one reported case (Duffy *et al.*, 1968) a radioactive thrombus later embolized to the lungs, implying that the M.A.A. particles had adhered to the thrombus itself. Webber *et al.* (1969) showed that labelled M.A.A. has an affinity for thrombus. In addition he and others (Webber *et al.*, 1969; Rosenthal and Greyson, 1970) showed that M.A.A. localizes at the site of venous thrombosis in both animals and man.

This radiopharmaceutical, which consists of denatured human serum albumin particles with a diameter of 20-50 μm is almost entirely removed during a single transit through the pulmonary capillary bed. Circulating radioactivity is therefore rapidly reduced to a fraction of the injected dose. Such a reduction in "background" activity increases the possibility of detecting labelled M.A.A. attached to the thrombi by a simple scintillation detector. M.A.A. apparently is only loosely fixed to thrombi (D'Auria and Duffy, unpublished observations). This suggests that there will be a gradual reduction in radioactivity, even from legs containing thrombi, but a more rapid reduction in radioactivity will occur from legs free of thrombosis. We therefore measured the radioactivity at selected sites at five-minute intervals for 25 minutes after injection with a simple portable scintillation detector. Analysis of the results showed two clearance patterns of M.A.A. particles—rapid and delayed.

We correlated these clearance patterns with phlebography. The delayed clearance patterns gave 86% agreement with the presence of thrombosis as shown by phlebography, and the rapid clearance pattern gave 90% agreement with absence of thrombi. An attempt to correlate the site of thrombosis by both methods, however, showed lesser agreement.

Patients and Methods

Thirty-one patients (16 male, 15 female) drawn from the medical, surgical, and gynaecological wards of St. Vincent's Hospital, Dublin, were studied. Their ages ranged from 16 to 82 years. All had clinical evidence of deep vein thrombosis in the legs.

Sodium iodide 100 mg was given by mouth to each patient before injecting the radiopharmaceutical and daily for five days in order to block the uptake of ^{131}I by the thyroid. A commercial preparation of ^{131}I -labelled M.A.A. (Radiochemical Centre, Amersham) was used. This material was allowed to warm to room temperature and the particles were resuspended by gentle shaking. Approximately 75-100 μCi of M.A.A. containing 0.1-0.4 mg of albumin was withdrawn into a sterile disposable syringe and the volume made up to 2.0 ml with normal saline. Two tourniquets were applied to the leg, one above the ankle and one above the knee. Seven points 10-13 cm apart on each leg were marked as shown in fig. 1. The lowest point was about 5 cm above the ankle tourniquet. The radioactive mixture was again gently shaken and injected through a 19-gauge needle into a superficial vein on the dorsum of the foot. This was followed by 15 ml of normal saline injected through the side-arm of a three-way stopcock.

The scintillation detector system consisted of a commercial battery-operated scintillation detector with a 2.5 by 2.5 cm sodium iodine crystal attached to a ratemeter (Pitman isotope localization monitor, model 235). The crystal was applied direct to the skin without forward collimation but with 1 cm of sideway

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FIG. 1—Sites on leg at which radioactivity was measured.

protective lead shielding. The pulse height analyser switch was set for the ¹³¹I position (347 ± 8 keV). The radioactivity was measured as counts per second on the "slow" 12-sec time constant. Readings were obtained at the selected points on both legs five minutes after the injection, with the tourniquet still applied. This reading enables the examiners to ensure that radioactivity has been distributed throughout the leg. The tourniquets were then released and the readings recorded at selected points at 10, 15, 20, and 25 minutes after the injection.

The maximum counts obtained over the anterior lung field with the tourniquets still applied were obtained in the first few patients to verify that an adequate flushing dose had been given to propel labelled M.A.A. particles through the deep system beyond the tourniquets. This measurement was found to be unnecessary as no patient was seen in whom the M.A.A. particles failed to reach the lung fields, using 15 ml as a flushing volume.

Within 24 hours after completion of the radioactive test all patients underwent phlebography according to the technique described by Nicolaides *et al.* (1971) but with the following modifications. Two tourniquets were used instead of three, and crêpe bandaging, massage, and tilting of the bed were omitted. The procedure was carried out with television monitoring.

Results

The clearance of ¹³¹I-M.A.A. from the leg veins fell into two easily distinguishable patterns: one in which ¹³¹I-M.A.A. particles were retained in the leg, and the other in which they were cleared rapidly from it (fig. 2). The following easy-to-apply criteria appear adequate to separate these two groups. Delayed clearance is present if after removal of the tourniquets the radioactivity at any one point (c.p.s.) is five times that in the corresponding point on the opposite leg and this difference persists for 10 minutes or longer, or if the radioactivity at any three adjacent points is three times that at the three corresponding points on the opposite leg and the difference persists for 10 minutes or longer.

The correlation between the radioactive test and phlebography is shown in the table. Thrombi were shown in 21 patients

FIG. 2—Comparison of delayed and rapid clearance of ¹³¹I-M.A.A. from one point in the upper thigh in two patients.

Correlation between Phlebography and ¹³¹I-M.A.A. Clearance in 31 Patients

¹³¹ I-M.A.A. Clearance	Results of Phlebography	
	Abnormal (Thrombus Present)	Normal (Thrombus Absent)
Delayed (abnormal) (n = 19)	18 (86%)	1 (10%), false positive
Rapid (normal) (n = 12)	3 (14%), false negative	9 (90%)
Total patients	21 (100%)	10 (100%)

by phlebography. Eighteen of these were found to have a delayed M.A.A. clearance pattern (86% agreement). Ten patients appeared normal on phlebography and nine of these showed rapid M.A.A. clearance (90% agreement). In three patients with thrombi shown by phlebography there was a rapid M.A.A. clearance (14% false negative). One patient with normal phlebography findings showed delayed M.A.A. clearance (10% false positive).

In order to correlate the site of thrombosis as determined by both methods we divided the leg into two regions only, the calf (including the popliteal fossa) and the thigh. In the thigh area nine thrombi were identified by phlebography. In only five of these patients was the thrombus identified by the isotope method (54% agreement). Two additional patients had delayed clearance of M.A.A. from the thigh area but phlebography showed nothing abnormal.

Fourteen calf lesions were found by phlebography. The radio-isotope method located only 13, with agreement, however, in only 9 patients (64% agreement).

Discussion

Since the clinical signs of deep venous thrombosis are so unreliable and the consequences of failure to detect and initiate treatment are so dangerous it is important to have a test that will give an accurate diagnosis rapidly and with minimal risk and inconvenience to the patient. The ¹²⁵I-fibrinogen test is accurate in diagnosing thrombi of recent origin in the calf and lower third of the thigh (Browse, 1972), and can be performed with little inconvenience to the patient. The results, however, are not available for 48 hours and its accuracy diminishes in detecting established thrombi (Mavor *et al.*, 1972). In addition there is a

small but definite risk of serum hepatitis. The doppler ultrasound method is convenient and results are rapidly obtainable (Evans, 1970), but its application is limited to the detection of thrombi obstructing large vessels from the level of the popliteal fossa upwards into the thigh (Evans, 1970). The technique that we have described may be performed with minimal inconvenience to the patient and results are available in 30 minutes.

The radiopharmaceutical ^{131}I -M.A.A., which has been in common use as a lung scanning agent for about 10 years, has been shown to be safe at a dose three times higher than that used in this procedure. From the known affinity of M.A.A. particles for venous thrombi, both in vitro and in vivo (Webber *et al.*, 1969), it seemed likely that deep venous thrombosis would be associated with a retention or delayed clearance of M.A.A. particles from the limb after intravenous injection into the foot. It seemed possible that a simple scintillation detector system would be adequate to detect this altered clearance pattern.

The results obtained in our patients showed two distinct patterns of clearance, rapid and delayed. Definitive and easily applied criteria were chosen which separate these two clearance patterns. These patterns when compared with phlebography showed a high degree of correlation between delayed M.A.A. clearance and the presence of thrombi (86%), and between rapid M.A.A. clearance and the absence of thrombi (90%). Correlation of the site of thrombi, however, whether above or below the knee, showed less agreement between the two methods. An explanation for this discrepancy in localization is not readily evident. It may, however, be due to the known insensitivity of phlebography or to the relative insensitivity of both methods.

The test as performed here requires the use of the other leg as a control, and so evaluation of both legs simultaneously is not

possible. This is a serious limitation of this technique, as deep venous thrombosis is frequently bilateral. Attempts are being made to eliminate the use of the control leg by using another reference source—for example, a postinjection blood sample.

These preliminary studies indicate that this new isotope test is a safe, convenient, rapid, and accurate method of detecting thrombosis in leg veins, and thus it deserves further evaluation.

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MEDICAL MEMORANDA

Potassium Overdosage: A Potential Hazard of Non-rigid Parenteral Fluid Containers

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The use of non-rigid plastic parenteral fluid containers is becoming increasingly widespread in hospital practice. Recently the contamination of the contents of such containers by a plasticizer used in their manufacture has been reported (Jaeger and Rubin, 1972). The two cases reported here, of probable transient hyperkalaemia resulting from the addition of a supplement of potassium chloride to such a container, suggest a further potential hazard. Experimental evidence is offered to explain why this may have occurred.

Case Reports

Case 1.—A 30-year-old woman was treated with parenteral fluid therapy and nasogastric suction for suspected subacute intestinal obstruction. Her serum potassium on admission was 3.8 mmol/l.

Satisfactory progress followed maintenance on normal saline (159 mmol/l.) for eight hours at a rate of 250 ml an hour. A supplement of potassium chloride solution (13 mEq K⁺ in 5 ml) was injected into the dependent injection side-arm of the intravenous plastic fluid container (Viaflex 500 ml, Baxter Laboratories of Canada Ltd.). After about 10 minutes she became unconscious and clonic contractions of the right side of her body were observed. The radial pulse and blood pressure were unrecordable. Within five minutes she had fully recovered.

Case 2.—A 34-year-old man was similarly given parenteral fluid therapy for suspected intestinal obstruction. The serum potassium on admission was 3.9 mmol/l. Normal saline (500 ml) was infused at a rate of 300 ml an hour for three hours. A supplement of potassium chloride was added to the saline as in the previous case. After 10 minutes he complained of severe pain at the infusion site. He rapidly became restless, pale, and clammy and lost consciousness. A grand-mal convulsion lasting 30 seconds followed. Within 10 minutes he had made a complete recovery.

In each case the infusion was immediately stopped. Samples of the infusion fluid and of ampoules of potassium chloride belonging to the same batch were sent for bacteriological and biochemical analysis. No irregularity was found. It was thought that inadequate mixing of the injected potassium solution may have resulted in a transient hyperkalaemia which subsequently gave rise to the clinical presentation.

Experimental Method and Results

A half-litre of normal saline in a bottle and in a plastic container were arranged for infusion in the normal way. Potassium chloride solution (13 mEq K⁺ in 5 ml) was injected with a plastic syringe, over 10 seconds, through the bottle bung and

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