The clinical findings show that apart from the development of new varicose veins there was no significant difference in the incidence of fully developed or incipient post-thrombotic syndrome, as judged by the presence of pain, swelling, pigmentation, and ulceration, between the legs of patients treated solely with anticoagulants and the legs of those treated surgically. The prophylactic vein ligations gave an incidence of post-thrombotic syndrome similar to that of the thrombosed legs. Thus one may predict that venous surgery performed on a thrombosed leg will not worsen it, but prophylactic vein interruption may produce complications. These results substantially agree with those of Szilagyi and Alsop (1949), who studied a similar series of patients. Their results after surgery were no worse than ours yet most of their patients did not receive anticoagulants. Our 20 patients treated surgically represent approximately the number that would need surgery if 100 patients with embolism were investigated, and the proportion of the different forms of surgery were also typical (Browse *et al.*, 1969). The results are no different if the vena caval ligation and the three thrombectomies are removed.

The cause of the venous insufficiency found in 60% of the legs which had never been shown clinically or phlebographically to be the seat of venous thrombosis is not clear. The tendency for venous thrombosis to be bilateral is well known and it may be that there is a high incidence of undetected minor thrombosis in "normal" legs, but if so it is surprising that such a minor thrombosis can damage the veins to an extent that gives rise to severe postphlebitic symptoms.

The phlebograms show that the state of the deep veins of the leg after treatment with anticoagulants alone is similar to that seen after treatment with surgery and anticoagulants. All the iliac segments and most of the popliteal veins had recanalized but recanalization was rare in the superficial femoral vein, probably because of the pre-existence of a large, normal bypass system between the upper popliteal vein and the profunda femoris vein. The basic similarity between the phlebographic appearances of the two groups two years after the thrombosis confirms our contention that the addition of a surgical procedure to prevent embolism does not increase the prospect of post-thrombotic symptoms developing in a leg that is already the site of venous thrombosis. The similarity between the groups also raises grave doubts about the value of the surgical treatment of thrombosis in the absence of a need to protect against embolism.

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Low-dosage Ancrod for Prevention of Thrombotic Complications after Surgery for Fractured Neck of Femur

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British Medical Journal, 1974, **4**, 130-133

Summary

The effect of a low-dosage regimen of ancrod in the prevention of postoperative deep vein thrombosis was assessed in 24 patients having surgical repair of fractured neck femur and compared with 25 control patients who did not receive therapy. The objective of the therapy was to lower the preoperative fibrinogen level and produce a low concentration of fibrin degradation products yet avoid the haemorrhagic complications of total defibrination. Ancrod therapy proved feasible to carry out, was not associated with haemorrhagic complications, and produced sustained, predictable reductions in fibrinogen concentration. There were seven thromboembolic complications in the control patients compared to one such complication in the ancrod-treated patients. Five deaths occurred in the control group and one in the treated group. Though the incidence of deep vein thrombosis was not apparently affected by ancrod it appeared on venography that the thrombi in the treated patients were less extensive than those in the control patients. Finally, some discrepancies in the diagnosis of deep vein thrombosis by the three techniques of clinical examination, ^{125}I-fibrinogen scanning, and ascending venography were identified.

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Introduction

Pulmonary embolism, which is a serious cause of postoperative morbidity and mortality (Coon and Coller, 1959; Sevitt, 1962;

Hume *et al.*, 1970; Registrar General, 1972), is the major complication of postoperative deep vein thrombosis. The incidence of deep vein thrombosis varies from about 30% in general surgical patients (Kakkar and Flanc, 1968; Negus *et al.*, 1968; Flanc *et al.*, 1969) to 75% in those with fractured neck of femur (Kemble, 1971; Wood *et al.*, 1972), as detected by the ^{125}I-fibrinogen scanning technique. Though there have been encouraging reports about the prophylaxis of deep vein thrombosis by low-dose heparin (Kakkar *et al.*, 1971), dextran (Lambie *et al.*, 1970), and mechanical or electrical stimulation of the calf muscles (Doran and White, 1967, Sabri *et al.*, 1971) it seems that these agents may be less effective after surgical repair of fractured neck of femur (Kakkar *et al.*, 1972). It is possible that only oral anticoagulants are successful in this situation (Sevitt and Gallagher, 1959) though the difficulties of control have limited their usefulness.

The factors causing deep vein thrombosis are not well understood but may operate through the coagulation system since those drugs which inhibit fibrin formation, such as heparin and the oral anticoagulants, provide more satisfactory prophylaxis than the antiplatelet compounds (O'Brien *et al.*, 1971; Wood *et al.*, 1973). Further factors in development of postoperative deep vein thrombosis may be venous stasis and increased viscosity associated with raised preoperative fibrinogen levels (Dormandy and Edelman, 1973).

In view of the thrombotic problems after surgical repair of fractured neck of femur we made a preliminary assessment of the anticoagulant agent ancrod (Bell *et al.*, 1968; Reid and Chan, 1968; Sharp *et al.*, 1968) given in low dosage preoperatively and for three days postoperatively. Ancrod is an enzyme purified from the venom of *Agkistrodon rhodostoma*, the Malayan pit viper, and acts by converting fibrinogen to an unstable form of fibrin by removal of fibrinopeptide A (Ewart *et al.*, 1970; Holleman and Coen, 1970). The objective of low-dose ancrod therapy was to reduce the circulating fibrinogen level and prevent the high plasma viscosity, which may be associated with a tendency to thrombosis, yet obviate the haemorrhagic complications which would occur if therapeutic defibrination was carried out. Additionally, the formation of a low concentration of fibrinogen degradation products with their anticoagulant and antiplatelet action (Kowalski *et al.*, 1963; Larrieu *et al.*, 1966; Prentice *et al.*, 1969) would enhance the antithrombotic tendency of this agent.

Patients and Methods

Patients with fractured neck of femur were studied since they have a high incidence of deep vein thrombosis and present a uniform group with regard to operative treatment. Those with a history of deep vein thrombosis, hypertension, malignancy, peptic ulceration, or bleeding diathesis were excluded. Forty-nine patients entered the trial but as there were two deaths within 20 hours of entering the trial (one in the control group, one in the treated group) the remaining 47 patients were analysed. All patients were followed clinically for complications during their stay in hospital and convalescent wards and were reviewed six weeks after discharge. Since this was a pilot study the double-blind technique was not used, but groups of 10 patients were alternately treated with ancrod (Arvin, Twyford Pharmaceutical Services Ltd., High Wycombe, Bucks.) or used as controls without treatment. Ancrod was administered by continuous infusion starting between four and 12 hours preoperatively and continuing until 72 hours after the operation, except in the first four cases when the infusion was started immediately after operation. The dose used for the first 10 patients was 0·5 U/kg body weight/12 hr. For the remainder of the patients 1 U/kg body weight was given over the first 12 hours and thereafter maintenance therapy was continued with 0·5 U/kg body weight/12 hr. There were 25 control patients and 24 patients in the ancrod-treated series. The controls received only the routine intravenous requirements of dextrose and saline before and after operation. Oral anticoagulants were used solely in their conventional role for established pulmonary embolism or deep vein thrombosis.

The following investigations were performed preoperatively and on days one, two, three, five, and eight postoperatively: full blood count: W.B.C., packed cell volume, platelet count, measurement of fibrin degradation products by the tanned red cell haemagglutination inhibition technique of Merskey *et al.* (1966), fibrinogen by the method of Ratnoff and Menzie (1951), plasminogen, whole blood and plasma viscosity, and clot inspection. The full laboratory data will be reported separately.

DIAGNOSIS OF DEEP VEIN THROMBOSIS

Clinical.—The recorded clinical signs of deep vein thrombosis were leg oedema, increase in calf circumference, positive Homan's sign, and calf tenderness. The presence of unilateral oedema or a 2-cm increase in calf circumference was interpreted as evidence of deep vein thrombosis.

^{125}I-Fibrinogen Scanning.—After admission to hospital 60 mg of potassium iodide was given daily for five days. A total of 100 μCi of ^{125}I (Amersham) fibrinogen was given intravenously and scanning with a Pitman 235 portable scanner was carried out preoperatively, if possible, and on days one, three, five, and eight after operation using the method described by Kakkar *et al.* (1970). A 20% rise in counts sustained for two or more days was taken as evidence of deep vein thrombosis. The ancrod-treated patients required a repeat dose of fibrinogen on the third day after operation because of the rapid disappearance of the labelled fibrinogen.

Venography.—The last 22 patients in the series, 12 controls and 10 ancrod-treated patients, had bilateral ascending percutaneous venography performed eight to 11 days after operation by a modification of the method described by Thomas (1972). A venepuncture was performed on a vein on the dorsum of each foot and a tourniquet applied above the ankle. With the patient horizontal an initial bolus of 40 ml of Urografin 60 (Schering) was injected and serial films taken of the calf and thigh. A further bolus of 40 ml of contrast medium was injected and films taken of the pelvis. The films were coded and reported on by a panel of radiologists and clinicians who knew neither the treatment group of the patients nor the results of their isotope scans or clinical signs.

Results

The changes in fibrinogen and fibrin degradation product levels caused by the ancrod therapy are shown in fig. 1 and 2. Though the therapy was given for only 72 hours postoperatively the fibrinogen concentration remained significantly depressed for a longer period and at the eighth day after operation was

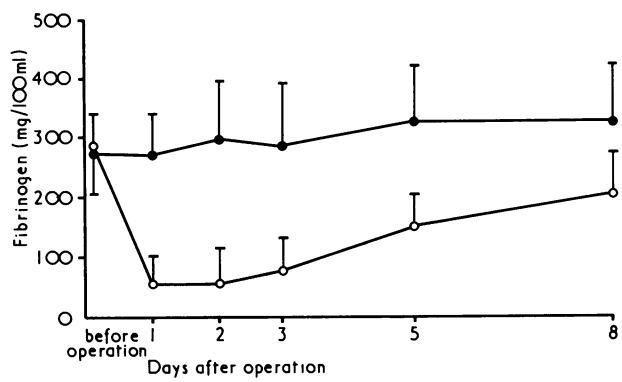

FIG. 1—Mean plasma fibrinogen levels (± 1 S.D.) in ancrod-treated patients (O) and in untreated controls (●). Differences are significant.

Deaths and Major Complications in Eight Untreated and Two Ancrod-treated Patients

Case No.	Age (Years)	Sex	Complication	Onset of Complication (Days after Operation)	Clinical Progress
			Control Patients		
1	90	F.	Pulmonary embolus	39	Died 2 days later
2	80	F.	Sudden collapse 24 hours after operation	1	Died within 1 hour
3	75	F.	Massive pulmonary embolus	13	Died immediately
4	88	F.	Pulmonary embolus	13	Died 2 days later
5	77	F.	Hepatic failure, haematemesis	21	Died 40 days after operation
6	83	F.	Pulmonary embolus	14	Recovered
7	77	F.	Bronchopneumonia, probable pulmonary embolus	20	Recovered
8	80	F.	Episode of acute dyspnoea, probable pulmonary embolus	28	Recovered
			Ancrod-treated Patients		
9	72	F.	Sudden collapse 24 hours after operation	1	Died of myocardial infarction
10	89	F.	Probable pulmonary embolus	12	Recovered

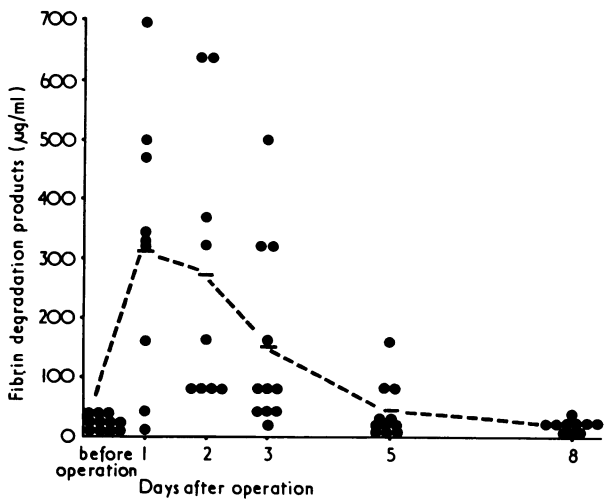

FIG. 2—Changes in levels of fibrin degradation products which mirror fall in fibrinogen produced by ancrod in treated patients.

significantly lower than the control values. The fibrin degradation products in the control patients did not rise above a value of 10 μg/ml, in contrast to the treated patients who showed characteristic early rise in fibrin degradation products.

In the clot observation test most of the ancrod-treated patients showed marked reduction of clot size, which did not usually diminish to "mini" clot size.

Side Effects of Ancrod Therapy.—No case of serious haemorrhage was seen. The ancrod infusion was stopped as a precautionary measure on two occasions because of the vomiting of brown coloured material but in neither patient did haemorrhage occur. One patient had transient haematuria thought to be due to trauma from an indwelling catheter. Operative blood loss was not considered to be significantly increased and postoperative wound problems were not increased in the treated group. The only serious wound complication in the series, an infected haematoma, occurred in the control group.

Deaths and Complications.—There were six deaths in the series—five in the control group and one in the ancrod-treated group (see table). In the control group three of the deaths were diagnosed as due to pulmonary embolism by clinicians with no knowledge of the patient's status in the trial, while the one death in the ancrod-treated group (case 9) was shown at necropsy to be due to myocardial infarction, the leg veins and pulmonary arteries being normal. In particular, there were no haemorrhagic areas in the myocardium or other tissues. Unfortunately, in the other patients who died necropsies could not be done. Another four patients in the series were considered on clinical grounds, supported by lung scanning, electrocardiograms, and radiology, to have non-fatal pulmonary emboli. Three of these patients were in the control group and one in the ancrod-treated group. All the 10 patients described in the table had ^{125}I-fibrinogen scans showing deep vein thrombosis. Of the remaining 37 patients who did not have overt clinical complications 30 had scans showing deep vein thrombosis; and only seven patients in the series had scans showing nothing abnormal. Venograms were carried out on four of the 10 patients with complications, and in three of these (cases 6, 8, and 10) the venogram was positive for thrombosis, whereas in one patient (case 1) who had a late embolus on the 39th postoperative day it showed nothing abnormal.

Incidence of Deep Vein Thrombosis.—The incidence of deep vein thrombosis in the patients who underwent venography is shown in fig. 3. There was no significant difference in deep vein thrombosis between the groups as diagnosed either by clinical signs, isotope scanning, or venography. There was a difference in the extent of the thrombus, however, between the control and ancrod-treated patients. Of the five control patients with venograms that showed deep vein thrombosis two had complete occlusion of the femoral vein and three had calf-vein thrombosis. In the three ancrod-treated patients with venograms showing thrombosis one had a 1-cm length of non-occlusive mural thrombus in the femoral vein and the other two had calf-vein thrombosis.

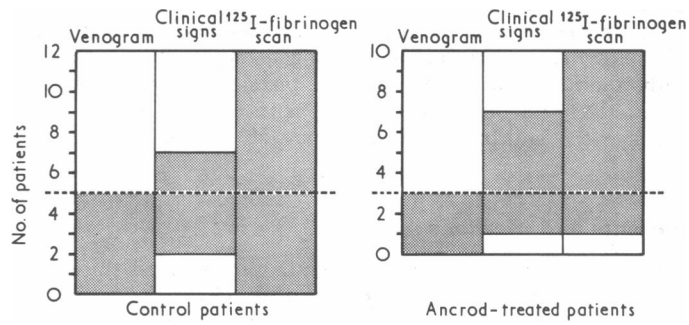

FIG. 3—Comparison of three methods used to detect deep vein thrombosis in controls and ancrod-treated patients. Stippled areas indicate positive diagnosis for deep vein thrombosis and plain areas negative diagnosis. Dotted line separates positive and negative groups as diagnosed by venography.

Interpretation of Data in Diagnosis of Deep Vein Thrombosis.—A problem arose when the results of the three methods of diagnosing deep vein thrombosis were compared. The venograms were considered to provide the most direct evidence of deep vein thrombosis, and the other two methods were compared with them.

There was poor correlation between the three methods of diagnosis (fig. 3). Of 11 patients (six ancrod-treated, five controls) with the clinical diagnosis of deep vein thrombosis six had normal venograms. Similarly, there were discrepancies between the results of the venograms and the fibrinogen scans. There were 14 patients with venograms that showed nothing abnormal who had had scans positive for thrombosis at some period after operation. Of these patients eight had scans showing deep vein thrombosis eight to 11 days after operation, when the venogram was carried out. The other six patients had scans

showing thrombosis which, however, showed nothing abnormal by the time of venography.

Preoperative Scans.—Of 25 preoperative scans performed 24 showed nothing abnormal. The one transient positive scan was at the knee on the injured side and was associated with a possible effusion.

Discussion

It seems from this study that ancrod, in a dosage less than that recommended for normal defibrination, can be given to patients during and after a surgical operation without the risk of increased haemorrhagic complications. As the control of ancrod therapy is usually easier than that of the oral anticoagulants ancrod may be a useful anticoagulant for the prevention of postoperative thrombotic complications.

Though the trial was designed to assess primarily the feasibility of giving ancrod therapy during and after surgery it was encouraging that the mortality and morbidity in the ancrod-treated group were less than in the control series and that the one death in the treated group was not due to pulmonary embolism. In the control group three of the five deaths were probably due to pulmonary emboli, and a further three patients in that group had non-fatal pulmonary emboli. Thus of the total of seven presumed embolic events all but one occurred in the control group. In view of these findings we intend to continue this treatment in a formal clinical trial.

The finding that low-dose ancrod seemed to reduce the complication of pulmonary embolism while not greatly reducing the incidence of deep vein thrombosis was unexpected. A similar discrepancy over the effect of aspirin in postoperative deep vein thrombosis has been noted, however, for though this drug does not affect the number of positive ^{125}I-fibrinogen scans postoperatively it apparently may reduce the number of postoperative thromboembolic complications (Zekert *et al.*, 1973). It may be that the present diagnostic techniques do not predict which type of deep vein thrombosis is liable to give rise to pulmonary embolism. In particular, it is known that many patients with ^{125}I-fibrinogen scans showing deep vein thrombosis suffer no clinical complications, presumably because the small thrombi are cleared spontaneously by the body (Kakkar *et al.*, 1969). Possibly a successful treatment may not affect the rate of formation of small thrombi which are detected solely by fibrinogen scans yet may prevent their extension and subsequent embolization. Some support to the suggestion that low-dose ancrod can prevent the development of dangerous thrombi is provided by the venogram results. In the control patients there were two instances of occlusive femoral vein thrombosis whereas in the treated patients there was only one small non-occlusive thrombus of the femoral vein.

A discrepancy was seen on comparing the results of the three diagnostic methods for detection of deep vein thrombosis. The fibrinogen scans gave an 85% incidence rate for postoperative deep vein thrombosis, which is similar to that obtained for other studies in fractured neck of femur (Wood *et al.*, 1972; Wood *et al.*, 1973). Only 53% of the patients with scans persistently showing thrombosis in the present study had venograms that showed thrombosis, however. This proportion is lower than that of other authors, who have found an 85% concordance between these investigations (Kakkar and Flanc, 1968). Though we accept that venography may be a less sensitive technique, which may miss the small calf-vein thrombi responsible for giving a positive scan, it is difficult to understand how five patients, two in the control group and three in the treated group, had both scans positive for deep vein thrombosis at the time of venography and leg swelling consistent with deep vein thrombosis yet had venograms showing nothing abnormal. If leg swelling is due to deep vein thrombosis there is a sufficient degree of venous occlusion for the condition to be readily shown on venography. Haeger (1969) reported similar findings when he performed venograms on patients with clinical signs suggestive of deep vein thrombosis. Why, then, can 25% of the patients have leg swelling with scans showing thrombosis yet show no venographic abnormality? Possibly a combination of operative trauma and immobility can cause inadequate muscle pump action and increased vascular permeability, resulting in oedema and extravasation of fibrinogen into the tissues. This problem requires further investigation. From a practical point of view we suggest that in studies on fractured neck of femur venography should be the definitive method of diagnosis.

We thank Miss Jeanette Grant for her expert technical help and the members of the accident and orthopaedic division for their co-operation. Ancrod was generously provided by Twyford Pharmaceutical Services Ltd., High Wycombe, Bucks. Dr. C. R. M. Prentice is supported by a grant from the Wellcome Trust.

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