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Prophylaxis of postoperative venous thrombosis

BY COMBINED LEG BANDAGING AND OXYPHENBUTAZONE

Clinical and experimental investigations

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INTRODUCTION, PURPOSE AND PLAN OF THE INVESTIGATION

In an endeavour to reduce the frequency of clinical thrombosis of patients who had undergone operation, in 1966 Arnoldi and Lindahl began to bandage the lower legs with a special technique. They reported the preliminary results of such treatment at the Congress of Angiologists in Essen in 1969 (Arnoldi–Lindahl 1970). By combining this treatment with administration of oxyphenbutazone (Tanderil®) Lindahl, later felt that such treatment practically eliminated the risk of postoperative clinical thrombosis.

The purpose of the present investigation was to test the validity of his opinion.

The plan of the investigation was as follows:

1. The frequency of postoperative thrombosis in patients treated with bandaging of the lower legs plus administration of oxyphenbutazone was compared with that in patients who had not received such prophylactic treatment. Both groups of patients were mobilised in the usual way.
2. Bandaging of the lower legs was studied for its effect on the velocity of the blood flow through the veins of the lower legs.
3. Oxyphenbutazone was studied in animal experiments for its effect on experimental thrombosis and on platelet aggregation.

I FREQUENCY AND FORMS OF THROMBOSIS

Gjöres (1956 and 1967) found in a representative sample of the population that 2.1 % had had thrombosis and that 96 % of these patients had post-thrombotic symptoms, which often reduced their working capacity. In a compilation of investigations of the frequency of clinical thrombosis after operation Borgström (1950) gave between 0.6 and 3.5 %. In a survey Jansen (1972) reported that the postoperative mortality from pulmonary embolism varied between 0.1 and 3 %.

Examination with phlebography or ^{125}I-labelled fibrinogen will reveal a higher frequency of postoperative thrombosis than will clinical methods. Table I shows frequencies ranging from 36 to 62 %. Patients operated upon because of arthrosis of the hip or femoral fracture appear to constitute a high risk group. Thromboembolism is thus a serious problem also in orthopaedic surgery.

Table I. Frequency of thrombosis diagnosed by phlebography and by ^{125}I.

Authors		*Trauma*	*Frequency of thrombosis (%)*
Phlebography			
Borgström et al	1965	Hip fractures	56
Ahlberg et al	1967	,,	36
Freeark et al	1967	,,	41
Johnsson et al	1967	,,	52
Hjelmstedt	1968	Tibia fractures	44
Myhre et al	1969	Hip fractures	40
Hamilton et al	1970	,,	49
Evarts et al	1971	Hip surgery	54
Field et al	1971	Hip fractures	62
Inwood et al	1973	Hip surgery	50
^{125}I			
Flanc et al	1969	Major surgery	44
Williams	1971	,,	41
Field et al	1972	Hip fractures	54
Gordon-Smith et al	1972	Major Surgery	42
Kakkar et al	1972	,,	42
Gallus et al	1973	Hip fractures	48

Kakkar et al (1970) found a significantly higher frequency of thrombosis in patients above 60 years than in patients below this age. Wright et al (1952) in a compilation found thrombosis to be more common in the left leg than in the right. Jansen (1972) reported the frequency of thrombosis to be substantially higher in women than in men. He also showed that the frequency of thrombosis increased significantly with the volume of blood lost at operation and with the duration of the operation. He also reported that a high E.S.R. implies an increased risk of thrombosis. Kakkar et al (1970) found a significantly increased risk of thrombosis among patients who had had thrombosis on some earlier occasion. In that investigation they also found a significantly increased frequency of thrombosis in overweight patients. Some other factors, such as cardiac insufficiency, malignant diseases, arterial hypertension, varices and diabetes mellitus have also been described as increasing the risk of thrombosis (Breneman 1965 and Duckert et al 1966).

A distinction is made between arterial and venous thrombosis as well as between deep and superficial venous thrombosis, so called thrombophlebitis. Arterial thrombi consist mainly of platelets, i.e. a white thrombus, while venous thrombi consist of a relatively small white head and a longer red tail (Anderson 1971). There is thus a difference in the development of the two types of thrombi but not in the initial phase; the difference is quantitative and not qualitative. Poole (1967) concluded that "there is at present nothing to suggest any really fundamental difference in the nature of the processes leading to the formation of thrombi in blood vessels of different types". Hume (1966 a, b) found no difference in respect of platelet count, adhesiveness, thrombelastogram or thromboplastin time between arterial and deep or superficial venous thrombi. Nilsson (1967, 1971) felt that the difference was probably due to the fact that the blood flows almost twice as fast through arteries as through veins and that therefore thrombi in an artery cannot grow so quickly as in a vein.

II THROMBOGENESIS

In microscopic studies of the frog's foot as early as 1851 Wharton-Jones found that "when the blood flow is retarded, adhesion is allowed to take place, and the result is accumulation of colourless corpuscles in great numbers". He also found that "... on pressing the web over the artery or vein—a large vein especially—pretty firmly with a blunt point, an agglomeration of colourless corpuscles with a few red ones held together apparently by coagulated fibrin, occurs...".

Virchow (1856) summarised the causes of thrombosis in his classical triad: vascular injury, decreased flow and changed coagulation conditions. These causes of thrombosis are also widely accepted to-day (Nilsson 1971).

Significance of the vessel wall

That traumatisation of a vessel wall can lead to thrombosis was thus observed already in 1851 by Wharton-Jones. Zahn (1875) clamped the vessels in the frog's foot with tweezers or punctured the vessel with an injection needle and thereby produced thrombosis. Many investigators feel that thrombosis is mainly a manifestation of vessel injury and that it cannot occur unless a vessel is injured (Hirsch et al 1946, Rosenberg et al 1959, Nordöy 1963 and Spaet et al 1966). Traumatisation of vessels is also often used to produce thrombosis in experimental animals (Henry 1962).

Thrombosis has also been induced by traumatising the vein walls with an electric impulse. Sawyer et al (1953, 1955, 1960) found that the intima of the aorta in the dog had an electronegative charge, while the adventitia was positively charged. The difference in potential is about 2–5 mV. Traumatisation of vessels caused a change in potential—the charge of the intima becoming positive and that of the adventitia negative—with adhesion of platelets to the intima as a result. Sawyer et al (1955) found both in vitro and in vivo that platelets aggregated on the positive electrode, but not on the negative one. Electric traumatisation of the vessel or application of a positive charge is now a common method used for inducing thrombosis under standardised experimental conditions (Williams et al 1959, Reber 1966, Poliwoda et al 1968).

O'Neill (1947) devised a method for studying changes in the endothelium of the veins with the aid of silver nitrate staining. With this method after traumatisation of veins it has been found that the endothelial cells form a syncytium of large, multinucleated conglomerates (McGovern 1955). It has also been found that traumatisation causes splitting of the endothelial layer with exposure of the basement membrane, which is built up mainly of collagen. Platelets afterwards adhere to these denuded areas (O'Neill 1947, Samuels et al 1952, Mc Govern 1955 and Wiener et al 1962).

The above investigations were performed on experimental animals but investigations in man are more difficult. Breaking up of the endothelium with exposure of the basement membrane and the occurence of multinuclear endothelial cell syncytia have, however, also been found in man at examination of thrombotised vessels post mortem (Short 1954, McGovern 1955 and Impallomeni 1955).

Role played by platelets

In investigations of the mesenterium of the rabbit and the guineapig Bizzozero (1882) found an accumulation of white corpuscles at the site of traumatisation of the vessels. He called these corpuscles blood platelets. He also noticed that these platelets were adhesive. Hellem (1960) distinguished between adhesiveness and aggregation of platelets: adhesion designating the affinity between the platelets and glass and other tissues; aggregation, the affinity between the platelets themselves, i.e. their tendency to clump.

Several investigations have shown that platelets adhere specifically to collagen and tissues rich in collagen, such as the basement membrane of the veins (Hugues 1962, Kjærheim et al 1962, Zucker et al 1962, Spaet et al 1966 and Baumgartner et al 1967). Testing of the aggregation of platelets in the presence of collagen has therefore become a well standardised method for assessing platelet adhesion in vitro (Bridges et al 1965, Hume 1966 a, b, Ham et al 1967, Mason et al 1972 and Jobin et al 1972).

On adhesion platelets release ADP (Kjærheim et al 1962 and Hovig 1963), which causes the platelets to aggregate (Gaarder et al 1961). In an ordinary light microscope Eberth & Schimmelbuch (1886) studied these platelet clumps, which resembled an amorphous mass. They called this process viscous metamorphosis. Electron microscopic examination have, however, shown that the platelets are closely packed but have their membranes intact (Kjærheim et al 1962 and Poole 1967).

The accumulation of platelets initially formed is reversible and the platelets can separate again. In some species, such as the rat, the platelet aggregates remain reversible (Born et al 1972). In contrast with some other animal

species, in man, thrombin occurs on the surface of the platelets, and this thrombin deposits fibrin on platelet aggregates with the result that the plug becomes stable or irreversible (Kjærheim et al 1962), i.e. the white thrombus is formed (Fig. 1 a).

After operation the platelets have been found to be changed both in number and properties. During the first few postoperative days thrombocytopenia occurs, which after some days leads to reactive thrombocythaemia, which is gradually followed by a return of the platelet count to preoperative level (Emmons et al 1965 and Ham et al 1967). Operation is also followed by increased adhesiveness (Ham et al 1967 and Negus et al 1969) as well as by increased tendency to aggregation (Emmons et al 1965). Becker (1972) found that the postoperative increase in the frequency of thrombosis was correlated with the increased adhesiveness of the platelets. Hume (1966 a, b) found both the adhesiveness and the number of platelets in the blood in

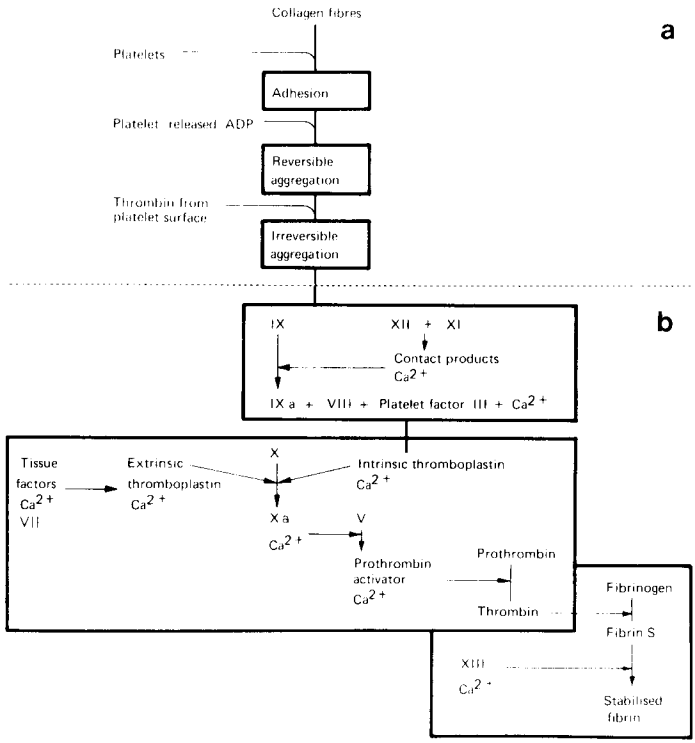

Fig. 1. a) Formation of white thrombus (After Owren 1965)
b) Formation of red thrombus (After B Blombäck 1966)

patients with thrombosis to be increased compared with the findings in a control series without thrombosis.

Changes in the number and properties of platelets resembling those seen after operation have been observed also in diseases known to be associated with an increased tendency to thrombosis. Levin et al (1964) found a marked increase in the number of platelets in the blood in malignant diseases. Platelet adhesiveness has been found to be increased in diabetes mellitus (Bridges et al 1965), in angina pectoris (McDonald et al 1958) and in polycythaemia vera (Duckert et al 1966).

Significance of coagulation factors

The coagulation factors in the circulating blood appear to have but little effect on the formation of the white thrombus. But aggregation of platelets is followed by release of contact factors, which activate factors XI and XII and stimulate the coagulation system with the formation of a red thrombus (Fig. 1 b) as a result.

Gibbs (1957) concluded that "at the present time there is no proof that altered coagulability of the blood is a significant aetiological factor in the production of venous thrombosis". This assertion appears to hold also today (Nilsson 1971, Hampton et al 1972 and Hæger 1973).

That the coagulation factors are of less significance in the causation of thrombosis is elucidated also by the fact that thrombosis and embolism can occur also in patients without some of these factors (Godal et al 1962, Hall et al 1964, Duckert et al 1966 and Ratnoff et al 1968).

Anticoagulants have, however, long been used in the prophylaxis of thrombosis. Several controlled investigations on random groups with objective diagnostic methods, such as phlebography or ^{125}I-labelled fibrinogen, have been reported. Table II gives a survey of such investigations. The control groups in this table are patients who had not received specific treatment. Treatment with heparin consists of both heparin given i.v. or subcutaneous low dose heparinisation. The heading "Coumarols" comprises investigations with both coumarin, warfarin or phenindione. The dextran group comprises both dextran 40 (Rheomacrodex®) and dextran 70 (Macrodex®). Analysis of significance was done by the author with Fischer's significance test.

Significance of flow

"Bei normal schnellem oder mässig verlangsamten Blutstrom kommen also die Blutplättchen mit den Gefässwänden gar nicht in Berührung und es ensteht unter diesen Umständen keine Thrombose, wenn auch die Gefässe

Table II. Frequency (%) of thrombosis in investigations of different types of prophylaxis.

Authors	Year	Control	Heparin	Coumarols	Dextran	p<
Borgström et al	1965	56		9		0.001
Ahlberg et al	1967	36			13	0.01
Johnsson et al	1967	53			6	0.001
Lambie et al	1969			30	10	0.05
Myhre et al	1969	40		18	20	0.05/0.05
Hamilton et al	1970	49		26		0.05
Pinto	1970	32		36		N.S.
Bronge et al	1971			34	42	N.S.
Evarts et al	1971	54			14	0.001
Myrvold et al	1971		39		36	N.S.
Williams	1971	41	15			0.05
Becker	1972	31			31	N.S.
Gordon-Smith et al	1972	42	11			0.001
Kakkar et al	1972	42	8			0.001
Gallus et al	1973	48	13			0.05

N.S. = not significant ($p>0.05$)

verletzt sind" (Eberth et al 1886). But the authors found that when the flow was slow, the platelets deviated from their axial course out towards the vessel wall.

Hewson's classical experiment (cited by Jansen 1972) with ligation of a segment of the vein for three hours produced no thrombosis and that experiment is often referred to as evidence that a slow flow or even stasis is of no significance in the causation of thrombosis. Samuels et al (1952) repeated Hewson's experiment and found platelet aggregates. McGovern (1955) found experimentally that thrombosis can be induced by vessel injury alone, but that thrombosis occured more often in the experimental animals when the flow velocity was decreased. On ligation of the femoral vein of the rabbit Borgström et al (1959) found thrombosis in 5 %. When also afferent veins were ligated the frequency of thrombosis increased to 70 %. The authors ascribed this to the reduced flow.

III VENOUS FLOW THROUGH THE LEGS

Experimental investigations of volume and velocity of flow

Comparisons of the velocity of the blood flow before and after operation with the aid of phlebography (Friemann-Dahl 1935), with the sodium cyanide test (Smith et al 1940), and with the use of ^{24}Na-technique (Jönsson 1951 and Wright et al 1951) showed the velocity to be lower after operation. Wright et al found the velocity to decrease successively to reach a minimum of 60 % of the preoperative value 14 days after operation. Makin (1970) found the velocity to be decreased during operation, while Jansen (1972) reported an increase after operation. The former author used ultrasound and the latter hippuran labelled with ^{131}I.

Wright et al (1952) found an increase in the velocity of the flow by 91 % when the foot-end of the bed was raised 10° and McLachlin et al (1960), who used phlebography, reported that raising of the leg 15° resulted in shortening of the emptying time to one sixth of the corresponding value in the horizontal position. According to Beaconsfield (1970), who used occlusion plethysmography, the arterial flow volume was increased when the foot-end of the bed was raised 15°, but was reduced when the leg was raised 45° because in the latter position venous return may be obstructed by the inguinal ligament. Calnan et al (1970), who used an electromagnetic flowmeter, found that the flow volume in the femoral vein increased when the leg was raised 15°, but returned to its original volume after the leg had been raised for a short while.

Wright et al (1952) reported a reduction of the velocity of the venous blood on change of position of the patient from lying to sitting in a chair, and Beaconsfield (1970) found the arterial flow volume to de decreased when the leg was lowered 45°.

Active loaded or unloaded movements of the foot increases the flow velocity (Wright et al 1952). McLachlin et al (1960) showed that during muscle activity the venous return was accelerated to one third of the resting value. Almén et al (1962) and Arnoldi (1964) demonstrated a similar effect by serial phlebography.

Also passive movements appear to affect the flow. With the use of a so-called foot-mover or soleus-ergometer (Gibbs 1959) during operation, Goldsmith (1966) demonstrated with thermography an increased perfusion of blood through the lower limbs. Roberts et al (1971), who used an electromagnetic flowmeter and the patient's other leg as a control, found passive movement with a foot-mover to increase the flow. According to Calnan et al (1970) the blood flow could be increased by application of a pump arrangement to the calf and that the same effect was obtained by electric stimulation of the calf muscles. This latter method was devised by Doran et al (1964) who, with the aid of ^{24}Na, showed an increase in the flow velocity in the electrically stimulated leg, compared with that in the patient's other leg.

The effect of constant external compression on blood flow in the leg by application of elastic bandages has also been studied. Stanton et al (1949) showed phlebographically that the use of an elastic bandage accelerated venous return. An increased flow volume after application of an elastic bandage was also found by Clark et al (1968), who used a thermodilution technique, and by Calnan et al (1970), who used an electromagnetic flowmeter. With the aid of radioactive iodine it has been demonstrated that use of an elastic stocking increases the flow velocity in the leg (Meyerowitz et al 1964 and Makin et al 1969).

Spiro et al (1970) criticised the therapeutic use of elastic compression. He found wearing of an elastic stocking to reduce the flow volume and thus increase the risk of stasis. Sabri et al (1971) also found that gentle external compression markedly reduced the arterial supply. In a controlled experiment with strain-gauge plethysmography of the big toe, Ginsberg et al (1967) demonstrated that compression of the lower leg by up to 25 mm Hg had no demonstrable effect on perfusion and that perfusion did not fall to nil before application of a pressure of 50 mm Hg.

Various types of compression have been used. Ordinary bandages have been used by Ochsner et al (1941), Stanton et al (1949), Sigg (1952, 1954), Arnoldi (1966 b), Hæger (1966 b) and Arnoldi et al (1970). Elastic stockings have been used by Stanton et al (1949), Meyerowitz et al (1964), Hobbs (1968), Makin et al (1969) and Tsapogas et al (1971). Inflatable splints have been used by Husni et al (1968), Calnan et al (1970), Spiro et al (1970), Sabri et al (1971) and Hills et al (1972). Hæger (1966 b) and Husni et al (1970) reported that the pressure should be highest peripherally and decrease proximally. In experienced hands it is immaterial whether a stocking is used or a bandage of good quality (Stanton et al 1949, Hæger 1966 b and Spiro et al 1970). To avoid stasis, the pressure applied over the calf should not be too excessive, and Makin et al (1969) and Spiro et al (1970), for example, gave 15 mm Hg

as the upper limit, while other authors permit an upper limit of 20 mm Hg (Husni et al 1968, 1970 and Roberts 1971). Ginsberg et al (1967) gave an upper limit of 25 mm Hg, while Stanton et al (1949) showed that a pressure of up to 35 mm Hg is permissible.

Ochsner (1941) bandaged the entire leg, though, as a rule, only the lower leg is bandaged. Husni et al (1968), who used phlebography, reported that application of a pressure of 10 mm Hg over the knee was sufficient to narrow the lumen of, or even occlude, the popliteal vein with a notable risk of stasis. In view of this and the fact that autopsy (Paterson et al 1954, Gibbs 1957 and Roberts 1963), phlebography (Bauer 1940 and Frykholm 1940) and ^{125}I-fibrinogen (Flanc et al 1968 and Kakkar et al 1969) have shown that thrombosis usually begins in the lower leg, it appears reasonable to limit the bandaging to the lower leg.

Inactivity, mobilisation and thrombosis

It has long been generally recognised that early postoperative mobilisation reduces the risk of thrombosis. In autopsy series Gibbs (1957), Sevitt et al (1960/61) and Roberts (1963) showed that the frequency of thrombosis increased with the duration of confinement to bed before death. Their results are demonstrated in fig. 2.

Mobilisation often meant that the patients were out of bed and just sitting on a chair (Hæger 1973). That prolonged sitting predisposes to thrombosis has been shown by Simpson (1940), who during the war found an overrepresentation of pulmonary embolism in patients who had been sitting for a long time in bomb shelters. Hæger (1966 a) found an overrepresentation of thrombosis in patients who had been sitting a long time in aeroplanes.

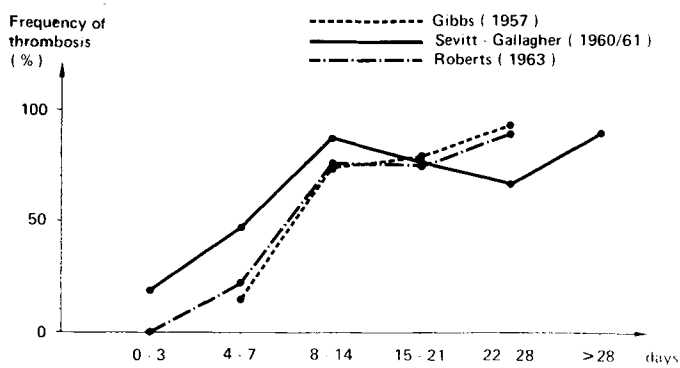

Fig. 2. Post-mortem incidence of thrombosis related to duration of confinement to bed before death.

Powers (1947) emphasised how necessary it was to define what should be understood by mobilisation. He divided his material into three groups: group 1 comprising patients who walked up within 24 hours after the operation, group 2 those who were walking 2-4 days after operation, while group 3 represented "traditional ambulation" on the fifth postoperative day or later. The author found no significant difference between group 1 and group 2, but the frequency of pulmonary embolism was significantly higher in group 3. Borgström (1950) compared a large series, mobilised within two days of operation with a group of patients mobilised later than two days. He found the frequency of clinical thrombosis to be 53 % lower in those mobilised early.

Stimulation of the calf and thrombosis

With a pump described by Calnan et al (1970) and the diagnostic aid of ^{125}I, Hills et al (1972) showed that such stimulation reduced the frequency of thrombosis from 39 % to 3 % in comparison with a control series not treated with the pump.

Electric stimulation of the calf muscles (Doran et al 1964) had, according to the same authors (1967), a prophylactic effect on thrombosis. The patient's leg was stimulated during operation, while the other leg served as a control. The frequency of clinically diagnosed thrombosis was significantly lower in the stimulated leg than in the non-stimulated leg. Later Doran et al (1970), using the same investigation method, found no difference between the effect on the frequency of thrombosis after electric stimulation or raising of the patient's leg during operation. In a randomised investigation with ^{125}I as a diagnostic aid, Becker (1972) found that the frequency of thrombosis in a group of patients in whom the calves had been electrically stimulated during the operation, was 31.4 % in the control group, but only 5.1 % in the treated group.

Bandaging and thrombosis

Sigg (1952) found no instance of pulmonary embolism among 850 patients in whom the lower legs had been bandaged. Wilkins et al (1952 and 1953) found a significant reduction in the frequency of pulmonary embolism at autopsy of patients treated with elastic stockings compared with a control group which had not received such treatment.

Hobbs (1968) found the use or elastic stockings (Tubigrip) to reduce the postoperative frequency of thrombosis from 17.5 to 0 % in patients who had undergone chest surgery. In that investigation the author used a special diagnostic method, so-called refined Loewenberg's test. He concluded that for

"various reasons" the elastic stocking appears to have no effect and that the cause of the reduced frequency of thrombosis was that the patients found the stockings so uncomfortable that they moved the legs more than otherwise. Makin et al (1969) found "Tubigrip" to lower the frequency of thrombosis, as diagnosed on clinical grounds, by 70 %. Several other authors have not found any significant difference in the frequency of thrombosis between patients treated with elastic stockings and those who had not received any prophylactic treatment (Flanc et al 1969, Rosengarten et al 1970 and Tsapogas et al 1971). Flanc et al (1969) treated their patients not only with elastic stockings but also with active mobilisation and intense physiotherapy. Nevertheless, they did not find any significant reduction in the frequency of thrombosis.

IV PYRAZOLE COMPOUNDS AND THROMBOSIS

Phenylbutazone (Butazolidin®) was synthetised in 1946 by Stentzl (Rechenberg 1961). Sigg (1954) found the compound to have a favourable effect on pain, swelling and elevation of body temperature of superficial and deep venous thrombosis. He therefore recommended the use of phenylbutazone in the prophylaxis and therapy of thrombosis. Burns et al (1955) charted the metabolism of phenylbutazone and thereby discovered oxyphenbutazone (Tanderil®) and sulphinpyrazone (Anturan®). Herrmann (1960) found that within a couple of hours half of the administrated dose of phenylbutazone was circulating in the blood as oxyphenbutazone. It was also found that the antiphlogistic effect of oxyphenbutazone was equal to (Yü et al 1958, Connell et al 1959) or even better than that of the ancestral substance (Domenjoz 1960 and Pent et al 1960). Investigations have also shown that the frequency of adverse effects of oxyphenbutazone is not so high as that of phenylbutazone (Connell et al 1959, Domenjoz 1960). Oxyphenbutazone is therefore widely used, especially in the treatment of thrombophlebitis (Pent et al 1960 and Hæger 1963).

Experimental investigations on animals

Pyrazole derivatives have been described as having a stabilising effect on the platelets (Rechenberg 1961). According to Packham et al (1967) and Mustard (1970), phenylbutazone and sulphinpyrazone have a stabilising effect on the cell membranes of the platelets in rabbits, because of the prevention of releasing of adenosine diphospate (ADP) from the platelets. This finding was confirmed by Peterson et al (1970), likewise in rabbits. Packham et al (1967) also showed that phenylbutazone and sulphinpyrazone significantly increased the duration of survival of platelets in rabbits.

Reber (1968) showed that adhesiveness of platelets in the rabbit decreased after administration of phenylbutazone.

Packham et al (1967) found collagen-induced platelet aggregation to be inhibited in rabbits treated with phenylbutazone and sulphinpyrazone.

Reber (1968) showed that phenylbutazone inhibits ADP-induced platelet aggregation in rabbits, while Packham et al (1967) were unable to demon-

strate any inhibition of ADP- or thrombin-induced platelet aggregation by phenylbutazone or sulphinpyrazone in rabbits or pigs.

Packham et al (1967) found phenylbutazone to prolong the bleeding time from mesenterial vessels in the rabbits, and Johnsson (1973) from the dog's skin.

According to Eichholtz (1961) phenylbutazone suppresses electrically induced thrombosis of the jugular vein in the cat. Zbinden (1968) showed that phenylbutazone, but not sulphinpyrazone, inhibits the formation of laurate-induced thrombosis in rabbits and Renaud et al (1970) found suppression of thrombosis induced by a lipopolysaccharide after oral administration of phenylbutazone, oxyphenbutazone or sulphinpyrazone. Their experiments were carried out on rats fed a high-fat diet. Peterson et al (1970) found no reduction of trauma-induced thrombosis in rabbits treated with phenylbutazone in comparison with untreated controls.

Investigations in man

Sulphinpyrazone prolongs the survival of the platelets (Smythe et al 1965 and Packham et al 1967) or normalises postoperatively reduced platelet survival time (Weily et al 1970).

Sulphinpyrazone suppresses platelet adhesiveness (Smythe et al 1965, Weily et al 1970 and Mason et al 1972). The last mentioned authors reported also reduced platelet adhesiveness after administration of phenylbutazone. Breddin (1968), however, found phenylbutazone to have no effect on platelet adhesiveness.

Collagen-induced platelet aggregation is inhibited by phenylbutazone and sulphinpyrazone (Packham et al 1967 and Mason et al 1972). On the other hand, Weily et al (1970) found no inhibition of collagen-induced platelet aggregation by sulphinpyrazone.

According to Fantl (1967) and Mason et al (1972), ADP-induced platelet aggregation is inhibited by phenylbutazone and oxyphenbutazone. Mason et al also found sulphinpyrazone to have such an effect. Weily et al (1970) were unable to demonstrate any inhibition of ADP-induced platelet aggregation after administration of sulphinpyrazone.

Thrombin-induced platelet aggregation is not inhibited by phenylbutazone or sulphinpyrazone (Packham et al 1967 and Mason et al 1972).

Clinical trials of pyrazole compounds and frequency of thrombosis

As mentioned in the introduction, Sigg (1954) treated thrombosis and thrombophlebitis with phenylbutazone and apparently with a good effect. Similar

results have been presented by other investigators in the treatment of superficial thrombosis, so-called thrombophlebitis, with the use of phenylbutazone (Bloch et al 1957, Stamm et al 1957 and Willenegger et al 1957). Pent et al (1960) and Hæger (1963) reported successful treatment of thrombophlebitis with oxyphenbutazone.

Several investigators have compared the effect of phenylbutazone on deep venous thrombosis in patients with untreated controls. Several investigators have found phenylbutazone to have no significant effect on the frequency of clinically diagnosed thrombosis (Aeppli et al 1957, Bloch et al 1957, Stamm et al 1957 and Willenegger et al 1957). Kaufmann (1957) and Lemaire et al (1969) found no significant difference in the frequency of thrombosis between a series treated with phenylbutazone and one treated with coumarol. Dargent et al (1972) reported a significantly lower frequency of clinical thrombosis in patients treated with oxyphenbutazone than in an untreated control group, but no difference between the frequency in patients treated with oxyphenbutazone, with coumarol or with Rheomacrodex®. Castaing et al (1972) found no difference in the frequency of clinical thrombosis after treatment with oxyphenbutazone or coumarol and an untreated control group.

Aeppli et al (1957) reported a significantly lower frequency of pulmonary embolism in a group treated with phenylbutazone than in a control group. Some investigators have, however, found no significant decrease in the frequency of pulmonary embolism (Baerlocher 1957, Stamm et al 1957 and Willenegger et al 1957), while Bloch et al (1957) found a significant increase in the total frequency of pulmonary embolism as well as of fatal pulmonary embolism.

Adverse effects of oxyphenbutazone

Oxyphenbutazone is widely used and several investigations of the frequency of its side-effects have been published. A survey by Ciba-Geigy AG (1966) reports 290 investigations.

A few serious complications have been reported, such as exfoliative dermatitis (Andersson et al 1962), thrombocytopenic purpura (Armstrong et al 1961), leukemoid reaction (Perers et al 1966) and liver damage (Gaisford 1962). Some of these cases occurred after a short time of treatment. However, it could often be difficult to verify a causal relationship between the drug and the complication with certainty (Råde 1966). Böttiger et al (1973) reported an increased risk of aplastic anaemia during long-term treatment with oxyphenbutazone.

Phenylbutazone causes oedema with a maximum after 6–8 days treatment, after which the oedema disappears despite continued treatment. Figdor (1964,

1967) found no difference between phenylbutazone and oxyphenbutazone in this respect. He found an increase in weight by 1.5 to 6.6 kg in 13 of all together 45 patients examined. He also found a decrease in the hematocrit, Hb and number of erythrocytes as well as a decreased production and increased specific weight of the urine. He also reported a decreased excretion of sodium in the urine and an increased amount of sodium in the blood. On the other hand, no change in the potassium content of the blood was observed. The tendency of phenylbutazone to cause oedema was not dose-dependent.

The oxyphenbutazone has also been described as capable of causing gastric ulcer, but so far no case has ever been reported to the Adverse Drug Reaction Section, Department of Drugs, National Board of Health and Welfare between the years 1965 to 1973. On the other hand, gastrointestinal haemorrhage has been reported on three occasions (Strandberg 1974). Whether such haemorrhage is due to local irritation by the preparation, to allergy, or to a generalised effect via the hypophysis and/or adrenals is still obscure (Johansson et al 1971). Schmid et al (1965) found oxyphenbutazone in an oral dose of 800 mg a day in man to increase the secretion of the gastric juice, to produce a small decrease in pH, and to inhibit gastric peristalsis, but to have no effect on the pepsin activity. Johansson et al (1971) showed oxyphenbutazone per os to reduce the mucin content of the gastric mucosa in rats. They also deposited the drug directly in the duodenum via a tube and found it to have a similar effect on the gastric mucosa and therefore concluded that the effect was generalised. The drug also reduced the carbohydrate content and thereby rendered the mucin more readily digestible by trypsin and pepsin.

Between the years 1965 to 1973 a few cases of other types of adverse effects such as pancreatitis, parotitis, icterus, glossitis and sialoadenitis as well as skin changes have been reported to the Adverse Drug Reaction Section (Strandberg 1974).

Effects of the types described above occur mainly after long-term treatment. Sperling (1969) reported side-effects in 7.8 % of patients who had been treated up to 10 years because of rheumatic diseases, but in only 0.7 % were the side-effects such as to indicate withdrawal of the preparation; in one of all together 562 patients the side-effect was oedema and in three gastric ulcer.

Billow et al (1962) reported mild side-effects with a frequency of 3.2 % during short treatment. These side-effects did not, however, make it necessary to discontinue treatment. Hæger (1965) reported mild side-effects in a frequency of 1.7 %. In controlled short-term trials of all together 777 patients with oxyphenbutazone no side-effects were observed (Allgöwer et al 1963,

Berghagen et al 1963, Hipps et al 1963, Mikkelsen 1963, Ivarsson et al 1964, Ekblom et al 1966 and Wisborg 1966).

On the basis of extensive experience with the use of the drug Sperling (1969) concluded that "this drug has been found exceptionally safe for short-term and medium-term treatment . . .". He felt that occasional serious side-effects may occur owing to hypersensitivity.

Present investigations

Part I CLINICAL STUDIES

V MATERIAL

The present material consisted of a consecutive series of patients, aged above 50 years and admitted to the department of orthopaedic surgery, Regional Hospital, Linköping, for operation of the hip.

The patients were randomly distributed between two groups, a control group and a treated group (see VI, Statistical Methods).

In Table III the patients are grouped according to age, sex, side operated upon and relative weight calculated according to the principle given by Arvidsson et al (1973).

Table III. Survey of material (number of patients)

		Control group	Treated group
Age	mean	68 years 7 months	68 years 7 months
	range	(50—83)	(53—89)
Sex	men	8	10
	women	15	17
Operated side	right	11	16
	left	12	11
Relative weight	<90	4	3
	90—110	5	4
	>110	14	20

Relevant laboratory data are given in Table IV.

One of the controls and one of the patients treated had also Parkinson's disease. Of the patients treated, one had chronic tibial osteomyelitis, and one diabetes mellitus. One of the controls and two of the patients treated had been operated upon earlier because of varices.

Table IV. Laboratory data (means, ranges within brackets)

	Control group	Treated group
E.S.R mm/hr	28	28
	(9—81)	(4—113)
Platelets	229 854	235 082
(Normal 140—400 000/μl)	(53—309 000)	(84—421 000)
Normotest®	107	102
(Normal 80—120 %)	(86—160)	(72—145)
APTT®	37	38
(Normal 30—45 sec)	(25—44)	(30—53)
Hematocrit	39	38
(Normal men 41—50 %	(35—46)	(32—45)
women 36—42 %)		
Leukocytes	6513	6433
(Normal 4—9,000/μl)	(3,100—13,200)	(3,500—11.500)
Sodium	141	141
(Normal 138—150 mEq/l serum)	(136—147)	(138—146)
Potassium	4.2	4.3
Normal 3.5—5 mEq/l serum)	(3.2—5.7)	(3.7—5.5)

VI METHODS

Methods of treatment

The circumference of the calf and that of the thigh were measured preoperatively in order to obtain reference values for follow-up examination for thrombosis (Table VI, page 29). Laboratory values given in Table IV (page 26) were determined. These determinations were made with conventional methods at the department of clinical chemistry. Regional Hospital, Linköping. Prothrombin time was determined with Normotest® (Nygaard, Oslo) and kaolin cephalin time was determined as activated partial thromboplastin time with APTT® (General Diagnostics, American Optical Co Ltd).

All patients were premedicated subcutaneously with 0.5 mg atropine sulphate and 25 mg promethazine chloride (Lergigan®).

The anaesthetic procedure used throughout was as follows. General anaesthesia was induced by intravenous, shortacting barbiturate (Narkotal®) in a dose of, on the average, 330 mg (range 220 to 550 mg) (4–10 ml.) The patients were before intubation given an intravenous injection of 4.5 mg d-tubocurare (Tubocurarine®) and 75—100 mg suxamethonium chloride (Celocurin®). The anaesthesia was maintained with oxygen and nitrous oxide, usually in equal amounts and with a flow of 3 liters per minute of each gas and 0.5–1 % halothane (Fluothane®) with a vaporizer placed before the circle system. The patients breathed spontaneously during the anaesthesic period. During the operation usually one liter of sugar-electrolyte solution (Normodex®) was given slowly intravenously, but no plasma expanders, such as dextran (Rheomacrodex® or Macrodex®) or polypeptides (Haemacel®). In addition the blood lost at operation was carefully calculated by measuring the amount of blood in the suction bottle and immediately weighing the operation sponges used. Blood lost was substituted by transfusion, preferably with some overcompensation (Table V). The anaesthetic period was usually 35 to 50 minutes longer than the actual operation period.

The indications for operation as well as for the type of operation are given in Table V. The table also gives the duration of the operation and the loss of blood.

When postoperative analgetics were necessary the patients were given pethidine chloride (Pethidin®) or penthazocine (Fortalgesic®) parenterally or

Table V. Data on operations.

		Control group	Treated group
Indications for operation*)			
Osteoarthrosis coxae		11	15
St p fract colli fem		11	9
Rheumatoid arthritis		1	3
Types of operation*)			
Osteotomy		3	2
Arthroplasty a m Thompson		8	8
Arthroplasty a m McKee-Farrar		12	17
Duration of operation	(mean)	1 h 40 min	1 h 42 m
	(range)	(30—250 min)	(35—155 min)
Blood loss (ml) at operation	(mean)	1334	1231
	(range)	(300—3.600)	350—2.450)

*) Number of patients

paracetamol (Alvedon®) or dextropropoxyphene-paracetamol (Distalgesic®) by mouth. Acetylsalicylic acid preparations were avoided.

All the patients were mobilised the day after the operation. The patients were not allowed to sit on a chair for the first six days, but they were given walking exercise twice a day. In addition, patient received exercise of the operated hip and breathing exercises, likewise twice a day. This treatment was given by a physiotherapist who also instructed the patients how to exercise on their own.

The treated group received, in addition, as follows.

1. *Bandaging* of both lower legs. The bandages were applied with a special technique already at the operation theatre at the end of the operation. Beginning from the basis of the toes it was wound in pronation turns spirally round the leg, care being taken to cover the foot and lower leg as carefully as possible, each turn overlapping the preceeding one by about one third. During application the bandage was stretched by about one third of its length. The bandage was rewound twice a day or more often, if necessary. The bandage was worn also at night and all together for 14 days after the operation. The nurses and the physiotherapists responsible for the bandaging were given careful instructions and the bandaging was checked every day by the author. Lohmann Dauerbinde® "kräftig" was used and with a width of 10 or 12 cm, according to the size of the patient's foot and leg.

The foot-end of the bed was raised 15° two hours every day.

2. *Oxyphenbutazone* (Tanderil®) was given from the day of the operation until the 14th day inclusive after operation. In order to permit treatment

with the preparation already on the day of the operation, the drug was given in the form of suppositories, 250 mg in the morning and 250 mg in the evening.

Laboratory determinations (Table IV, page 26) were made on the 3rd, 6th, 9th and 14th day after the operation. In addition, faeces of those patients treated with oxyphenbutazone were examined for blood before operation and every 3rd day until the 18th day inclusive after the operation, i.e. also on two occasions after withdrawal of the drug. Faecal blood was determined semiquantitatively with the guajac test.

The patients were examined every day for conventional clinical signs of thrombosis (Table VI). When any three of the signs given in the table were demonstrated, thrombosis was suspected.

Phlebography was done at the earliest on the 14th day after the operation or earlier if the patient showed clinical signs of thrombosis.

Table VI. Clinical signs of thrombosis.

Tenderness of the calf
Palpatory firmness of the calf
Homan's sign
Swelling of the calf (measured 12 cm below the medial part of the joint space in the knee)
Increased venous marking
Tenderness over the adductor canal
Palpatory firmness of the adductor canal
Swelling of thigh (measured 15 cm above the medial part of the joint space in the knee)
Tachycardia (more than 100 beats per minute)
Elevation of body temperature (above 38°C)

Diagnosis of thrombosis

By Göran Stenport and Bengt Tillberg

See Appendix.

Statistical methods

By Lars Lindwall and Bengt Tillberg

The original material consisted of 51 patients randomly distributed between two groups, namely 25 controls and 26 patients treated. The randomisation was done by a reception nurse according to the randomisation table. It so happened that, owing to a misunderstanding between the reception nurse and the ward nurse, two patients assigned to the control group had been

erroneously assigned to the treatment group. This error was not regarded as systematic because the reception nurse was unaware of the purpose of the classification of the patients. The error could therefore be regarded as a random change of the original randomisation, which was thus a new randomisation. This misunderstanding was not considered to require any modification of the analysis of the results of the trial.

One of the patients in the group treated, an 85-year old woman, was in such a poor condition after the operation that the treatment planned could not be given. She was therefore excluded from the treatment group.

The final material accounted for in the present investigation thus consisted of 23 controls and 27 patients treated.

Fischer's exact test was used in the calculation of the significance of the difference in thrombosis frequency between the controls and the patients treated.

The significance of the differences between postoperative laboratory values between controls and the treated group was calculated with Student's t-test. The calculations were based on the deviations from preoperative values, which, according to definition, were randomised.

VII RESULTS

All together 18 cases of thrombosis, 13 in the control group and 5 in the treated group, were diagnosed phlebographically (Table VII). The difference between the two groups was significant ($p<0.01$).

Table VII. Frequency of thrombosis

Group	No of pat.	No.	Per cent
Control	23	13	56.5
Treated	27	5	18.5

$p<0.01$

In four cases the diagnosis was assumed on clinical grounds, in two on the ninth, in one on the tenth, and in one on the twelfth day after the operation. In three of these cases the diagnosis was confirmed phlebographically and these patients were treated with anticoagulants. The fourth patient, in whom the clinical diagnosis could not be confirmed phlebographically, did not receive anticoagulant therapy but was re-examined with phlebography according to schedule, i.e. at the earliest 14 days after the operation.

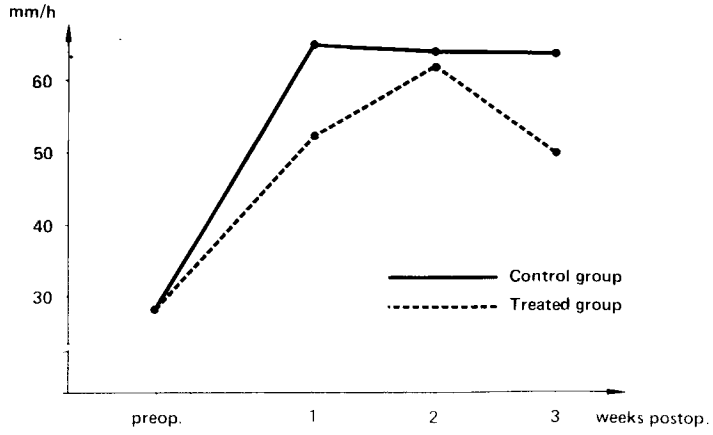

Fig. 3. Erythrocyte sedimentation rate (mean values).

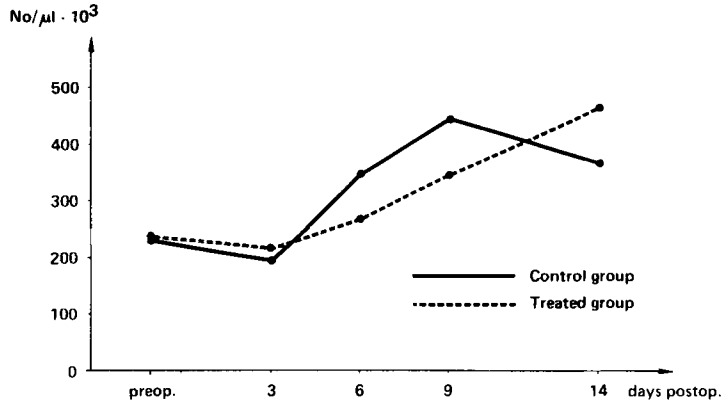

Fig. 4. Platelet counts (mean values).

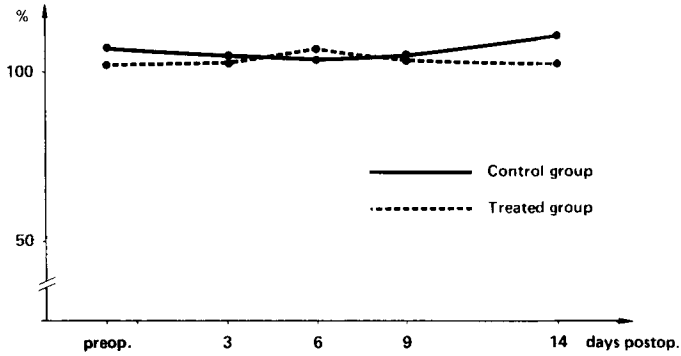

Fig. 5. Normotest® (mean values).

Fig. 3 gives changes in the sedimentation rate, one to three weeks after the operation. No significant differences were found between the controls and the treated group.

Fig. 4 shows the fluctuation of the platelet count. No significant differences were found between the controls and the group treated.

Fig. 5 gives the changes in the results of the Normotest®. Neither here were any significant differences found between the control group and the treated group. This also applies to APTT® (Fig. 6).

Table VIII shows the occurence of blood in the faeces of patients treated with oxyphenbutazone. The frequency of blood in the faeces before operation and before the beginning of treatment was 1 out of 27 (3.7 %), and during the first 18 days after operation, 6 out of 162 samples (3.7 %). No significant differ-

Table VIII. Semiquantitative traces of blood in faeces (number of patients)

Grade	Days after operation						
	preop.	3	6	9	12	15	18
neg	26	25	26	25	27	26	27
+	1	2	1	2	0	1	0
++	0	0	0	0	0	0	0
+++	0	0	0	0	0	0	0

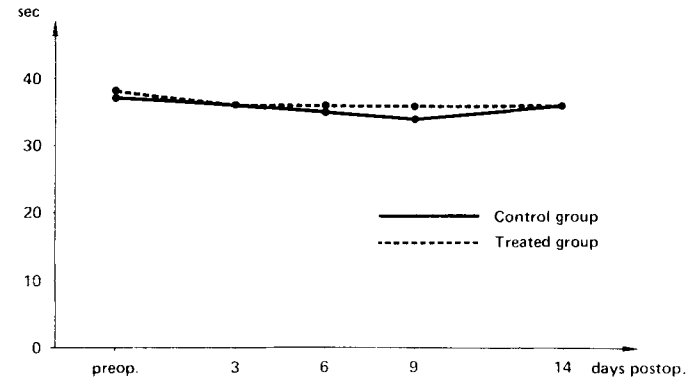

Fig. 6. APTT® (mean values).

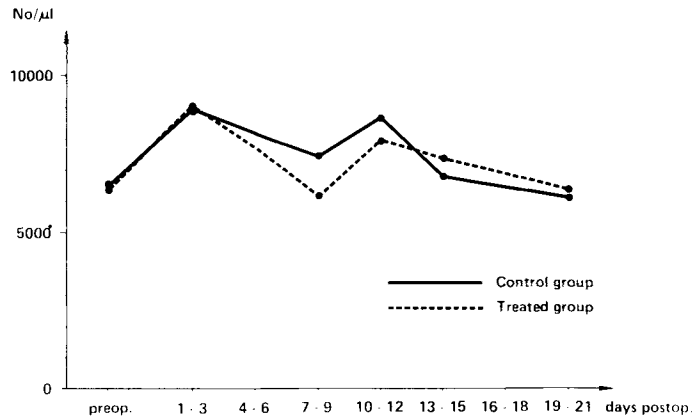

Fig. 7. Leukocyte counts (three-days means).

ence in this respect was found between the two groups before treatment with oxyphenbutazone, during or after treatment. In none of the cases was blood in the faeces demonstrable on more than one occasion.

The variation of the number of leukocytes is given in Fig. 7. No significant differences were found between the controls and the treated group.

Neither were any significant differences found between the two groups regarding the hematocrit (Fig. 8), serum sodium (Fig. 9) or serum potassium (Fig. 10).

One of the patients treated with oxyphenbutazone developed exanthema after seven days' treatment. The exanthema disappeared after withdrawal of the drug.

Table IX gives the postoperative complications in the control and the treated group.

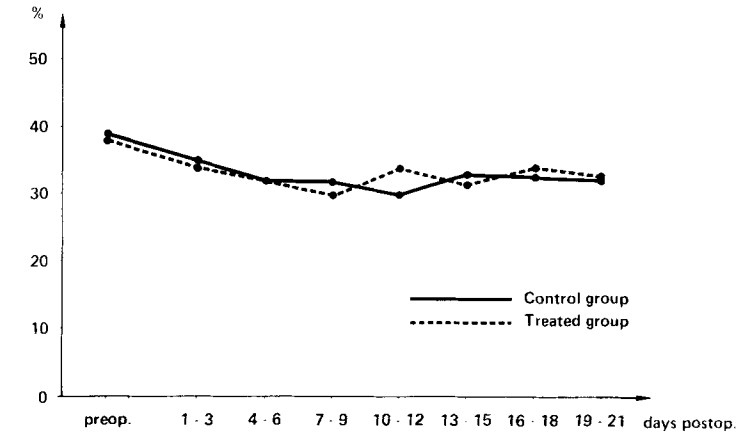

Fig. 8. Hematocrit (three-days means).

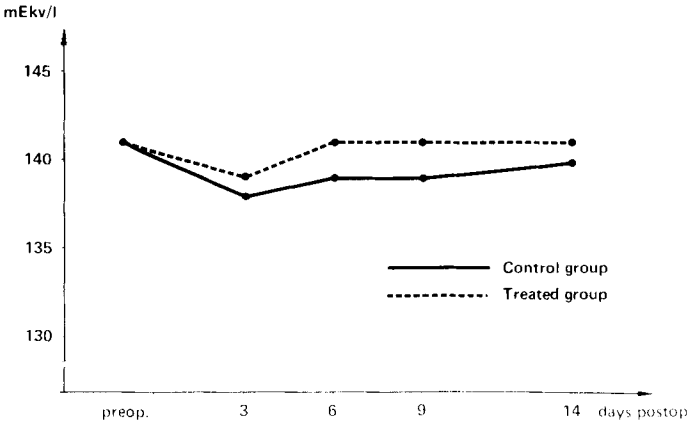

Fig. 9. Sodium in serum (mean values).

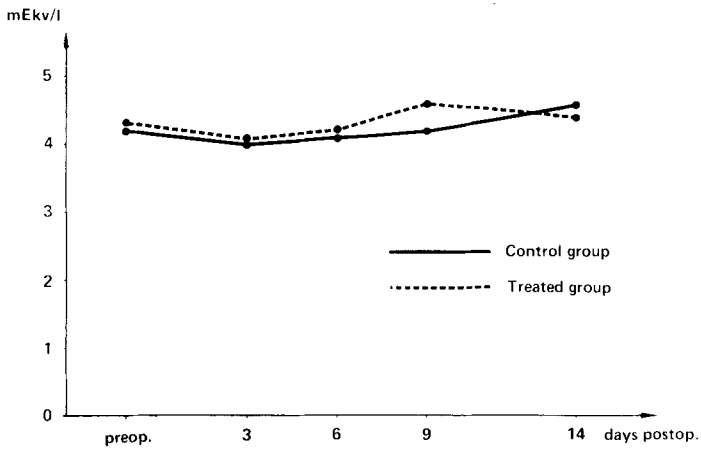

Fig. 10. Potassium in serum (mean values).

Table IX. Postoperative complications (number of patients)

Diagnosis	Control	Treated
Wound haematoma	2	1
„ infection (superficial)	1	1
„ „ (deep)	2	0
Transient peroneal palsy	0	2
Urinary infection	0	2
Bronchopneumonia	0	1

Part II. FLOW STUDIES

VIII VELOCITY OF VENOUS BLOOD FLOW THROUGH THE BANDAGED AND UNBANDAGED LOWER LEG

By Per Ask, Jan-Olov Linell and Bengt Tillberg

The purpose of the investigation was to find out whether bandaging of the lower legs according to the technique used in the clinical investigation had any effect on the flow velocity through the deep veins in the lower legs.

Material

The material originally consisted of 23 patients. In three of them, however, the curves obtained were so flat that they could not be used for any calculations. These three patients were therefore excluded. The remaining 20 patients (12 women and 8 men) had a mean age of 63.2 years (range 50 to 77) (Table X, page 41). Only patients who had not at the time of the examination, or previously, had clinical symptoms of circulatory diseases of the legs and who had not previously undergone operations on the lower legs, were accepted. Each patient served as his own control and the leg that was bandaged was also examined unbandaged, i.e. it likewise served as its own control.

Methods

The velocity of the venuos blood flow was estimated with the aid of injection of technetium-labelled albumin.

Examination method

With the patient sitting with the legs hanging and without application of venous occlusion, a small vein on the dorsum of the foot was punctured, usually the big toe, but in a few cases the lateral aspect of the dorsum of the foot. The puncture was made with a 1.00 intravenous catheter (venflon, Viggo®). The patient was afterwards allowed to lie and rest for a while, during which the blood pressure and pulse (ECG) were recorded. When these variables had become steady examination was started. The temperature

of the examination room was maintained at 21 to 22°C and the patient was covered by a blanket during the resting period.

The patients were examined lying on the side with the lower leg to be examined uppermost, and with the knee slightly bent. The leg to be examined was resting on its prominences of the knee and foot region with a sheet of foam rubber in between, care being taken that the soft tissues were free and the vessels not compressed. Whether the right or left leg should be examined was decided by chance.

It was also decided by random whether the legs should be examined first with or without bandages, i.e. with both lower legs bandaged or neither.

The legs were bandaged in the same way as in the clinical examination (VI, page 28) with a Dauerbinde® "kräftig".

The isotope was injected by hand and the time of the injection was noted on the curve. A scintillation detector was placed in the popliteal fossa and the site of the detector was marked on the patient's leg so that it could be placed in exactly the same position at the second examination. Care was also taken that the leg was placed in exactly the same position so that the detector geometry was identical at both examinations.

The isotope used ^{99m}Tc (AB Atomenergi, Sweden) was bound to human albumin (Kabi, Sweden). The half-time of the isotope is six hours and it is a pure gamma-emitter. The disappearance curve for the albumin follows a six-hour biological half-life (Smith 1965). Two per cent of the albumin leaves the blood stream within 15 minutes (Veall et al 1958). At every examination 50 μc bound to one ml of albumin was injected, i.e. each patient received in all 100 μc. This dose gives a whole body radiation dose of 1–2 mrad and to a total blood volume dose of 4–5 mrad (McAfee et al 1964).

Examination equipment

A scintillation detector 24 mm thick and 47 mm in diameter was used (Modell SI 8, Nukab AB, Sweden). To the detector was coupled a high voltage supply (Modell 644082, Picker, Connecticut, USA). The impulses were transmitted to a gamma-spectrometer (Modell 644-055, Picker, Connecticut, USA) coupled to a ratemeter (Modell 628-143, Picker, Connecticut, USA) equipped with a curve writer and digital writer.

Calculation of mean transit time (Hamilton et al 1928)

It is clear from Fig. 11 a that the curves obtained had a considerable "tail" because the background activity after the injection was higher than before. The average value for the background radiation before the injection was used as a base line. The "tail" was extrapolated in the conventional way (Broman et al 1971) by calculating the exponential function according to a

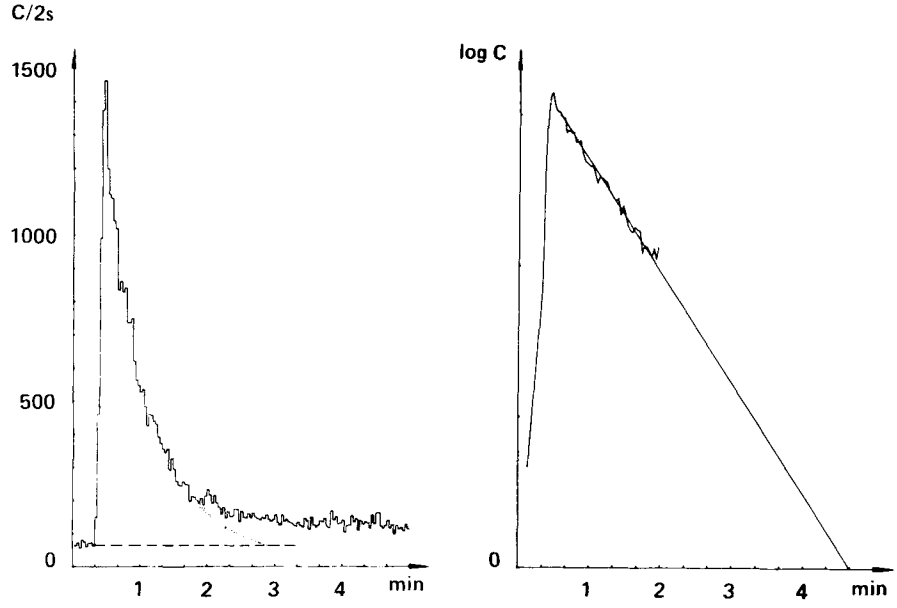

Fig. 11. a) Activity detected in popliteal fossa after injection of ^{99m}Tc-albumin, with extrapolation dotted.
b) Same curve in semilogarithmic scale. Straight line denotes the tangent of the curve. Injection at X=O.

semilogarithmic method. The tangent to the semilogarithmic curve (Fig. 11 b) was calculated approximatively, while other calculations were done exactly mathematically.

The mean transit time was afterwards calculated by integration of the curve according to the formula

$$\bar{t} = \frac{\int_0^\infty C(t) \cdot t \cdot dt}{\int_0^\infty C(t) \cdot dt}$$

where $\bar{t}$ = mean transit time
0 = point of injection time
C = activity detected

All the calculations were done with the aid of a calculator.

The results were treated statistically with Wilcoxon signed rank sum test-double tailed.

Analysis of sources of errors

To examine the shape of the curve after injection of the radioisotope into the superficial venous system the tracer was injected into the great saphenous vein ventrally to the medial malleolus. Each patient (five patients) was examined twice and the examinations were performed without bandaging. In all the cases the curves showed a rapidly ascending and rapidly descending slope. In addition, the velocity of flow was higher than when the injection was given into a small vein on the dorsal side of the foot (deep venous system). The average of the mean transit time of the flow in the superficial venous system was 25.2 sec. (range 21.1 to 35.5 seconds) and was significantly lower than the corresponding values for the deep venous system ($p<0.01$). Fig. 12 a illustrates a typical curve after injection into the great saphenous vein (superficial venous system) compared with a curve after injection into a small vein on the dorsal aspect of the foot—deep venous system (Fig. 12 b).

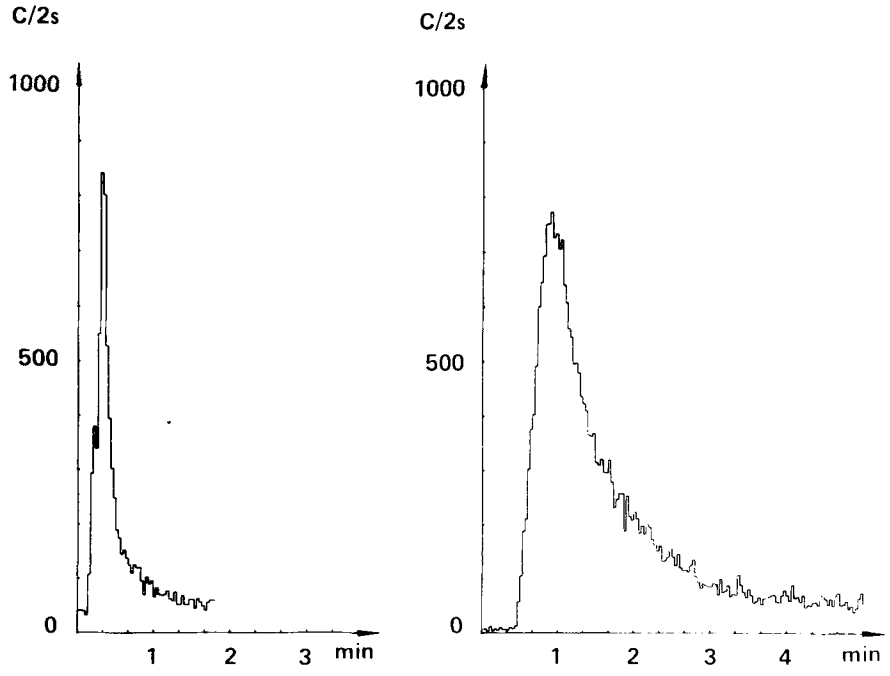

Fig. 12. Activity detected in popliteal fossa after injection of ^{99m}Tc-albumin into a) great saphenous vein at ankle (superficial venous system) and b) into a vein on dorsal aspect of foot (deep venous system).
Injection at X = 0.

The statistical error because of the randomised atomic decay follows Poisson's distribution. It was calculated according to the formula $\frac{1}{\sqrt{n}}$ where n denotes the total sum of counts, and the quotient denotes the mean error. This mean error varied between 1.3 and 0.55 % (mean = 0.95 %). These small numerical values neither change the result mathematically nor statistically because of the original randomisation.

The time of the beginning of injection was noted on the curves. Each injection required one to two seconds. Since the examiner knew the purpose of the investigation, manual marking of the points might have meant a systematic error, i.e. the beginning of the injection might have been unconsciously or unintentially marked later in some of the cases. Since also the time of the end of the injection was noted, one can hardly imagine prolongation of the injection time. Deviation of the injection time by at most two seconds, changed the mean transit time by 2.1 to 3.7 seconds. A decrease of the mean transit time with maximum 3.7 seconds for the unbandaged legs, however, does not affect the definitive result of the significance of the difference.

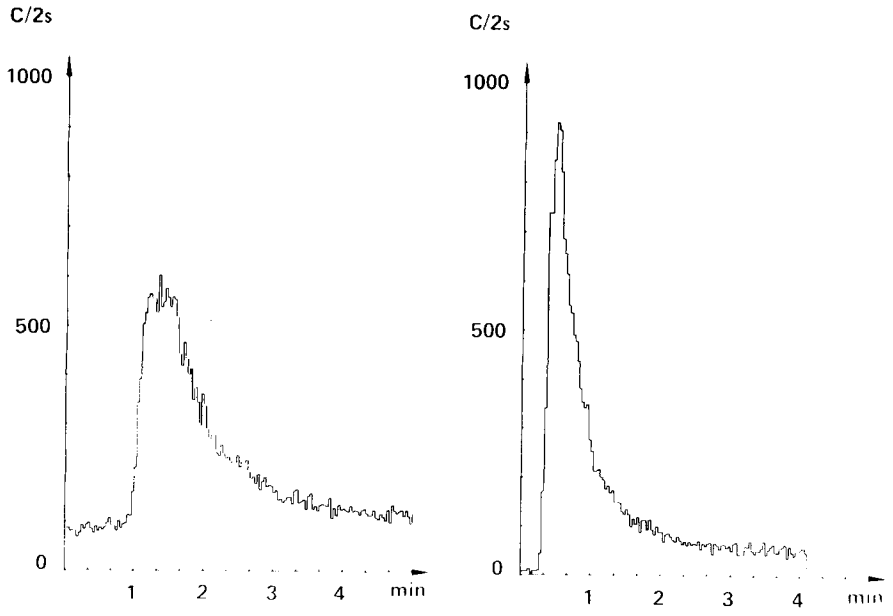

Fig. 13. Activity detected in popliteal fossa after injection of ^{99m}Tc-albumin into small vein on dorsal aspect of foot (deep venous system). a) Lower legs not bandaged. b) Lower legs bandaged.
Injection at X = 0.

The reproducibility of the examination was tested in the way described below. The reproduction test was made on another ten patients because it was not considered justified to inject the isotope more than twice (100 μc) in each patient. It was found that the mean transit time for the second investigation was 0.2 to 6.4 seconds (mean=4.0 seconds) longer than for the first. Since the patients were randomised in respect of the first examination with or without bandaging, this systematic error had no effect on the final result.

In order to avoid subjective evaluation in the calculation of the tangent to the semilogarithmic curves, the calculation was done blind.

Results

Differences in the shape of the curve without and with the lower leg bandaged is given in Figs 13 a and b.

Table X. Velocity of blood flow expressed as mean transit time in seconds. Ranges given within brackets.

Age	Sex	Side	Mean transit time	
			Unbandaged	Bandaged
64	F	R	38	22
56	F	L	63	72
50	F	R	164	70
77	M	R	59	34
69	F	L	19	36
56	M	L	130	70
59	M	L	54	60
66	F	R	23	29
73	F	L	37	21
66	F	L	105	41
67	M	R	70	56
51	M	R	67	21
64	F	L	110	37
71	F	R	40	23
62	M	R	56	29
65	M	R	41	47
70	F	R	122	86
50	F	L	28	23
57	M	L	167	51
70	F	L	84	60
$\bar{X}$ = 63.2 (50–77)	12 F 8 M	10 R 10 L	$\bar{X}$ = 73.9 (19–167)	$\bar{X}$ = 44.4 (21–86)

$P<0.01$

In 15 of the 20 patients examined the mean transit time was shorter when the lower legs were bandaged than when they were not. In five of the cases the result was the reverse. The mean transit time in the unbandaged leg was, on the average, 73.9 sec. (range 19–167 sec.) and in the bandaged leg 44.4 sec. (range 21–86 sec.). The individual values are given in Table X. The increase in velocity of the flow in bandaged lower legs was significant ($p<0.01$).

Discussion

Three patients were excluded from the investigation because the curves were too flat to permit any calculations. Two of these flat curves represented examinations without and one with the lower legs bandaged. The flattening of the curve was thus presumably not due to bandaging. The flattening owing to escape of albumin to surrounding tissue within the period of at most four minutes that the examination required is minimal (Veall et al 1958). Free technetium, which may have escaped from the albumin, is only two per cent on the day of the examination and therefore cannot explain the flatness of the curve. One possible causal factor is that the patient, despite the absence of known thrombosis in his history, had nevertheless had thrombosis with vascular obstruction or occlusion with the result that the blood passed through several small collaterals and thereby caused flattening of the curves.

The importance of randomisation of the first examination with or without the legs bandaged is apparent from the investigation of the reproducibility of the method, which invariably showed a longer mean transit time at the second examination than at the first. This difference has apparently escaped attention in earlier investigations (Meyerowitz et al 1964 and Makin et al 1969).

In examinations of this type it is important that the same leg be used for both examinations in order to eliminate the sources of error due to possible differences in flow velocity between the two legs. Further, both legs should be either bandaged or unbandaged. For when only one leg is bandaged, there is a risk of a pooling occurring in the unbandaged leg, which might cause a change in the flow volume (Sabri et al 1971) and thereby of the flow velocity. No investigation on record has taken this source of error into consideration (Meyerowitz et al 1964 and Makin et al 1969).

When bandaging the lower leg the detector should, as in the present investigation, be placed in the popliteal fossa in order to permit registration of the flow velocity in the lower leg. The velocity of flow through the femoral vein may be altered by bandaging or any similar measures (Doran et al 1964, Meyerowitz et al 1964 and Makin et al 1969) and a change in velocity

of flow through the calf cannot be recorded in the groin (Doran et al 1964, Meyerowitz et al 1964 and Makin et al 1969).

The blood pressure and the pulse rate influence the venous flow velocity through the legs (Berne et al 1972). It is thus important, as was done in the present investigation, to let the patient rest until the blood pressure and the pulse rate have become steady.

^{99m}Tc was used as a tracer because the isotope is not only a gamma-emitter but also because it has a short half-time. Bound to albumin it follows the blood stream well (Veall et al 1958) and is also regarded as not requiring blocking of the thyroid (McAfee et al 1964). ^{133}Xe has not been used because other investigators (Jansen 1972) did not receive usable values, which Jansen ascribed to an escape into the surrounding tissue. ^{131}I also emits beta-rays which pass only a short distance through the tissues and thereby give a relatively strong local radiation dose, for which reason this isotope should not be used in human investigations.

In earlier investigations of venous flow, determinations were made at a time at which the injected bolus began to appear, so-called appearance time (Wright et al 1948, 1951, Doran et al 1964 and Jansen 1972). In the present investigation the appearance time was, on the average, 27.4 seconds (range 6 to 100 sec.) with increased flow velocity in 16 of the 20 patients examined, i.e. also a significant increase after bandaging. In the calculation of the appearance time, however, only the quickest circulating and, as far as thrombosis is concerned, the least important particles are taken into account. The slower particles in the bloodstream are probably most responsible for thrombus formation, and in the calculation of the mean transit time also the slower circulating particles are taken into account. The mean transit time should therefore be regarded as the most adequate measure of the velocity of the circulation at examinations of the present type regarding the possible effect of flow velocity on the development of thrombosis.

Earlier phlebographic investigations (Greitz 1954 and Jansen 1972) and our own (see Appendix) have shown that on injection of contrast medium into a small vein on the dorsal aspect of the foot, the contrast medium reaches the deep venous system. Since the same injection technique was used in the present investigation it can be assumed that the flow velocity in the deep venous system was measured. The higher flow velocity observed in the present investigation after injection in the great saphenous vein in comparison with the flow velocity on injection into a vein on the dorsal aspect of the foot coincides with earlier observations (Jansen 1972) and is verified also by comparison of the appearance of the curves (Fig. 12 a, b).

Meyerowitz et al (1964) and Makin et al (1969) examined the flow velocity through the veins of the leg with and without an elastic stocking. They

showed a significant increase in flow velocity after bandaging, but they give the results as centimeters per second and do not state the distance measured. Therefore, and because of the above mentioned sources of errors comparisons are not possible with the present material.

The present investigation showed that bandaging of the lower leg significantly increases the velocity of flow through the lower leg, which appears to warrant the conclusion that bandaging of the lower legs contributes to reduction of the frequency of thrombosis.

Part III. ANIMAL STUDIES

By Per-Olof Svärd, Louise Thor and Bengt Tillberg

IX EFFECT OF OXYPHENBUTAZONE ON COLLAGEN- AND ADP-INDUCED AGGREGATION OF PLATELETS IN VITRO

The purpose of the investigation was to find out whether collagen- or ADP-induced platelet aggregation could be influenced by oxyphenbutazone per os in rats. Platelet aggregation was determined turbidimetrically according to the method described by Born (1962).

Material

42 Sprague-Dawley rats (Anticimex, Sollentuna, Sweden) were randomly distributed in three groups with 14 animals in each group. The rats were 9–10 weeks old, they had been brought up on "Standard food for mice and rats" (Astra-Evos, Södertälje, Sweden) and they weighed, on the average, 257 g (range 240–275 g).

Methods

Collagen. Crushed, freeze-dried Achilles tendons were used (Collagen, Worthington Biochemical Corp., Freehold, N. J., USA). In the preparation of the suspension collagen was ground in a homogenisator (Ultraturrax, Janke & Kunkel KG, Saufen, Germany). The substance was mixed to a homogenous suspension in the ratio 20 mg collagen per ml solvent. The solvent consisted of one volume tris buffer and 9 volumes of physiological saline (pH=7.4). The suspension was centrifugated for 15 minutes at 900 *g* and the supernatant was used. The suspension was freshly prepared every day and kept on an ice-bath during the experiments. In every experiment 100 microliters was used.

Adenosine diphosphate (ADP, Sigma Chemical Corp., St Louis, Miss., USA) was used. A stock solution was prepared by dissolving ADP-substance in tris buffered physiological saline (pH=7.4) and with a calculated strength of 0.5 mg ADP per ml solvent. The stock solution was kept in a frozen state and a mixture was prepared freshly every day by thawing up the stock solution, which was afterwards diluted with the above mentioned solvent to a

strength of 3 micrograms ADP per 50 microliters solvent. 50 microliters was used for each examination of the aggregation. During the experiment the solution was kept on an ice-bath.

Platelet-poor plasma (PPP) was prepared by centrifuging citrate-blood of rat at room temperature at 3,600 *g* for 10 minutes. The plasma sucked off was stored at room temperature during the experiment.

Platelet-rich plasma (PRP) was prepared by centrifuging citrate-blood of rat at room temperature at 260 *g* for 10 minutes. The plasma was pipetted off and stored at room temperature during the experiment.

Catheters and tubes were made of styrene plastic material (Cerbo AB, Trollhättan, Sweden) and all glass ware was siliconised.

Platelet aggregation was measured turbidimetrically with an aggregometer (Modell AG-2, Bryston Manufacturing, Roxdale, Ontario, Canada) with a curve-writer. Magnetic stirring was done with a "spoon" of siliconised stainless steel 0.5 mm in diameter and 2–3 mm long. The mixture was stirred at a rate of 1,100 r.p.m.

Oxyphenbutazone (Ciba-Geigy AG, Basel, Switzerland, Op nr Mg 954) was mixed with 4 % gummi arabicum in a ratio of 50 mg oxyphenbutazone per ml gummi arabicum solution.

Pilot examinations. One hour and two hours after administration of 100 mg oxyphenbutazone per kg bodyweight via a stomach tube the PRP from the animals were examined (7 in each group) for collagen- and ADP-induced platelet aggregation according to the method described below. No notable differences were found between these determinations and these of PRP of controls.

On the other hand, differences were found at examination after 24 hours and 48 hours; these intervals were therefore chosen for further investigations.

Experimental procedure. One control group consisting of 14 animals was given 0.4 % gummi arabicum in a dose of two ml per kg bodyweight via a stomach tube. One experimental group was given oxyphenbutazone dissolved in gummi arabicum corresponding to 100 mg oxyphenbutazone per kg bodyweight (14 rats). Aggregation was measured 24 hours after administration of the mixture. Another experimental group (14 rats) received a dose of 100 mg per kg bodyweight for two days and aggregation was measured 24 hours after the last dose.

At the determination of aggregation the rats were anaesthetised by intraperitoneal administration of 60 mg of mebumal sodium (Nembutal®) per kg bodyweight (one ml of 6 % solution). A catheter was carefully introduced into the common carotid artery and the entire amount of blood was collected in a centrifuge tube containing one volume of 3.8 % citrate solution per nine volumes of blood. PPP and PRP were prepared in the way described above.

The determination of the aggregation was started one hour after the PRP-preparation.

Calibration of the aggregometer was done before every examination with maximal deviation of the writer (10 units) for PPP and zero for untreated PRP.

Collagen-induced aggregation was determined at 37°C and with addition of 100 microliters of collagen suspension per ml PRP.

ADP-induced aggregation was determined at 22°C and by addition of 50 microliters of the ADP-suspension (3 μg ADP per ml PRP).

The results were analysed statistically with the one-way variance analysis.

Results

In the control animals collagen produced an aggregation of, on the average, 6.5 units (range 2.0–8.0). After a single oral dose of oxyphenbutazone determination 24 hours later showed a decrease in aggregation to 4.6 units (range 0–7.5). After two day's treatment and determination 24 hours after the last dose aggregation was likewise decreased to, on the average, 3.3 units (range 0–6.9). The individual values in each experimental animal are given in Table XI. The depressive effect of oxyphenbutazone on the collagen-induced platelet aggregation was statistically significant ($p<0.05$).

Table XI. Collagen-induced platelet aggregation expressed in scale-units. Range within brackets.

Control	24 hrs	48 hrs
5.1	6.3	0*)
6.7	0	
7.6	0	1.2
7.7	7.3	—**)
7.7	7.3	6.3
7.5	6.6	6.8
7.3	7.0	5.9
2.0	6.9	6.9
6.7	7.3	2.8
4.2	7.5	0.8
6.0	0.7	5.4
7.7	1.0	1.0
6.6	5.4	0.6
8.0	1.3	1.8
$\bar{X} = 6.5$ (2.0—8.0)	$\bar{X} = 4.6$ (0—7.5)	$\bar{X} = 3.3$ (0—6.9)

*) Two samples pooled.
**) The rat died during preparation
$p<0.05$

Adenosine diphosphate produced an aggregation with a deflection of, on the average, 5.6 scale units (range 3.8–7.1) in the control animals. After a single oral dose of oxyphenbutazone, aggregation, estimated after 24 hours, was decreased to, on the average, 4.2 scale units (range 1.4–6.1). After two days' treatment and determination 24 hours after the last dose the aggregation was decreased to, on the average, 4.3 units (range 2.2–6.5). The individual values recorded in each animal are given in Table XII. The depressive effect of oxyphenbutazone on ADP-induced platelet aggregation was statistically significant ($p<0.05$).

Table XII. ADP-induced platelet aggregation expressed in scale-units. Range within brackets.

Control	24 hrs	48 hrs
7.1	1.4	3.9
6.8	2.6	3.1
6.0	4.8	5.0
6.2	3.4	6.5
4.7	2.8	5.7
5.6	4.4	5.9
6.2	1.8	6.1
5.6	5.5	5.3
5.3	6.0	2.6
6.4	5.8	4.2
4.5	3.2	2.6
3.8	6.1	2.2
5.5	4.9	3.0
4.0	5.7	—*)
$\overline{X} = 5.6$	$\overline{X} = 4.2$	$\overline{X} = 4.3$
(3.8—7.1)	(1.4—6.1)	(2.2—6.5)

*) The rat died during preparation.
$p<0.05$

X EFFECT OF OXYPHENBUTAZONE ON FREQUENCY OF EXPERIMENTAL THROMBOSIS IN VIVO

The purpose of the present investigation was to find out whether oxyphenbutazone by mouth can reduce the tendency to thrombosis in rats. Thrombosis was induced by electric traumatisation of a mesenteric vein according to the method reported by Reber (1966) and Poliwoda (1968).

Material

Thirty 8–9 weeks old Sprague-Dawley rats (Anticimex, Sollentuna, Sweden), brought up on "Standard food for mice and rats" (Astra-Ewos, Södertälje, Sweden) and weighing, on the average, 219 g (range 170–270 g) were randomly divided into two equal groups.

Methods

The examinations were made under a microscope (Labourlux, E Leitz, GMBH, Wetzlar, Germany) with a magnification of × 125. The object stage was made as a tray of plexiglass, of a size suitable for the animals used in the experiment.

As a source of energy we used a stimulator (Modell S4E, Grass Instrument Comp., Quincy, Mass., USA) which delivered a rectangular direct current pulse with a frequency of 52 per second. During the entire experiment the voltage was kept constant at 60 volts and the current at 0.2 mA, while the duration of the electric impulse was varied stepwise 0.1 msec a time up to 1 msec and afterwards by 0.5 msec a time. The cathode consisted of a silver wire loop 7 cm in diameter and 0.5 mm thickness of the wire. The loop was placed between the object stage and the experimental animal. The anode was made of wolfram wire which was tapered to a point of 2 μ. The anode were isolated, except at the actual tip, with plastic wax (Protective Coating 101, Letraset Ltd, London, England.

The cathode was manipulated with a micromanipulator (Modell 475763, E Leitz, GMBH, Wetzlar, Germany).

Oxyphenbutazone (Ciba-Geigy AG, Basel, Switzerland, Op nr Mg 954) was mixed with 4 % gummi arabicum in a ratio of 50 mg oxyphenbutazone per ml gummi arabicum solution.

Pilot studies. Three rats were given oxyphenbutazone solution (15 mg per kg bodyweight) intravenously, and thrombosis was induced 30 minutes later. The tendency to thrombosis in these animals did not differ from that in the controls.

Oxyphenbutazone was given via a stomach tube, 100 mg per kg bodyweight and the animals were examined for tendency to thrombosis 24 hours after the dose (7 rats). No difference was found in this respect between the experimental animals and the controls. On the other hand, after 7 days' medication and examination 24 hours after the last dose a difference was found between the treated and untreated animals. This interval was therefore chosen for the experiments proper.

Experimental design. One group of 15 animals served as controls and each animal was given 4 % gummi arabicum solution 0.2 ml per 100 g bodyweight via a stomach tube each day for 7 days and 24 hours after the last dose the animals were examined for any tendency to thrombosis. The second group (15 rats) served as the experimental group and were likewise given, through a stomach tube, oxyphenbutazone solution in a dose of 0.2 ml per 100 g bodyweight, corresponding to an oxyphenbutazone dose of 100 mg per kg bodyweight (LD_{50}=980 mg per kg bodyweight). The same dose was given every day for 7 days and the animals were examined for tendency to thrombosis 24 hours after the last dose.

At the examination for tendency to thrombosis the animals were anaesthetised by intramuscular administration of 60 mg of mebumal sodium (Nembutal®) per kg bodyweight.

The animals were tracheotomised and a tracheal tube was inserted to keep the airways clear. The intestines were afterwards carefully operatively lifted up and the mesenterium was stretched out on the stage of the microscope. A suitable vein, 30–40 μ in diameter, was identified in the mesenterium. The vein was traumatised electrically in the way described above. The time of traumatisation was increased stepwise as earlier described and the shortest duration of the impulse-time, when thrombosis appeared, was noted. This time was called the threshold value.

Thrombi were observed microscopically and no attempts were made to quantitate them because in rats thrombi are reversible (Born et al 1972).

The vessel was never traumatised at the same site on two occasions. During the entire experiment the mesenterium was continously perfused with Ringer's solution at a constant temperature of 37°.

The threshold values noted were judged statistically with the Student's t-test.

Results

The threshold value at which thrombosis began to appear was, on the average, 0.7 msec (range 0.4–1.0 msec) in the control animals and 2.1 msec (range 0.5–6 msec.) in the experimental animals. The individual values are given in Table XIII. The threshold values, i.e. reduction of the tendency to thrombosis, were significantly higher in the experimental animals than in the control group ($p<0.01$).

Discussion

The present experimental investigation in rats showed that oral oxyphenbutazone suppressed the tendency of platelet aggregation and of experimental thrombosis. It suppressed platelet aggregation induced by collagen and by adenosine diphosphate (ADP) and increased the magnitude of electric traumatisation necessary to produce thrombosis. Pilot studies revealed no inhibition of platelet aggregation one hour and two hours, respectively, after administration of the drug, but such inhibition was seen 24 hours after a single dose. Suppression was also noted, when the animals were given one dose on each of two consecutive days and examined on the third. The tendency to thrombosis of a mesenterial vein did not promptly respond to oxyphen-

Table XIII. Thresholds in msec for thrombosis-induction in control and oxyphenbutazone-treated rats.

Control	Treated
0.5	1.5
0.4	2.0
0.4	2.0
0.4	0.5
1.0	1.5
1.0	1.0
1.0	0.5
1.0	3.0
0.5	3.0
0.8	2.5
1.0	0.5
0.4	1.0
0.8	3.5
0.7	6.0
0.5	3.5
$\overline{X} = 0.69$	$\overline{X} = 2.13$
(0.4–1.0)	(0.5–6.0)

$p<0.01$

butazone intravenously; neither did one oral dose a day for two days produce any demonstrable effect, but when the compound was given for seven days a suppression of tendency to thrombosis was noted.

Renaud et al (1970) showed reduction of ADP-induced platelet aggregation within two hours after oral administration of oxyphenbutazone in a dose of 100 mg per kg bodyweight, i.e. the same dose as used in the present investigations. Renaud et al also found a decrease in thrombosis of the hepatic vein after such a dose and autopsy 24 hours later. They used rats fed a high-fat diet and induced thrombosis by intravenous injection of a S. typhosa-lipopolysaccharide. The aggregation was not assessed in blood from each animal separately but in a pool of platelet-rich plasma from three rats. The aggregation was calculated from triangulation and calculation of the surfaces. The latter procedure is not described in detail, for what reason the values could not be checked. In other words, our results cannot be compared with those reported by Renaud et al.

Judging from the present investigations, oxyphenbutazone produce a delayed suppression of platelet aggregation and a still more delayed of thrombus formation. The only conclusions that can be drawn with certainty, however, are that oxyphenbutazone suppresses the collagen- and ADP-induced platelet aggregation in the rat, and thereby, or in addition, experimentally induced thrombosis. The dose dependency of the effect of oxyphenbutazone, the time the drug requires to produce a demonstrable effect, to what extent and how much of the effects demonstrated in the rat hold for man must abide further research.

XI GENERAL DISCUSSION

The literature on thrombosis is very abundant. But "indeed few conditions in medicine have been subjected to so much analysis with so little elucidation" (deBakey 1954). Moreover, contributions are so contradictory that they will not permit any conclusions with certainty. Many investigations include no control group, or the control group is so inadequate as to be of little value. In all the older investigations thrombosis was diagnosed on clinical grounds alone, a method which is now known to be too unreliable (Kakkar et al 1968, Hæger 1969 and Thulesius 1974) to permit any conclusions. In what follows only investigations filling present-day requirements, i.e. controlled trials with diagnosis by phlebography or radioactively labelled fibrinogen, will be considered.

Prophylaxis of thrombosis has hitherto implied the use of anticoagulants (Table II, page 14). Some investigators have found heparin (Williams 1971, Kakkar et al 1972, Gordon-Smith et al 1972 and Gallus et al 1973) to reduce significantly the frequency of thrombosis while others (Myrvold et al 1971) found a relatively high and similar frequency by administration of heparin or dextran.

Also investigations with coumarol or coumarol-like compounds, such as warfarin and phenindione, have given contradictory results. Borgström et al (1965), Myhre et al (1969) and Hamilton et al (1970) found a significant reduction in the frequency of thrombosis, while Pinto (1970) could not demonstrate any such effect. Bronge et al (1971) reported a high and similar frequency of thrombosis after the use of coumarol or dextran, and Lambie et al (1969) found the frequency to be higher after the use of coumarol compounds than of dextran.

In some investigations dextran has been shown to reduce the frequency of thrombosis (Ahlberg et al 1967, Johnsson et al 1969 and Evarts et al 1971), but not in others (Becker 1972).

In the literature prophylaxis of thrombosis not attacking the coagulation factors is inappropriately referred to as "non-specific". Such "non-specific" treatment is peroperative electric stimulation of the calf. Becker (1972) found this metod to produce a significant reduction in the frequency of thrombosis. Another non-specific method is the use of the calf-pump (Calnan et al 1970).

Using this method Hills et al (1972) found a significant reduction in the frequency of thrombosis.

A search of the literature failed to reveal any investigation of the value of bandaging of the lower legs combined with administration of oxyphenbutazone in the prophylaxis of thrombosis. Use of elastic stockings of non-specified type (Flanc et al 1969) or "Tubigrip" (Rosengarten et al 1971 and Tsapogas et al 1971) has not been found to significantly reduce the frequency of thrombosis. It is quite possible that this might have been due to the effect of the elastic stocking alone being too small to produce any significant effect on the small series used. It is also possible that the use of an elastic stocking is not so effective as an elastic bandage, especially since the former does not permit such an individualised fit as the latter.

No investigations filling the above mentioned present-day requirements and using oxyphenbutazone alone are available. Clinical experience, however, suggests that the compound has a prophylactic effect on thrombosis (Castaing et al 1972, Dargent et al 1972 and Lindahl). Oxyphenbutazone alone may not, perhaps, have an effect strong enough to be demonstrable in an investigation of what may be regarded as a reasonable number of patients. In the present investigation a significant decrease in the frequency of thrombosis was demonstrated by the use of bandaging combined with administration of oxyphenbutazone. This effect of bandaging may be explained by the added or possibly potentiating effect of oxyphenbutazone.

Experiments were carried out to find out whether either of the two components of prophylaxis, i.e. bandaging and oxyphenbutazone, had any effect by itself. It was found that bandaging of the lower legs increased the flow velocity and, judging from previous investigations (see III), this should reduce the disposition to thrombosis. Oxyphenbutazone was found experimentally to decrease the tendency of formation of thrombi in vivo in rat and to inhibit the effect of respectively collagen- and adenosine diphosphate-induced platelet aggregation in vitro. Though it cannot be said with certainty that the results in these animals hold also for man, there is apparently few reasons why they should not.

According to Wessler et al (1973) an ideal prophylactic agent should be well tolerated by the patient, it should have no side-effects, it should not cause hæmorrhage, it should be easy to give and it should not require laboratory resources. The treatment given in the present investigation was well tolerated, none of the patients found bandaging inconvenient, and only one patient reported discomfort from oxyphenbutazone suppositories.

The frequency of side-effects of oxyphenbutazone during short-term treatment is low (Sperling 1969) or negligible (Allgöwer et al 1963, Berghagen et al 1963, Hipps et al 1963, Mikkelsen 1963, Ivarsson et al 1964, Ekblom et al

1966 and Wisborg 1966). This was verified in the present investigation in which only one side-effect, viz. exanthema, of the drug, occurred.

The number of leukocytes in the patients treated did not differ from that in the control group. The platelet count, Normotest® and APTT® did not differ postoperatively from normal or from the values in the control group. There was no increased bleeding tendency; on the contrary, the number of wound hæmatomas was lower than in the control group, but the material was too small to permit any conclusion with certainty concerning the frequency of wound hæmatoma.

Gastrointestinal bleeding has been described as a side-effect of treatment with oxyphenbutazone. Administration in suppositories does not probably make any difference, because the bleeding is due to a systemic reaction and not to a local effect on the mucosa (Johansson et al 1971). In the present investigation blood in faeces was equally common before as during and after medication and was not such as to require withdrawal of the compound.

A tendency to œdema has been described as a side-effect of oxyphenbutazone. In the present investigation increase in weight was not measured because of standardisation difficulties due to the postoperative bandage, bleeding into the bandage etc. But the hematocrit was checked and no difference in this respect was found between the controls and the patients treated, which argues against any substantial dilution effect. Neither was any increase on the serum sodium or potassium observed.

The method described for prophylaxis of thrombosis, i.e. bandaging the lower legs combined with administration of oxyphenbutazone (Tanderil®) has proved to have a preventive effect on thrombosis. The effect of the components has also been demonstrated experimentally. The treatment is simple and easy to give, easy to control and involves no risk of overdosage, mostly mild and few side-effects, it is tolerated well by the patients and does not require any particular laboratory resources.

SUMMARY

Bandaging of both legs for the first 14 days after operation, combined with administration of 500 mg oxyphenbutazone (Tanderil®) a day as suppositories, was studied for its preventive effect on postoperative thrombosis in 27 patients operated upon because of coxarthrosis and 23 operated controls. Only thrombosis demonstrated phlebographically were accepted. Phlebography revealed thrombosis in 56.5 % of the controls, who had not received any special prophylactic treatment, compared with 18.5 % in the patients treated. The difference was statistically significant ($p<0.01$).

Flow velocity of the venous blood in the unbandaged and bandaged lower legs of 20 patients, to be operated upon because of arthroses, was studied with a radioisotope method. Bandaging significantly increased the flow velocity, i.e. the mean transit time was decreased ($p<0.01$).

In investigations of the effect of oxyphenbutazone administrated orally in rats it was found

a) that the compound significantly suppressed collagen- and adenosine diphosphate-induced platelet aggregation in vitro ($p<0.05$) and

b) that the compound significantly suppressed electrically induced thrombosis of the mesenterial veins in vivo ($p<0.01$).

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PHLEBOGRAPHIC DIAGNOSIS OF THROMBOSIS

By
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This paper concerns a comparison of two groups of patients regarding the frequency of phlebographically confirmed postoperative thrombosis after surgery of the hip. In one group the patients were not given any particular prophylactic treatment; in the other, the lower legs were bandaged according to a special technique and the patients were given oxyphenbutazone (Tanderil®) in a dose of 500 mg a day (Tillberg 1974).

Diagnostic methods

Formerly thrombosis was diagnosed mainly on clinical grounds alone (Table II). But such a procedure is unreliable (Kakkar et al 1968 and Hæger 1969). Becker (1972), for example, found that only 29 % of clinically diagnosed cases of thrombosis could be verified phlebographically and those of the cases in which phlebographic examination revealed thrombosis, only 35 % had been diagnosed clinically. Clinical diagnosis is thus neither very specific nor sensitive. Borgström (1950) found that thrombosis had not been diagnosed intra vitam in 72 % of cases of fatal pulmonary embolism, verified at autopsy, and deBakey (1954) gave a corresponding figure of 85—90 % in a compilation of various clinical series.

Phlebography was introduced as an examination method by Bauer in 1940, since when it has been used, evaluated and standardised (Greitz 1954, 1955, Borgström et al 1965, Arnoldi 1967, Nylander 1968, Bergvall et al 1971). But the method is time consuming and laborious and sometimes inconvenient for the patient, sometimes painful. Several "screening-methods" have therefore been proposed.

Atkins et al (1965 and 1968), Lambie et al (1970) and Kakkar et al (1968 and 1970) have used ^{125}I-labelled fibrinogen. Sigel et al (1968) have described an ultrasonic method. Different types of plethysmography have been used—

Table I. Reliability of various methods for diagnosing thrombosis (After Thulesius 1974).

Examination method	Sensitivity %	Specificity %
Phlebography	98	--
^{125}I-fibrinogen	96	93
Ultrasonics	76	91
Occlusion plethysmography	95	82
Impedance phlebography	91	--

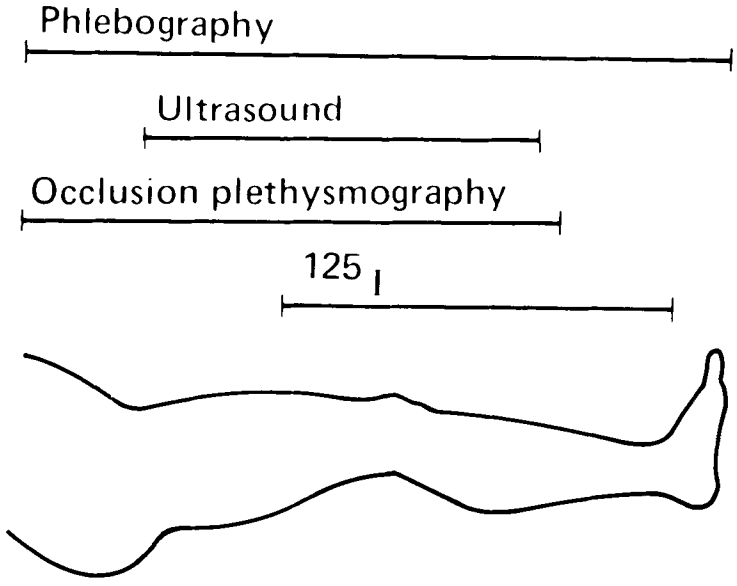

Fig. 1. Segments of the leg covered by different diagnostic methods (After Thulesius 1973).

with a water-filled cuff (Dahn 1967, Dahn et al 1968 and Boijsen et al 1968), with a cuff with a strain-gauge (Hallböök et al 1971), and with impedance phlebography (Mullick et al 1970 and Wheeler et al 1972).

The relative reliability and the applicability of various methods have been given by Thulesius (1973 and 1974) (Table I and fig. 1). The applicability illustrated in the drawing refers to the diagnosis of thrombosis in departments of internal medicine and of general surgery. After operation on the lower limbs however, œdema of the legs and accumulation of fibrinogen in the

operative wound are not uncommon and may then give rise to sources of error, especially if ^{125}I-labelled fibrinogen is used. Moreover the methods do not diagnose thrombi in the entire length of the limb (Fig. 1). It was therefore considered necessary to use phlebography in the present investigation.

Material

The material consisted of 50 patients above 50 years who had undergone an operation of the hip. These patients were randomly distributed between two groups: 23 were assigned to one group (control group) and received no special treatment, while the remaining 27 were referred to a group given prophylactic treatment (T-group). All the patients were mobilised the day after the operation and given physiotherapy, including exercise of the operated hip, and respiratory exercises. In the T-group, the lower legs were bandaged on the day of operation for 14 days according to a special technique and the patients were given oxyphenbutazone (Tanderil®) in a dose of 500 mg a day in the form of suppositories.

Methods

Clinical examination. The circumference of the calf and that of the thigh were measured on admission and every day after the operation. The patient was also examined every day for clinical signs of thrombosis. Demonstration of any 3 or more of the signs given in table II was considered to warrant a clinical diagnosis of thrombosis.

Phlebography. All the patients were examined with phlebography at the earliest 14 days after the operation, or earlier if thrombosis was suspected on clinical grounds.

Table II. Clinical signs of thrombosis

Tenderness of the calf
Palpatory firmness of the calf
Homan's sign
Swelling of the calf (measured 12 cm below the medial part of the joint space in the knee)
Increased venous marking
Tenderness over the adductor canal
Palpatory firmness of the adductor canal
Swelling of thigh (measured 15 cm above the medial part of the joint space in the knee)
Tachycardia (more than 100 beats per minute)
Elevation of body temperature (above 38°C)

The patients were examined on a tiltable table with the foot-end lowered so that the table subtended an angle of 60° with the horizontal plane.

An ordinary tourniquet of rubber tubing was applied tightly above the ancle of the leg to be examined. A vein on the dorsal aspect of the big toe or the foot was punctured with a 21- or 23-gauge-needle. The needle was connected, via a tube, to an injection syringe. The contrast medium was injected by hand during a period of about 2 minutes. The contrast medium used was Angiografin® (methylglutamate salt of tri-iodo-benzoic acid containing 306 mg I/ml) and 60 ml was injected. The exposures were started at the end of the injection. The flow of the contrast medium was followed fluoroscopically, and the rate at which the exposures were made was adjusted according to the rate of which the vessels filled. Two a-p and two lateral projections were obtained of the lower leg, one lateral projection in the region of the knee and 1—2 a-p projections of the thigh. In a few cases the filling was insufficient and a second dose of contrast medium was injected.

A filling defect in an otherwise well filled vein was regarded as warranting a diagnosis of thrombosis, provided that the defect did not change in character or site between 2 films taken at an interval of at least 20 seconds, that at least part of the defect was surrounded by blood and well outlined by the contrast medium. Imperfect filling of a vein or part of a vein was not accepted as a sign of thrombosis except in those cases where no filling was obtained of any deep veins despite administration of an adequate volume of contrast medium. In such cases the films were interpreted as thrombosis with subfascial hypertension.

It was not considered possible to distinguish between recent and older thrombi.

The phlebograms were interpreted independently by two roentgenologists who were unaware of the group to which a given patient belonged.

Results

All together 18 cases of thrombosis, 13 in the control group and 5 in the treated group were diagnosed phlebographically (Table III). The difference, as judged with the significance test according to Fischer, between the two groups was significant ($p<0.01$).

Table III. Frequency of thrombosis

Group	No of pat.	No.	Per cent
Control	23	13	56.5
Treated	27	5	18.5

$p<0.01$

In four cases the diagnosis of thrombosis was made on clinical grounds, in two on the ninth, in one on the tenth, and in one on the twelfth day, after the operation. In three of these cases the diagnosis was confirmed phlebographically and these patients were treated with anticoagulants. The fourth patient, in whom the clinical diagnosis could not be confirmed phlebographically, did not receive anticoagulant therapy and was re-examined with phlebography according to the predetermined time-table, i.e. at the earliest 14 days after the operation. Of the 50 patients, then, 49 were examined with phlebography on one occasion and one on two. For practical reasons the phlebographic examinations were performed at somewhat different intervals after the operation. In the control group the examinations were made between 14 and 27 days after the operation (mean = 18.9 days) and in the treated group between 14 and 30 days (mean = 18.5 days). The difference in this respect between the two groups was not significant.

None of the 51 phlebographic examinations were unsuccessful, the films obtained always permitting interpretation according to the above mentioned criteria. No side-effects of the contrast medium were observed.

In none of the cases was there any discordance between the interpretation of the films by the rœntgenologist on duty and by the author.

Discussion

The diagnosis of thrombosis on clinical grounds is unsatisfactory, and especially because oxyphenbutazone suppresses pain, swelling and elevation of the temperature (Sigg 1954).

It was not considered possible to differentiate between recent and old thrombi (Rabinov 1971). In order to obtain a reliable figure for the number of recent thrombi would require both pre- and postoperative phlebography. For practical reasons such a procedure is impracticable and the risk of re-phlebography being unsuccessful is substantial. None of the present patients reported postthrombotic symptoms and none of them showed clinical signs of thrombosis. Moreover, the frequency of preoperative thrombosis is low (Becker 1972). In addition, it may be assumed that since the patients were randomly distributed between the two groups, the frequency of old thrombi would be equal in both.

In fracture of the femoral neck and at operation of a limb there is a risk of thrombosis occuring also on the unoperated side (Freeark et al 1967 & Field et al 1972). In the present investigation phlebography was confined to the operated side. Theoretically, then, some cases of thrombosis might have been missed. But then again one must assume that the risk of thrombosis on the unoperated side was equal in both groups and that the random selection eliminated this source of error.

Phlebography should not be done too soon after the operation. In the present investigation a minimum interval of 14 days was chosen in order to detect at least most cases of thrombosis (Jansen 1972). The fact that the interval was sometimes longer was probably of no importance because there is presumably no risk of recanalisation within such a short time (Bergwall et al 1968 & Becker 1972). Moreover, the interval in the control group did not differ significantly from that in the treated group so that any error due to prolongation of the period between the operation and the examination may be excluded.

The frequency of thrombosis in patients not given specific prophylaxis was largely the same in the present investigation as in published series (Borgström et al 1965. Freeark et al 1967, Johnsson et al 1967. Evarts et al 1971 & Field et al 1972). The frequency of thrombosis in the treated group was also roughly the same (Borgström et al 1965, Myhre et al 1969 & Williams 1971) or maybe lower (Lambie et al 1969, Pinto 1970, Hamilton et al 1970, Bronge et al 1971 & Myrvold et al 1971) than those reported in patients treated prophylactically with anticoagulants. The results also appear to be equal to (Ahlberg et al 1967, Myhre et al 1969) or maybe better than (Bronge et al 1971, Myrvold et al 1971 & Becker 1972) those achieved in patients treated phophylactically with dextran. From a strictly statistical point of view direct comparisons with other investigations regarding the prophylaxis of thrombosis is not possible. But the prophylactic method used by us appears useful. The method is simple, the drug and bandaging is easy to administer, it has seldom serious side-effects and it does not require laboratory facilities.

Summary

A series of patients who had undergone surgical operations on the hip were randomly divided into two groups, one in which the patients received no prophylaxis of thrombosis (23 patients) and served as controls, and one consisting of 27 patients in which the lower legs were bandaged for the first 14 days after the operation and in which the patients were given 500 mg oxyphenbutazone (Tanderil®) a day in the form of suppositories. At the end of treatment the patients were examined phlebographically for thrombosis. The treatment given produced a significant reduction in the frequency of thrombosis from 56.5 to 18.5 %. Of the 50 patients, 49 were examined with phlebography once, and one patient twice. The phlebograms obtained were satisfactory in all cases. The examiner performing phlebography was unaware of the group to which a given patient belonged and the films were interpreted independently by two rœntgenologists.

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