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ANTICOAGULANT THERAPY IN PATIENTS WITH SPINAL CORD INJURY

By H. J. HACHEN, M.D.

Spinal Injuries Centre, Geneva University Hospital, Switzerland

IN spite of better understanding and considerable improvement in the management and early care of patients with spinal cord injury, venous thrombo-embolism still remains a major complication during the acute stage after admission. The high morbidity of this vascular pathology in paraplegics has been thoroughly investigated by Walsh (1965), Watson (1968) and Dollfuss (1971), who reported an incidence of thrombo-embolic complications of 13 per cent in their units.

Concepts regarding the mechanism of phlebothrombosis have continuously changed over the years, emphasis being initially on hypercoagulation, then on modified platelet behaviour and more recently on endothelial damage. Consequently therapeutic efforts relied on anticoagulants, then on aggregation inhibitors and finally on angioprotectors.

TABLE I

Incidence of deep-vein thrombosis

Author	Clinical field	Incidence of DVT	Assessment
		%	
Walsh, J. J. (1965)	Paraplegia	14	Clinical
Watson, N. (1968)	Paraplegia	18	Clinical
Hachen, H. J. (1973)	Paraplegia	21	Clinical
Kakkar, V. V. (1970)	General surgery	30	FUT
Williams, H. T. (1971)	General surgery	41	FUT
Mayo, M. E. (1971)	Urological surgery	50	FUT
Field, E. S. (1972)	Orthopaedic surgery	54	FUT
Friend, J. R. (1972)	Gynaecology	18	FUT

FREQUENCY OF THROMBO-EMBOLISM

The development of new diagnostic techniques such as the fibrin-uptake test (FUT) with ^{125}I-fibrinogen shows an unexpectedly high rate of deep-vein thrombosis in immobilised patients. Routine screening with this method indicates that practically one out of three patients develops thrombosis in the calf veins within 36 hours after major surgery or accidental trauma (Table I). Clinically these

obliterations are apparent once only out of seven cases. As long as the thrombus remains confined to the calf, the risk of subsequent pulmonary embolism is minimal. Involvement of the proximal veins which occurs in 15 to 20 per cent is followed by pulmonary embolism in every second patient. There is actually no doubt that embolism may also occur directly from primary sites within the ileo-femoral vessels without participation of more peripheral structures. Due to technical limitations of FUT the exact proportion of these high proximal occlusions remains unknown.

MECHANISM OF THROMBOGENESIS

The last ten years have been characterised by an ever-increasing effort toward better understanding of the relative importance of hypercoagulation, platelet aggregation and parietal vascular injury in thrombogenesis. The complexity of the problem became apparent when one detected the existence of multiple micro-thrombi that developed in spite of apparently satisfactory anticoagulation (Browse, 1974). In the light of recent findings, particular emphasis is now put on modified platelet-endothelial interaction.

Already back in the 'sixties Gaarder recognised the intimate linkage between the platelet release-reaction and platelet hyperaggregation. Today we know that an uninterrupted, morphologically normal endothelial lining affords the best protection against thrombus formation. In the event of endothelial damage, platelets exhibit a strong tendency for elective adhesion to the underlying collagen fibrils of the basement membrane (Gottlob, 1972; Jorgensen, 1973). This platelet-collagen interaction initiates the release-phenomenon. ADP, 5-hydroxytryptamin and platelet factor are set free in amounts sufficient to enhance further platelet fixation on the primary thrombus. From the therapeutical point of view it should be emphasised that this sequence of events follows its course regardless of the clotting-mechanism, *i.e.* it is in no way inhibited by the administration of anticoagulants (Weiss, 1973).

Recent electron microscopic studies (Baumgartner, 1974) indicate that sub-endothelial tissue components differ markedly in their reactivity towards platelets. Their affinity decreases in the following order: collagen fibrils, basement membrane, microfibrils and elastin.

Tissue trauma activates factor X which is of major importance both in the intrinsic and extrinsic mechanism of coagulation. Heparin has been shown to inhibit factor X activation (Thibault, 1972). Its early administration after injury should therefore be considered in all patients confined to strict bed rest for several days.

It is a well-accepted fact that reduced blood flow velocity favours venous thrombosis. Current rheologic investigations point to the existence of two basically quite different mechanisms of thrombogenesis depending on blood flow velocity. Fibrin deposition mostly occurs at slow and mural platelet fixation at high flow velocity. Since after multiple trauma our prophylactic measures are essentially aimed against venous rather than arterial thrombi, I suggest that heparin has a better chance than aggregation inhibitors in preventing thrombo-embolic complications.

Schamaun (1974) has recently shown strong evidence that enhanced release of coagulation-promoting tissue factors, modified platelet behaviour and disorders

in peripheral microcirculation may explain the transient post-traumatic consumption coagulopathy which we have diagnosed in close to 40 per cent of our patients during the first 48 hours after the lesion.

The current concepts of thrombogenesis are outlined in Table II. These are our ideas today; we may certainly have to change them in the future.

TABLE II

Current concepts of thrombogenesis

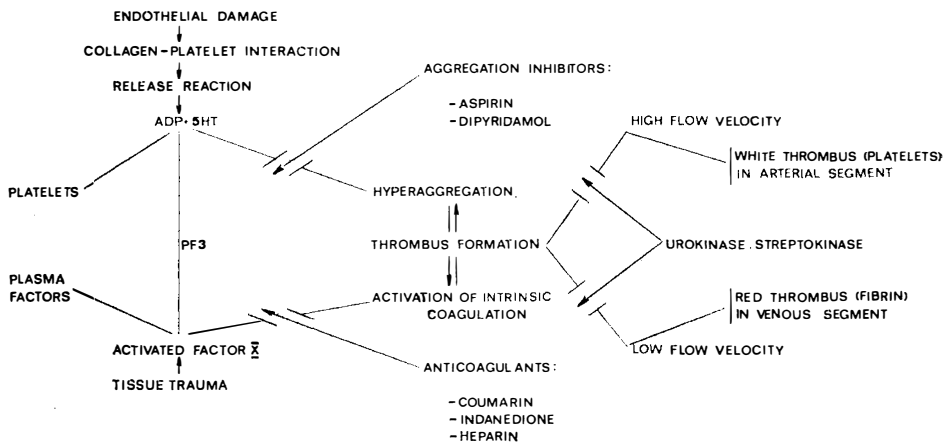

TABLE III

Laboratory investigations of venous thrombosis

Available methods	Advantage	Disadvantage
Fibrinogen uptake test (FUT)	Follow-up of thrombus for 6 days	Unsuitable for emergency Calf veins only
Ultrasound flow detection (UFD)	Screening of femoro-popliteal veins (3 min.)	Venous obliteration must be at least 50 per cent
Venous occlusion plethysmography	Similar to UFD	Rather unpractical and time consuming
Phlebography	Most accurate diagnosis of thrombus location	Only suitable for deep vein screening

DIAGNOSTIC TECHNIQUES

Four methods are actually available for precise assessment of phlebothrombosis. Their respective advantages and disadvantages are outlined in Table III.

Fibrinogen-uptake test with ^{125}I-fibrinogen is particularly accurate for the early detection of venous obstruction in the calf. 100 microCi. of the radiopharmaceutical are injected intravenously after previous blocking of the thyroid with potassium iodide. A Pitman 235 isotope-localisation monitor is used to identify the thrombus. Recordings are usually first made after 24 hours, then daily for one week, thus providing valuable information on day-to-day changes in the size of the thrombus. Evidently this test is not suitable for emergency situations.

Ultrasound flow detection is mostly used in screening for femoral thrombosis. Results can be read within two to three minutes. Unfortunately this test is not 100 per cent accurate since vessels must be obstructed by at least 50 per cent to indicate thrombosis.

Venous occlusion plethysmography studies the speed of peripheral drainage after previous venous occlusion. Today it has largely been replaced by UFD.

Phlebography probably still remains the most reliable method of investigation. It should be carried out in all situations requiring enzymatic thrombolysis or thrombectomy.

THERAPEUTIC ASPECTS

Let us briefly analyse the characteristics and indications of the three groups of pharmaceutical agents that have found wide use in antithrombotic therapy.

Anticoagulants. Wessler (1968) is right when he states that in anticoagulant therapy one is invariably reminded of one's failures but never of one's successes. Thirty-eight years after the first clinical trial with coumarins, much controversy still remains regarding their true efficacy in prevention and treatment of vascular occlusion and their optimal range of safety and efficacy (Raby, 1969). The doubts and practical difficulties involved with oral anticoagulants are very apparent to all of us who have been working with these drugs for several years. The crucial problem with anticoagulants is that any substance capable of preventing thrombus formation may, incorrectly administered, lead to severe haemorrhagic complications (Leman, 1968). It doesn't come as a surprise, therefore, that bleeding of virtually any kind has been reported by Bel (1968), Fearn (1968), Hachen (1968), Oldenkott (1966) and Smith (1969). In a previous paper read at the annual meeting two years ago—a report which dealt with spontaneous hypoprothrombinaemic states in acutely injured paraplegics—I already analysed some of the pitfalls and hazards of oral anticoagulants.

One fact that must be considered is the common observation that after administration of coumarin or indandione, the hepatic synthesis of plasma factors II, VII, IX and X is not affected to the same degree. For acenocoumarol our own laboratory investigations yield an interval of 38 to 42 hours between the administration of the first dose and the development of presumably safe prothrombin levels. Another point that should be considered is the fact that in the event of severe haemorrhagic complications, the prescription of vitamin K has no immediate effect and therefore the patient continues to bleed until the plasma levels of the

previously depressed clotting factors have reached a protective range of 30 to 40 per cent. Oral anticoagulants are characterised by a particularly narrow range between safe and effective dosage. Last but not least, the long and continuously growing list of drugs known to interfere with oral anticoagulants—both as activators and inhibitors—further complicates the situation (Table IV).

TABLE IV

Drug interference with oral anticoagulants

Drug	Mechanism of interference	Result
Phenobarbial Chloral hydrate Meprobamate Glutethimide (Doriden®) Haloperidol (Haldol®)	Increased microsomal enzyme activity in the liver Increased metabolic degradation of AC	Inhibition
Phenyramidol (Analexin®)	Inhibited metabolic degradation	Potentiation
Phenylbutazone (Butazolidin®) Oxyphenbutazone (Tandearil®) Diphenylhydantoin (Dilantin®) Salicylates (Aspirin®)	Prevention of protein-binding peak levels of AC increased	Potentiation
Tetracyclines Neomycin Sulfisoxazole	Inhibited bacterial synthesis of vit. K	Potentiation
Clofibrate (Atromid®)	Unknown	Potentiation

Heparin, especially subcutaneous Calciparin®, has been both safe and highly effective in preventing venous thrombo-embolism (Cornu, 1967; Courbier, 1967; Giehl, 1968). With a proper injection technique local complications are exceedingly rare. Bleeding due to overdosage is exceptional and rapidly compensated with protamine. The problem of drug interference does not exist (Griffith, 1964). Some of the practical advantages of heparin over oral anticoagulants are mentioned in Table V. In polytraumatized patients, Calciparin® has been shown to prevent factor X activation, to normalise increased platelet adhesiveness (Negus, 1971) and to inhibit intrinsic thromboplastin generation.

Back in 1970 Sharnoff and De Blasio had already claimed that in major surgery heparin in low dosage significantly decreases the incidence of pulmonary embolism. Among close to 19,000 consecutive cases operated upon without heparin prophylaxis fatal thrombo-embolism was three times higher than among 750 similar cases on low-dose heparin. In the meantime published evidence and clinical experience have added strong support to these findings.

In major surgery four teams of investigators have recently published the results of their prospective randomised trials on the antithrombotic action of low-dose subcutaneous heparin (Table VI). Gordon-Smith (1972) and Nicolaides

(1972) used sodium heparin—Kakkar (1972) and Van Vroonhoven (1974) used calcium heparin.

TABLE V

Oral anticoagulants versus heparin in the prevention of phlebothrombosis

Drug	Acenocoumarol (Sintrom®)	Ca-heparin (Calciparin®)
Dosage	Individually adjusted (Ad quick = 25 per cent)	Fixed time-dose schedule 10,000 i.u./12 hours
Mode of administration	Orally	Subcutaneously
Mode of action	Inhibition of synthesis of factors II, VII, IX and X	Inhibition of: Thrombin generation Factor X activation Platelet aggregation
Therapeutic levels	Within 36 to 48 hours	Within 1 to 2 hours
Biological half-life	Close to 24 hours	4 to 5 hours
Laboratory monitoring	Obligatory (quick/P and P)	Not required (HTT/ Howell)
Haemorrhagic complications	Frequent/often severe	Exceptional/usually benign
Drug compensation	Slow (vit. K)	Rapid (protamine)
Drug interactions	Very common	Practically unknown

TABLE VI

Efficacy of low doses of heparin in prevention of post-operative deep-vein thrombosis. Results of four controlled clinical trials

Author	Number of cases	Heparin dosage	Incidence of post-operative DVT	
			Heparin	Control
			%	%
Gordon-Smith (1972)	150	5,000 i.u. Na-heparin 12 hours/1½ days	13·5	42
Kakkar (1972)	78	5,000 i.u. Ca-heparin 12 hours/7 days	8·0	42
Nicolaides (1972)	215	5,000 i.u. Na-heparin 12 hours/7 days	0·8	24
Van Vroonhoven (1974)	100	5,000 i.u. Ca-heparin 12 hours/8 days	2·0	18 (oral anticoag.)

FUT-assessment clearly showed that the incidence of deep-vein thrombosis (DVT) was significantly lower in the treated patients than in the controls. Concurrently pulmonary emboli were recognised in one case only out of 200, a proportion similar to the one reported by Sharnoff (1970).

We are quite aware that the results of these trials, carried out in major surgery, cannot be directly extrapolated to spinal cord injury. On the other hand we know that the incidence of phlebothrombosis in acutely injured patients is just as high, if not higher than among surgical patients and that the mechanism of thrombus formation is very much alike.

TABLE VII

Platelet Aggregation Inducers (Depress c-AMP)		*Platelet Aggregation Inhibitors* (Increase c-AMP)	
		(1) Tranquilisers:	Amitriptyline Chlorpromazine Imipramine
(1) Thrombin	Ca^{++} not required	(2) Anti-inflammatory drugs:	Aspirin Phenylbutazone Indomethacine
(2) Collagen Immune complexes		(3) Sympatholytic agents:	Phentolamine Tolazoline Propanolol Pronetalol
(3) ADP Adrenaline Noradrenaline 5-Hydroxytryptamine	Ca^{++} essential	(4) Coronary dilators:	Dipyridamol
		(5) PGE_1	

Aggregation Inhibitors. The most common chemical compounds that act as aggregation inhibitors or activators figure in Table VII. It may be interesting to note that all aggregation activators depress cyclic AMP whereas inhibitors act in the opposite sense.

Aspirin and other non-steroidal drugs such as indomethacine, ibuprofen, mefenamic acid and paracetamol inhibit collagen-induced platelet aggregation by preventing the release-reaction (O'Brien, 1970). The inhibitory effect of a single dose of aspirin on platelet aggregation and ADP-release can still be detected as long as five days after a single administration. It is probably directly related to acetylation of some membrane constituent.

To a lesser degree phenothiazines, tricyclic antidepressants and antihistamines also counteract ADP-release (Weiss, 1973).

Prostaglandine E_1 and methylxanthines increase platelet AMP and thus also act as aggregation inhibitors.

Dipyridamol and Dextran act by their stabilising effect on the platelet membrane rather than through changes in intrinsic platelet function (Zucker, 1971).

CLINICAL INVESTIGATIONS

Eighteen months ago we initiated a controlled comparative trial on the prophylactic efficacy of subcutaneous, low-dose heparin in the prevention of deep-vein thrombosis and pulmonary embolism after acute spinal injury. The results obtained in this group have been statistically analysed and compared with the ones

found in a similar group of patients admitted to the Genevan Spinal Injuries Centre between 1969 and 1972 and treated with a coumarin compound (Sintrom®).

MATERIAL AND METHODS

Essential data characterising the two groups are given in Table VIII.

(*a*) Seventy-six patients with acute spinal cord injury (43 paraplegics, 33 tetraplegics) have been anticoagulated with Sintrom®, therapy being initiated on the sixth to seventh day after the lesion. Dosage had been individually adjusted

TABLE VIII

Low-dose subcutaneous heparin versus oral anticoagulants in the prevention of thrombosis and fatal pulmonary embolism

	Period of investigation	
	1969-1972	1973-1974
Number of acute cases	76 (43 P/33 T)	44 (29 P/15 T)
Standard risk (SR)	52	28
'High risk' (HR)	24	16
Average age	34	26
Anticoagulation—Drug Dosage Start	Acenocoumarol (Sintrom®) AD Quick 25-40% 6-7th day	Ca-heparin (Calciparin®) 10,000 i.u./12 hours 2nd day
Deep-vein thrombosis (DVT)	16 (21%) 11 HR/5 SR	3 (6·8%) 2 HR/1 SR
Fatal pulmonary embolism (PE)	5 (6·5%) 3 HR/2 SR	0 (0%)
Haemorrhagic complications	4 (5·3%)	2 (4·5%)

to maintain a stable Quick one-stage prothrombin level between 25 and 40 per cent. The patients average age was 34 years.

(*b*) Forty-four patients (29 paraplegics, 15 tetraplegics) of an average age of 26 years have been anticoagulated with low-dose subcutaneous heparin (Calciparin®, Choay). In the absence of severe haemorrhagic lesions such as massive haemothorax due to pulmonary contusions (one case) or retroperitoneal haematoma caused by a ruptured kidney (one case), treatment was systematically started 36 hours after spinal injury. A fixed time-dose schedule of 10,000 i.u. of Ca-heparin 12-hourly has been adopted in all cases. Drug-monitoring did not seem required. Several reports have shown that a ten-day course of heparin in severely injured patients is insufficient to assure adequate antithrombotic protection. We therefore

maintained this treatment for three full weeks. After that period heparin was substituted by Sintrom®, the change in medication being effected within 48 hours.

No other method of antithrombotic prophylaxis has been used apart from routine physiotherapy five times daily during the first week, three times daily thereafter. Anticoagulation has been maintained in both groups until the patients were fully active in the wheelchair. According to their peripheral vascular state and metabolic condition, the cases were attributed either to high- or standard-risk sub-groups (Table IX).

TABLE IX

HR-SR distribution of patients on oral anticoagulants or heparin	Group I ($N = 76$) Acenocoumarol	Group II ($N = 44$) Ca-heparin
High risk	24	16
Age	13	5
Obesity	3	4
Hypertension	2	3
Surgical treatment	1	1
History of phlebothrombosis	5	4
Varicose veins	8	2
Lipid/carbohydrate disorders	3	2
Standard Risk	52	28

Calcium heparin has been administered as previously prescribed by Kakkar and Corrigan (1972). These authors emphasise the importance of carefully instructing the nursing staff in appropriate injection technique: a fold of skin in the para-umbilical region is carefully raised and disinfected without rubbing or traumatising the area. 0·4 ml. of calcium heparin are then injected through a 26-gauge needle inserted at right angles to the skin. The sites of injection should be regularly changed in order to avoid local haemorrhagic complications.

RESULTS

In the group of 76 patients receiving Sintrom® deep-vein thrombosis has been observed 16 times (21 per cent), fatal pulmonary embolism five times (6·5 per cent). Among the 44 cases on a three-week course of Calciparin® followed by Sintrom® thrombosis occurred on three occasions (6·8 per cent). The strongest argument in favour of low-dose heparin is the striking absence of fatal embolism.

The difference in the incidence of thrombo-embolic complications in groups (*a*) and (*b*) is statistically highly significant ($P < 0{\cdot}001$).

COMPLICATIONS

In the low-dose heparin group three patients developed venous thrombosis and two showed haemorrhagic complications. Possible reasons for these therapeutic failures will be analysed hereafter.

Deep-vein thrombosis was diagnosed in two high-risk and one standard-risk patient on the fourth, tenth and eighteenth day respectively after spinal cord injury.

L. F., a 55-year-old tetraplegic with a complete bilateral level C4-C5 had signs of obliteration of his left popliteal vein on the fourth day after admission. He was rated 'high-risk' considering his obesity, severe disorders of lipid and carbohydrate metabolism and long previous history of venous insufficiency.

J. E., a 45-year-old woman with a complete C4-C5 lesion developed considerable oedema in both lower extremities on the tenth day after injury. Ultrasound flow detection showed bilateral occlusion of the deep femoral veins. This patient was also considered a 'high risk' since her personal history mentioned several episodes of severe thrombophlebitis during pregnancy eight years ago.

R. P., a 20-year-old boy with a bilateral complete Th1-Th2 lesion showed signs of left femoro-popliteal venous thrombosis on the eighteenth day after admission.

In two of these patients who had excessive overweight our dosage of Calciparin® probably was not sufficient to afford adequate protection. In all three cases thrombi had started in the calf veins; secondary extension to the femoral veins was diagnosed twice with UFD.

In the above-mentioned three cases with thrombosis, Calciparin® was discontinued. Na-heparin was given instead in a continuous i.v. drip at a rate of 6,000 u. every four hours. In all patients, satisfactory venous drainage was restored within five days.

Heparin treatment was monitored with the activated partial thromboplastin time which proved to be a rapid, fairly reproducible and sensitive test to evaluate individual heparin tolerance. The rapid return of a satisfactory venous flow may be explained by an accelerated disintegration of a thrombus that had developed during anticoagulation (Spector, 1967; Degnan, 1969).

On two occasions treatment had to be interrupted because of haemorrhagic complications.

B. R., an 18-year-old paraplegic girl who had sustained a compression fracture of Th10 developed a large retroperitoneal haematoma on the eighteenth day of heparin therapy. The haematocrit fell to 19 per cent, haemoglobin to 58 per cent. Three blood transfusions of 450 ml. were required to obtain satisfactory compensation.

R. F., a 28-year-old tetraplegic with a complete C5-C6 lesion was admitted to the Centre three days after cervical spondylodesis C4-C6. On the eleventh post-operative day he developed a haematoma at the right iliac crest where the graft had been removed.

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