Review Article

Thrombosis: the relationship of hemostatic mechanisms to drug therapy

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The mechanisms of arteriovenous and microcirculatory thrombosis and embolism are presented. Drugs affecting the hemostatic balance and their specific actions and indications are reviewed.

KEY WORDS: thrombosis • embolism • drug prophylaxis • thrombolytic agent • antiplatelet agent • fibrinolysis • anticoagulant drug • heparin • warfarin • enzyme

THROMBOSIS is a phenomenon, not a disease; yet it complicates the course and contributes to the lethal nature of several major killers in American society. The impact of thromboembolism on mortality and morbidity in the United States is impressive. Arterial thrombosis plays a role in the initiation, growth, and terminal occlusion of the atherosclerotic lesion, and is a major contributor to mortality in acute myocardial infarction and stroke — the Number 1 and 3 causes of death in the United States. In addition, thromboembolic events are frequently associated with valvular heart disease, cardiac arrhythmias, congestive failure, and intimal damage to arteries in the cerebral, cervical, aortoiliac, visceral, and peripheral areas of the circulation. Some inborn errors of metabolism, infections, blood dyscrasias, trauma, drugs, and certain diseases of unknown etiology are also associated with arterial thrombosis.

Venous thromboembolism causes approximately 300,000 patients annually to be hospitalized in the United States, of whom more than 50,000 die, primarily in hospitals, rehabilitation centers, and nursing homes. Pulmonary embolism is a major threat to life in the postoperative state. It is the most frequent nonsurgical cause of death among patients hospitalized for major orthopedic reconstructive surgery, a not uncommon cause of mortality following neurosurgical procedures, the most frequent non-obstetric cause of postpartum death, a major factor in mortality among the extensive population of patients with chronic cardiac and pulmonary disease, and among an equally large group who are subjected to prolonged immobilization because of a variety of medical and surgical conditions. Indeed, in hospitalized adult patients who die, careful autopsy examinations disclose evidence of antemortem pulmonary embolism in more than 60% of cases.

Thromboembolism induced by contact of blood with foreign surfaces is a major unresolved problem in the development of artificial organs for extracorporeal circulation or for implantation within the heart and blood vessels. This phenomenon is a significant obstacle to advances in clinical care associated with prosthetic heart valves, extracorporeal cardiopulmonary bypass, cardiac assistance, respiratory assistance through extracorporeal circulation, intravascular catheters, electrodes, artificial hearts, artificial blood vessels, arteriovenous shunts, vascular sutures, and all other applications in which the blood comes into contact with a nonbiological surface.
Thrombosis related to microcirculatory disturbances, unlike that of arteries and veins, cannot be expressed in precise terms, but can best be appreciated by a partial listing of disciplines and diseases in which such disturbances are important. The microcirculation, deranged by thrombosis, is often contributory and even a primary mechanism for the induction of pathology in hypertension, stroke, diabetes, cancer, infection, inflammation, autoimmune disease, host graft rejection, hemolytic anemia, drug toxicity, mismatched blood transfusions, liver disease, pancreatitis, and glomerulonephritis. Thus, clinically, thromboembolic obstruction to three major components of the circulation — arterial, venous, and microcirculatory — contributes materially to early death in our society.

Derangements in at least six systems have been identified as causing or contributing to obstruction to blood flow: the endothelium and its subjacent structures; platelets; the plasma clotting proteins and their co-factors; fibrinolysis; plasma inhibitors of both coagulation and fibrinolysis; and rheology or the flow characteristics of fluid blood. The subtle interrelationships between these systems is complex and incompletely understood. Alterations in the delicate balance among them can result in serious hemorrhage or major thrombosis. The focus of the discussion that follows will relate to those basic aspects of hemostasis involved in arterial and venous thrombosis, together with their therapeutic implications.

### Mechanisms Responsible for Intravascular Coagulation

#### Arterial Thrombosis

In the artery, thrombosis can be readily visualized as an extension or exaggeration of the hemostatic plug that forms in response to injury, such as may be seen on atheromatous plaques. Intact endothelial cells prevent platelet aggregation by at least two mechanisms: They act as a physical barrier between thrombocytes and subendothelial structures, such as collagen, that can initiate platelet aggregation. They also have the capacity to synthesize a prostaglandin, prostacyclin (PGI₂), that is a potent inhibitor of platelet aggregation.

Damage or disruption of the integrity of the endothelium by a variety of agents can initiate thrombosis, a phenomenon that may potentiate the earliest phase of atherosclerosis. Although platelets do not attach to intact endothelial cells, they do adhere to exposed collagen when the endothelial barrier is disrupted, whereupon the platelet undergoes a series of changes termed the "release reaction." Included in this reaction is the release from platelet storage pools of adenosine diphosphate (ADP) that causes additional reversible thrombocyte aggregation and further release of ADP, thus sustaining the initial platelet aggregation that is still reversible. Platelet aggregation, moreover, results in the release of phospholipid (platelet Factor III), an element essential to the coagulation process.

The exposed subendothelial structures, in addition to their effect on platelet function, also activate the clotting sequence leading to the production of thrombin, a serine protease that converts fibrinogen into fibrin. Thrombin can also induce irreversible platelet aggregation by initiating the synthesis of thromboxane A₂, as well as induce platelet actomyosin contraction, which, along with the production of fibrin, consolidates the platelet plug.

It has been suggested that blood responds to intravascular stimuli as it does to vessel wall injury. Here, too, platelet aggregation may be the pivotal thrombotic reaction to such intravascular stimuli as antigen-antibody complexes, viruses, bacteria, endotoxin, epinephrine, serotonin, thrombin, and trypsin. This view has been supported and extended by electron microscopic studies demonstrating that vascular injury in rabbits may follow a single dose of *Escherichia coli* endotoxin.

These overall series of reactions yield what is known classically as the white thrombus. It is this type of lesion — an exaggeration of the hemostatic plug formed in response to injury — that represents the morphology of the typical arterial thrombus. It is this type of thrombus, moreover, that is not susceptible to coumarin therapy nor to heparin, insofar as the latter agent has been tested in arterial thrombosis. On the basis of the role of platelets in hemostasis, however, it is natural that antiplatelet agents be tested for efficacy in the prevention of arterial thrombosis. Most of the studies have been conducted in vitro or in animals, but in recent years these agents have been subjected to clinical trials. Although this field is currently an exciting area of clinical investigation, the published data, as we shall see, require that enthusiasm be tempered with patience. For, thrombosis is a multifactorial process with divergent morphological constituents and varying rates of formation and extension in which the end organ response depends on collateral circulation and the nature of the ischemic cells.

#### Venous Thrombosis

Venous occlusions present essentially as coagulation or red thrombi consisting principally of fibrin and erythrocytes with white blood cells and platelets randomly distributed. The morphology cannot be explained by analogy to the hemostatic plug. Under light microscopy, one finds red blood cells enmeshed with fibrin. With the scanning electron microscope, this thrombus is readily seen to consist primarily of erythrocytes and fibrin strands wherein one rarely sees platelets or platelet debris.

In the venous circulation, it is the coagulation sequence, in contrast to the endothelium and the platelet
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in arterial circuits, that plays a key role in the formation and extension of venous thrombi. Coagulation can be viewed as a series of zymogen activations to proteinase and extension of venous thrombi. Coagulation initiation via the intrinsic system or by the traumatic release of tissue thromboplastin via the extrinsic system. The two pathways converge at clotting Factor X (an important focus for the molecular action of low-dose heparin regimens) and continue along a common pathway to fibrin gel formation. These biochemical reactions have important therapeutic implications for the effective use of the classical anticoagulants, regular-dose heparin, and the coumarin compounds.

**Contributions of Rheology to Thrombosis**

Although the relationship between various parameters of blood flow and thrombosis are still being unraveled, certain generalizations can be provided. Retarded blood flow, while it cannot cause intravascular coagulation, does facilitate the thrombotic process once it is initiated. Stasis can occur not only in veins, but also in arteries at bends and bifurcations. If a thrombus is effective in halting, or nearly halting, the flow of blood, such static effect will facilitate the thrombotic process by mechanically protecting it from being "washed away" by fluid blood. Through studies of fluid mechanics it can be proposed that, in areas of retarded flow, thrombus evolution would be favored in a plasma phase within the static red cell network, because thrombin and other serine proteases would be protected from dilution to subcritical concentrations, from inflow of plasma inhibitors, and from clearance of proteases by the liver; and because nascent fibrin would be protected from premature dispersion. It is formulations such as this that justify efforts, in the peripheral venous circulation, where such an approach is feasible, to reduce or prevent thrombosis by mechanical devices that accelerate venous blood flow, either in place of or in conjunction with antithrombotic agents. The value of pulsatile limb compression following neurosurgical procedures has already been demonstrated in controlled trials.

**Compounds Affecting the Hemostatic Balance**

**Drugs Acting on the Fibrinolytic System**

**Thrombolytic Agents.** For almost 50 years it has been known that streptococci produced an enzyme that lysed fibrin and for over 20 years it has been appreciated that this material, streptokinase, can potentiate the dissolution of thrombi in man. Streptokinase activates the fibrinolytic system by combining with plasminogen to form a 1:1 complex of activator and plasminogen which, by proteolytic cleavage, converts plasminogen to plasmin.

Urokinase directly activates plasminogen to plasmin. Dissolution of the thrombus probably results from the action of either the activator or the formed plasmin within the thrombus. The enzymatic effect of plasmin on clotting zymogens in flowing blood is usually feeble because of the presence of plasmin inhibitors in the circulation.

Both streptokinase and urokinase have been tried in a host of conditions, including acute myocardial infarction, stroke, peripheral arterial occlusion, retinal artery occlusion, priapism, disseminated intravascular coagulation, and thrombosed valve prostheses, with inconclusive or negative results. Thrombolytic agents are primarily effective against recent thrombi, and are currently recommended for consideration only in the treatment of extensive pulmonary embolism, massive deep venous thrombosis, and partially occluded arteriovenous cannulae. Upon discontinuance of fibrinolytic therapy, heparinization is usually necessary to prevent rethrombosis. Thrombolytic agents entail a substantial risk of hemorrhage and should not be used concurrently with heparin or the coumarin compounds nor in recently traumatized patients. Accordingly, they are contraindicated following neurosurgical procedures.

**Anti thrombolytic Agents.** Blood in the subarachnoid space stimulates fibrinolytic activity that may lead to thrombolysis and hemorrhage. Epsilon-aminocaproic acid (EACA) and transexamic acid (AMCA) bind both to plasmin and plasminogen competitively dissociating these proteins from fibrin. This is accomplished through the interaction of these drugs with the lysine binding site of the protein involved in fibrin binding. The Ki values for these two drugs are of sufficient magnitude to permit inhibition of plasmin binding to fibrin at the plasma concentrations prevailing during their therapeutic use.

Although a hazard of these compounds is the potential of intravascular coagulation by preventing fibrinolysis in other portions of the vascular tree, both EACA and AMCA have been employed in the management of ruptured intracerebral aneurysms.

**Prophylactic Antithrombotic Drugs**

There are presently available several classes of compounds that inhibit or control thrombosis. These include antiplatelet agents such as aspirin, dipyridamole, and sulfipyrazone; vitamin K antagonists such as warfarin; antithrombin III potentiators such as heparin; depletors of fibrinogen such as ancrod; and the dextrans that have a variety of antithrombotic actions.

**Antiplatelet Agents.** Aspirin acetylates a protein, prostaglandin cyclo-oxygenase, thereby inhibiting
this enzyme and blocking synthesis of prostaglandin endoperoxides which are potent platelet aggregants. Aspirin, in addition, partially blocks the production of thromboxane A₂, another potent platelet aggregator. On the other hand, aspirin also blocks prostaglandin synthesis in endothelial cells. One of these endothelial prostaglandins, PG₁₂, is a potent platelet anti-aggregant. By blocking the synthesis of PG₁₂, therefore, one may possibly counteract the anticoagulant effect of aspirin on the platelet. Aspirin action on platelets is irreversible, accounting for the duration of the effect of this compound on platelet function for the lifetime of the thrombocyte (7 to 10 days). The effect on endothelial cells is transient, due to the continuous turnover of proteins in these cells. These observations offer the potential of tailoring the dose of aspirin depending on the effect desired — an issue that is presently under intense scrutiny.

Sulfinpyrazone is a potent synthetic inhibitor of platelet prostaglandin synthetase activity. Unlike aspirin, however, its effect is only transient. The action of sulfinpyrazone on endothelial prostaglandin synthesis, specifically PG₁₂, has not yet been determined.

Dipyridamole in vitro inhibits ADP-induced platelet aggregation, as well as the platelet release reaction. The drug blocks platelet cyclic adenosine monophosphate (AMP) phosphodiesterase activity, thereby inhibiting the conversion of the potent anti-aggregant cyclic AMP to AMP. The mechanism whereby dipyridamole inhibits platelet aggregation is still to be firmly established.

Heparin. Heparin functions as an anticoagulant by accelerating antithrombin III neutralization of essentially all of the clotting serine proteases with the exception of activated clotting Factor VII in the extrinsic system. Thus, heparin has a major role in preventing thrombosis initiated via the intrinsic clotting system, as well as in the final common pathway leading to fibrin gel formation and irreversible platelet aggregation. Heparin acts as a catalyst requiring antithrombin III for its efficacy, and increasing the rate of the inhibitor-protease reaction without being consumed and without altering the final products of the reaction.

Warfarin. Warfarin, by inhibiting the carboxylation of glutamic acid to γ-carboxyglutamic acid residues, alters the synthesis of four vitamin K-dependent clotting proteins (Factors II, VII, X, and IX), as well as other K-dependent proteins. The warfarin-induced changes in the first three of these zymogens is reflected by the prothrombin time, which provides a guide to dosage of the oral anticoagulants. Recent studies in animals have identified two anti-thrombotic actions of warfarin: the first is an early effect directed against tissue thromboplastin-initiated coagulation (such as occurs in major trauma) commencing 6 hours after drug administration and reaching a peak in 48 hours, and the second is an additive, antithrombotic action that after 6 days of therapy potentiates the natural inhibitory action of plasma.

Dextran. In its original form, dextran is a branched polysaccharide of about 200,000 glucose units with a molecular weight of approximately 40 million. The glucose units in the main chain are bound together through 1:6 glucosidic linkages; those in shorter branches, through 1:4 linkages. By means of partial hydrolysis and subsequent fractionation, native dextran can be converted to polysaccharides of any desired range of molecular weight. In general, it is fair to say that clinical complications increase with higher average molecular weight, broader molecular weight distribution, and a more pronounced degree of branching of the molecule. The two most important preparations currently in use are a 70,000 molecular weight preparation (MacrodeX or Dextran 70) and a 40,000 molecular weight compound (Rheomacrodex or Dextran 40).

Fibrin deposited in the presence of dextran is morphologically different from fibrin in normal clots, resulting in a decrease in its mechanical strength and in an increase in its porosity. These properties favor both the inability of the fibrin clot to withstand shear stress in flowing blood and the rate at which fibrinolysis can occur. Dextran also decreases platelet aggregability and increases the rate of blood flow.

Venoms. Various snake venoms have striking effects on the coagulation and fibrinolytic systems. The venom from the Malayan pit viper contains a protein, anclay, that is capable of converting plasma fibrinogen to fibrin. However, since the fibrin-stabilizing factor (clotting Factor XIII) is not activated, the resulting fibrin cannot form a stabilized precipitate. Accordingly, the unstabilized thrombus can be readily broken up and promptly removed from the circulation.

Antifibrinolytic Management of Intracranial Aneurysm

The past decade has been marked by major improvements in the treatment of ruptured intracranial aneurysms to which contributions have been made by microsurgery, neuroanesthesia, and the use of a variety of drugs including antifibrinolytic agents. The potential value of these latter compounds rests on the thesis that fibrinolytic activity in the cerebrospinal fluid lyses the thrombus that is sealing off the leaking aneurysm, and that this localized activity can be safely prevented by systemic antifibrinolytic therapy. Such treatment, so the reasoning goes, should reduce both rebleeding and postoperative hemorrhage. There is a modest literature on the issue of the benefits of EACA and AMCA. As might be expected from anecdotal reports and trials of varied sophistication, not infrequently complicated by other new concomitant therapies, there is yet no unanimity of opinion on benefit.
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Overall, however, the drugs appear not to have induced tragic thrombotic complications, and the data suggest that the incidence of rebleeding is diminished among patients receiving antifibrinolytic therapy intravenously during and after surgery. It has also been suggested that the drug may be of benefit for the 2-week period between the onset of subarachnoid bleeding and surgery, as well as of value, at least for short periods of time, after bleeding in patients whose lesions are not amenable to surgery.49

To prevent postoperative venous thromboembolism, intermittent pneumatic calf compression, alone or followed by a low-dose heparin regimen, has been considered.49 Such prophylactic strategies should also be considered for patients who are not candidates for surgery.

Drug Prophylaxis of Arterial Thrombosis

If atherosclerosis could be prevented, thrombosis would essentially be eliminated as a major contributor to arterial occlusive disease, except for intravascular coagulation on prosthetic devices within the arteries and cardiac chambers. On the other hand, if arterial thrombosis could be prevented, the clinical effects of slowly growing atheroma would be ameliorated by the compensatory development of collateral circulation in physiologically end-arterial circuits such as are found in the heart and brain.

The treatment of an already formed arterial thrombosis, per se, as opposed to therapy of the target organ and in contrast to the prophylaxis of thrombus formation, has been largely dependent on surgical approaches that either remove the thrombus or bypass the obstructed area by an appropriate graft. The immediate success of the surgical attack depends on a number of variables: 1) identification of the obstructed arterial segment that is responsible for the ischemia and amenable to surgery, 2) technical completion of the operation without producing further ischemia or damage to important collaterals, 3) adequate distal "runoff," and 4) the allowable time lapse between the onset of occlusion and irreversible ischemia. The variables in this last factor include the extent of the preformed interarterial collateral circulation, the rate of formation and length of the thrombus, and the "viability time" of the ischemic organ. It is the rapid, irreversible vulnerability of nerve tissue to ischemia that forecloses antithrombotic therapy for acute (spontaneous or traumatic) occlusions of cerebral, brain stem, or spinal cord arteries.

Warning signs of occlusion such as transient cerebral ischemia, onset or change in angina pectoris, intestinal angina, or intermittent claudication can be helpful in the initiation of diagnostic studies that may lead to prophylactic medical or surgical intervention prior to thrombosis. Surgical success in this clinical subset of patients, however, rarely guarantees avoidance of postoperative thrombosis, for which therapy is currently available.

Aspirin

There have been several early reports on the value of aspirin in patients with transient ischemic attacks (TIA). The goals were cessation of TIA, prevention of stroke, and a decrease in the death rate (the majority of which comes from heart disease rather than from cerebrovascular accidents). These publications consist of case reports, and retrospective and prospective trials.43,46,47,48,49

One stimulus for these studies came from a variety of reports suggesting that aspirin users have a remarkably low incidence of coronary artery disease. In one of these investigations, the incidence of TIA was found to be significantly reduced, but comparable advantages for stroke and mortality rate were not obtained.53 In addition, the soundness of the trial design itself has been questioned.44 More recently, a controlled trial has demonstrated benefit from aspirin among patients with TIA.54 Like many trials, this well designed study has also been criticized.49,55 The benefit, interestingly, was restricted to men. This sex difference with aspirin has also been observed in trials of the drug for the prevention of venous thrombosis following hip arthroplasty,56 and confirmed in experimental thrombosis in animals.57 The phenomenon is as yet without explanation and is not seen among other indications for aspirin. The benefit of aspirin on recurrent infarction and mortality rate has now been evaluated in several studies. Two early trials showed favorable trends, but did not reach statistical significance.58,59 More recently, two secondary prevention trials evaluated the efficacy of aspirin among patients who had recovered from acute myocardial infarction.60,61 No statistically significant benefit was found in either study. Finally, in arteriovenous shunts among patients on hemodialysis and in hemodialyzers, aspirin does appear to have significantly reduced the incidence of thrombosis. Recently, benefit was reported in this clinical situation with low doses of aspirin.62

Aspirin, in combination with dipyridamole, has corrected platelet consumption observed among patients with prosthetic heart valves.63 The role of aspirin alone on this effect is unknown, and whether correction of increased platelet consumption can be correlated with an antithrombotic effect is still questioned.

Sulfinpyrazone

Several reports have indicated a favorable effect of sulfinpyrazone on recurrences of TIA.64,65,66 and in one of these trials improvement in survival was noted.67 Sulfinpyrazone also appeared in this latter trial to have a survival benefit among patients with a previous myocardial infarct. On the other hand, the favorable aspirin-TIA trial mentioned above12 caused many patients to be treated with sulfinpyrazone, without benefit.

Recently, a randomized double-blind multicenter
trial comparing sulfinpyrazone with a placebo demonstrated a significant reduction in sudden cardiac death among treated patients compared to the control group during the first year after myocardial infarction. A follow-up study of this same trial 1 year later showed no incremental survival. Although the basis for the benefit has not been established, despite wide speculation, the results appear striking. This trial has been criticized and acclaimed. Among patients with prosthetic mitral valves, sulfinpyrazone has returned shortened platelet survival times toward normal; still, a significant antithrombotic effect has not yet been established.

**Dipyridamole**

In a single trial of dipyridamole among patients with cerebrovascular disease, no benefit was recognized. Similarly, in a large number of trials of this drug among patients with coronary artery disease, no mortality benefit was observed; but, more recently, in an experimental study of infarct size in animals, a definite reduction in infarct size was attributable to dipyridamole. In patients with mitral valve disease, shortened platelet survival has been returned to normal, but an antithrombotic benefit has only been demonstrated when dipyridamole was used with another antithrombotic agent.

**Drug Prophylaxis of Venous Thromboembolism and Systemic Emboli From the Heart**

**Heparin**

**Low-Dose Heparin.** In the past decade, a series of investigations led to the suggestion that a primary function of heparin in preventing thrombosis before the initiation of intravascular coagulation was its potentiation of the inhibition of activated Factor X (Xa) by its natural inhibitor, antithrombin III. Based on the thesis of biochemical amplification in blood coagulation and the ability of antithrombin III to inhibit Xa rapidly in the presence of small quantities of heparin, it was proposed that less heparin would be required to inhibit thrombosis before thrombin formation than afterward. Pari passu with these developments came a series of clinical trials demonstrating that 5000 units of heparin initiated subcutaneously 2 hours prior to general abdominal and thoracic surgery and continued on either an 8- or 12-hourly schedule reduced significantly the incidence of isotopically measured postoperative calf vein thrombi. These studies were followed by three larger trials that showed at autopsy a marked decrease in the incidence of large pulmonary emboli. Although no overall mortality benefit could be recognized, it was inferred that decreases in isotopic calf thrombi and in large pulmonary emboli at autopsy offered a potential for increased survival that justified the slight but definite increase in wound hematomas among the heparinized patients.

Even if the indirect arguments for the antithrombotic efficacy of low-dose heparin remain persuasive, they do not assure the widespread use of this form of prophylaxis in clinical practice, unless the risk-benefit ratio is acceptable. Guidelines to minimize risk in surgical patients have been published; nevertheless, the occurrence of drug-induced hemorrhage, even if thought by some to be minor, must be acknowledged. In most published trials no clear effort was made to eliminate aspirin, or other antiplatelet agents, before the operative procedure. Aspirin itself can cause bleeding in surgical patients, and the combination of aspirin and low doses of heparin induces a double hemostatic defect with a greater frequency of hemorrhage than with either drug alone. Aspirin may, in fact, account for some of the bleeding observed among control patients in many of the trials.

It is of interest that, while general surgeons continue to evaluate the risk-benefit ratios of routine low-dose heparin prophylaxis, three studies have recently been published indicating that the bleeding risk in a wide range of neurosurgical procedures is acceptable and in one of the studies significant decreases in isotopic calf thrombi were observed among the heparin-treated patients compared to controls. There is general agreement that low-dose heparin regimens are ineffective in patients with an active thrombotic process.

**Regular-Dose Heparin.** Once venous thromboembolism has been recognized in the postoperative state and that individual is determined to be hemostatically competent by clinical and laboratory evaluation, a regular-dose heparin regimen may be initiated. For most patients 40,000 to 60,000 units of heparin/day may be administered for the first 48 hours. Beyond 2 days, any schedule is complicated by the fact that the antithrombotic effect and hemorrhage do not proceed in parallel. But the risk of hemorrhage simplifies the decision-making process; for, in clinical practice, the likelihood of hemorrhage controls dosage at least after 48 hours of heparinization. It is rare, in a hemostatically competent patient, to encounter spontaneous (as opposed to traumatic) bleeding during the first 2 days of a regimen of 40,000 to 60,000 units of heparin/day. Subsequently, the risk is real and unpredictable, even with laboratory monitoring. Thus, in the majority of patients, the dose of heparin after 48 hours should be reduced to the range of 30,000 units for the 3rd day and to 20,000 units by the 5th day, provided the thrombotic episode is not progressing as determined by clinical evaluation (proximal limb extension of pain, tenderness or edema, increasing dyspnea, or chest pain) or laboratory findings (iodine-125 limb scanning, impedance plethysmography, lung scan, or angiography). If anticoagulation with warfarin is to be continued beyond the hospital stay, it is desirable to overlap the warfarin with heparin for 6 days after the prothrombin time has reached the therapeutic range. The rationale for this latter...
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recommendation is provided in the section below under warfarin.

For patients with extensive thromboembolism, investigators have used initial doses of as much as 120,000 units of heparin/day. These large doses should clearly be reserved for patients with massive pulmonary embolism and shock, and should be reduced to the lower dose range previously described within 12 to 24 hours after therapy is initiated, and then further reduced as clinical progress dictates.

Data regarding the relative frequency of bleeding complications when heparin is given by constant intravenous drip or intermittently on a 4-hourly schedule are conflicting, and in most studies the number of units of heparin/24 hours was significantly higher in the intermittent group. One may conclude that either technique may produce hemorrhagic complications, if full dosage schedules are maintained beyond 48 hours.

There is no clear evidence that the calcium salt is preferable to the sodium salt of heparin, that there is at present any clear preference between heparin prepared from lung or gut, or that body weight is a useful criterion of dose in adults. Although it has been suggested that older women on standard doses of heparin may bleed more readily than comparably aged men, this issue may be resolved by the dosage schedule outlined above.

The antithrombotic action of heparin depends on the presence of a normal quantity of the plasma inhibitor, antithrombin III, prior to the institution of therapy — a determination that can be made by one of several available assays. In addition, a normal partial thromboplastin time prior to therapy that is increased promptly after drug administration will demonstrate that heparin is circulating. Subsequent partial thromboplastin time determinations will not protect the patient from hemorrhage, nor is the test of value as a measure of the antithrombotic potency of the drug. The primary reason for performing the assay daily is to ensure that the patient is receiving heparin. Heparin-induced thrombocytopenia, severe enough to induce hemorrhage and on rare occasions accompanied by arterial thrombosis, is a real if uncommon phenomenon. Platelet counts every 2 to 3 days will suffice to recognize this toxic effect of heparin, which is reversed by cessation of the anticoagulant. Further details concerning heparin may be found in a recent review.

Warfarin

Oral anticoagulants have been repeatedly demonstrated to be effective prophylactic agents against postoperative venous thromboembolism (a not uncommon event after paralytic strokes and neurosurgical procedures, particularly those accompanied by marked or prolonged immobilization). The value of coumarin agents has also been shown against systemic emboli that arise from mural thrombi in hearts with organic disease and major arrhythmias, following acute myocardial infarction, and after the insertion of valvular prostheses. It is only if anticoagulant therapy is initiated in these patients prior to embolization that any significant decrease in cerebral emboli will occur.

Therapy may be initiated with 10 to 15 mg of the drug (without a loading dose), and subsequent daily doses regulated by the prothrombin time to obtain a value that is in the so-called therapeutic range of 1½ to 2 times the control time in seconds. This therapeutic range has been shown to provide adequate antithrombotic protection, while minimizing the likelihood of bleeding. Should serious hemorrhage occur, immediate reversal of the warfarin-induced clotting defect can be attained by transfusion with blood or plasma. Because the warfarin-depressed clotting factors are stable, ordinary bank blood, bank plasma, or lyophilized plasma are fully potent. Three units of blood or plasma will generally suffice. In patients with limited cardiac reserve such volumes may precipitate pulmonary edema unless blood loss has been significant. Vitamin K$_1$ is also effective in reversing excessive anticoagulant action. Administered intravenously, subcutaneously, or by mouth (in this order of preference for obtaining most rapid action), some correction is demonstrable within a few hours and full correction is usually attained within 24 hours. Depending on the urgency of the situation, vitamin K$_1$ or blood-plasma may be given alone or together. If the patient is to remain on anticoagulant therapy, 0.5 to 1.0 mg of vitamin K$_1$ is usually adequate. Higher amounts, in multiple doses up to 10 mg, are recommended if warfarin therapy is to be terminated. Large amounts of vitamin K$_1$ (25 to 50 mg) may cause the patient to be resistant to coumarin therapy for several weeks, and effective anticoagulation may be difficult to achieve during that time.

Recent studies on the antithrombotic actions of warfarin, together with prior clinical experience, form the basis for the recommendation that warfarin should overlap with heparin for 6 days after the prothrombin time has reached the therapeutic range. Such a regimen would take full advantage of both the immediate and delayed antithrombotic actions of the coumarin compounds as described above.

Physicians should recognize that the list of drugs potentiating or antagonizing the anticoagulant action of warfarin is continuously expanding. The number of compounds is so extensive that, rather than maintain such a list, the physician should advise patients receiving warfarin to report to him promptly when any drug is deleted from or added to the therapeutic regimen. Frequent prothrombin time determinations will permit appropriate dose adjustments. While in the hospital, the daily prothrombin time offers protection from the frequently changing drug schedules. Finally, it should be appreciated that there are rare patients who are congenitally resistant to coumarin therapy, in
which situation heparin offers an appropriate alternative treatment.

Other Antithrombotic Compounds

Compared to the observations on heparin and warfarin, data concerning the value of the platelet antaggregants in the prevention of venous thromboembolism in elective surgery and medical conditions have been conflicting. However, there is evidence for the efficacy of aspirin among patients with fractured hips and in hip arthroplasty. In the latter instance, the benefit appears to be limited to men.

Both Dextran 40 and Dextran 70 have been employed to prevent thromboembolism, and effective results have been obtained in surgical patients. Although these compounds may have a special role in orthopedic surgery and in patients with trauma, there are occasional allergic reactions, and, in patients with limited cardiac reserve, the drugs may precipitate pulmonary edema. It is not clear, however, that the dextrans are superior to heparin or warfarin.

In man, the intravenous administration of the snake venom, ancord, results in a hypocoagulable state that can prevent thrombosis, but one that also produces hemorrhage at venipuncture sites as well as easy bruising. Although used abroad, the drug has not yet received Federal Drug Administration approval, and, consequently, is not presently available for routine use in the United States.

Drug Prophylaxis for Thrombosis Resulting from Trauma to the Head, Neck, and Spinal Cord

Low-dose heparin regimens do not offer adequate protection against thromboembolism induced by major trauma, because intravascular coagulation has already been initiated by the time the patient receives medical care, and, as noted earlier, it is well recognized that low-dose regimens are inadequate once the coagulation sequence has been activated. Among patients with head injuries there may be the associated syndrome of disseminated intravascular coagulation (DIC). The recognition and management of DIC have been discussed in a previous issue of this Journal. Care must be taken through evaluation of appropriate clinical and laboratory findings to determine in each patient whether DIC is present, and, if so, whether carefully monitored doses of heparin are indicated.

Moreover, as with major trauma elsewhere in the body, the administration of anticoagulant agents must be deferred for hours to days after injury to the head, neck, and spinal cord until the surgeon is secure that traumatic bleeding has ceased. If such a conclusion cannot be reached, anticoagulants must be withheld. Delay in anticoagulation implies acceptance of the fact that in many of these patients arterial or venous thrombosis in the traumatized area as well as venous thrombosis in the lower extremities will have already occurred. If such events are clinically silent, they should give the surgeon neither a false sense of security nor justification for failing to initiate delayed drug prophylaxis, for delayed anticoagulation can still prevent thrombus propagation, embolization, and an unforeseen lethal outcome — a situation not rare in neurological and neurosurgical experience.

It is possible, however, to propose an interim solution to this dilemma by offering early protection to the neurosurgical patient with pulsatile boots followed by delayed anticoagulation. A recent trial described the failure of 10,000 units of heparin to inhibit repeat thrombosis in the thigh in patients with preexisting recent proximal vein occlusion. In that study, warfarin in regular doses completely prevented thigh rethrombosis, although with some degree of associated hemorrhage. As-yet-unpublished findings from an ongoing trial by the same group suggest that approximately 20,000 units of heparin/24 hours is equivalent to warfarin in preventing thigh rethrombosis. Of importance in terms of risk-benefit ratios is the fact that, although the antithrombotic power of the two drugs was comparable, no bleeding occurred with the heparin regimen, in contrast to the warfarin-treated patients.

These clinical observations permit the recommendation that, when traumatic bleeding has clearly ceased (a variable number of days after injury), delayed augmented prophylaxis with 20,000 units of heparin will prevent further thrombosis with essentially no risk of hemorrhage in a hemostatically competent patient free of wound bleeding. If anticoagulation is to be continued, warfarin can be overlapped with heparin and the latter drug discontinued 6 days after the prothrombin time has reached the therapeutic level. In this regard delayed heparin and warfarin prophylaxis has been reported to be effective among patients with spinal cord injuries.

Summary

The mechanism of action and present clinical role of drugs affecting hemostasis in the therapy of spontaneous, postoperative, and posttraumatic arterial thrombosis, arterial embolism, venous thrombosis, pulmonary embolism, and intracranial aneurysm have been reviewed. Both the management of neurosurgical problems and the development of antithrombotic regimens are improving. In regard to the use of drug therapy, discussed herein, each surgeon will reach his own decision based on his findings in the individual patient, and may wisely elect in specific situations not to employ drug therapy. The comments offered in this analysis are to be construed as suggestions not mandates, as they will undoubtedly undergo modification with time. In closing, it is appropriate to recall a famous Chinese curse: "May you live," it reads, "in a time of transition."
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