GUIDELINES FOR THE MANAGEMENT OF ANTICOAGULANT THERAPY

Victor Gurewich, M.D.

Anticoagulant therapy has certain unique features that tend to complicate its appropriate use. For example, the beneficial effect of anticoagulants can usually be appreciated only by a statistical evaluation of clinical trials. By contrast, the hemorrhagic complications are all too obvious in the individual patient. This places a special onus on physicians who see their therapeutic failures and not their successes. Second, dosage is determined by coagulation tests which are insufficiently standardized and tend to be poorly understood by the clinician. Third, anticoagulant treatment is often directed against a "hypercoagulable state" whose existence has defied reliable laboratory identification. Duration of therapy therefore remains largely empirical. Finally, oral anticoagulants interact with numerous other drugs, causing inhibition or potentiation of pharmacologic effect, which may result in inadequate therapy or hemorrhagic complications.

These features of anticoagulant treatment are compounded by the inadequacy of scientific understanding of intravascular fibrin formation and its clinical detection. It is therefore not surprising that the clinical application, dosage, routes of administration and methods of control of anticoagulant drugs lack standardization and remain highly variable. Alternative methods of treatment (usually surgical) of thrombotic disorders are commonly utilized in some institutions and rarely in others. The choice is often determined by the interpretation of certain findings suggesting that medical management has been inadequate, a judgment which may be influenced by whether the attending or consulting physician is a surgeon or an internist. Preferably, the criteria which constitute "anticoagulant failure" should be examined critically in the light of current knowledge of the pathophysiology of thrombosis before a judgment is made.

In this chapter, an effort will be made to provide some guidelines for the optimal use of anticoagulant drugs. The recommendations will be based on a summary of relevant, published findings. The introduction of some bias is unavoidable, since only a selective review of the literature is possible.

GENERAL CONSIDERATIONS

The principle effect of anticoagulants is to inhibit fibrin formation by interfering with certain reactions in the coagulation sequence. Although anticoagulants

From the Vascular Laboratory, Lemmuel Shattuck Hospital, Boston, Mass.

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have no direct fibrinolytic effect, heparin has been shown to enhance clot dissolution in experimental animals [1,2]. The drugs cause little or no direct inhibition of platelet aggregation and therefore are of limited value in the prevention of most arterial thrombosis in which platelet adhesion is a cardinal feature [3,4]. When properly administered in the appropriate clinical setting, anticoagulants are among our most effective therapeutic agents.

Clinical Indications for Heparin or Oral Anticoagulants

Established

1. Venous thromboembolic disease (prophylaxis and therapy)
2. Mitral valve disease with atrial fibrillation

Probable

1. Transient ischemic attacks
2. Prosthetic heart valves
3. Preparation for cardioversion
4. Disseminated intravascular coagulation
5. Arterial emboli

Possible

1. Myocardial infarction
2. Cancer

HEPARIN

Heparin is a naturally occurring mucopolysaccharide (MW approx. 12,000) found in the mast cells of many tissues. It was first identified by McLean [5] in 1916 and was sufficiently purified for use in man by Best and co-workers in 1933 [6]. The ability to extract a concentrated, pure preparation of sodium heparin has improved to such an extent that the potency of currently available preparations has increased considerably. For this reason, heparin should always be prescribed in U.S.P. units and not milligrams. It is available as an aqueous solution in concentrations ranging from 1,000–40,000 units per milliliter. For intravenous administration, a low concentration of heparin should be used since heparin is highly acidic and irritating to the intima. Elimination of exogenous heparin is mostly by degradation in the liver but about 20% appears in the urine. In the presence of liver disease or renal failure, some modification of dosage is likely to be necessary.

Anticoagulant Properties

During blood coagulation, the enzyme, thrombin, is formed from its precursor, prothrombin. The specific proteolytic action of this enzyme on fibrinogen results in the formation of soluble fibrin monomer which polymerizes to form insoluble fibrin. Heparin prevents fibrin formation both *in vitro* and *in vivo* by interfering with the coagulation sequence at several sites (Fig. 1). It was demonstrated by Brinkhous et al. that this anticoagulant effect required the presence of a plasma

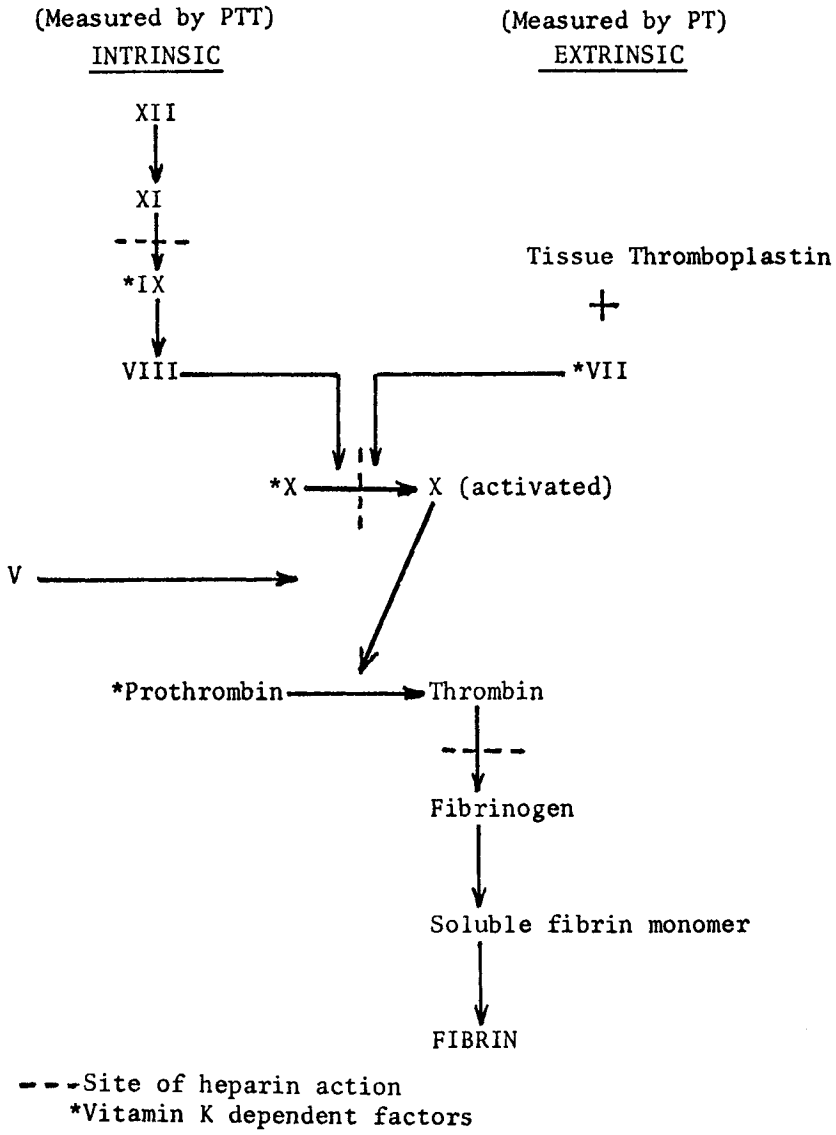

FIG. 1. Basic Coagulation Sequence

component which they called heparin co-factor [7]. This co-factor was shown by several investigators to be closely related to plasma antithrombin activity [8–11] as well as to the inhibitor of factor X activation [12–14]. Studies by Yin, Wessler and Stoll lead to the conclusion that heparin co-factor, antithrombin III and the inhibitor to factor X^a are probably the same blood proteinase inhibitor [15]. Heparin has the property of potentiating the action of this inhibitor [16,17]. The mechanism by which heparin accelerates the interaction between this inhibitor and certain clotting enzymes has recently been described by Damus, Hicks and Rosenberg [18].

The studies of Yin et al. suggest that more heparin is required to neutralize thrombin than is needed to prevent factor X activation [16]. The clinical corollary of this finding is that the heparin dosage in the prethrombotic state is less than that required after thrombin elaboration has taken place. This may be especially true for thrombin attached to fibrin on a thrombus. Animal experiments have shown that thromboemboli removed from the lungs of animals still have active thrombin on their surface [19]. Unneutralized thrombin is never found in the circulating blood. As a thrombus retracts or is lysed, more thrombin may be liberated and cause further clotting of fibrinogen. Still higher concentrations of heparin are required to inhibit thrombin-platelet interaction compared with what is needed to prevent thrombin-fibrinogen interaction [20].

It should be apparent from this brief review of the mechanism of heparin anticlotting activity, that the dosage selected clinically depends on the therapeutic objectives and should be predicated on our understanding of the pathophysiology of a particular thrombotic condition. Although our knowledge is far from complete, it is possible to formulate some reasonable guidelines to make the current use of anticoagulants more rational, effective and safe. As Genton recently concluded, "Frequently, where there has been a 'therapeutic failure' with heparin, it is really a physician's failure—in the method of administration or dosage—rather than true failure of the drug" [21]. It may be said that the application of our scientific understanding of the thrombotic disorders to their treatment has been far from optimal.

Routes of Administration

Heparin may be given intravenously or subcutaneously. It should never be given by the intramuscular route because of the high incidence of significant bleeding at the injection site.

The intravenous route has important advantages for the treatment of active thrombotic disorders. It provides an immediate onset of action whose duration is dose-dependent and readily controlled by one of the appropriate laboratory tests. The duration of action is short, allowing for a prompt discontinuation of effect in case bleeding develops or surgical intervention is necessary.

Intermittent intravenous injection through a rubber capped scalp vein infusion set strapped to the forearm is a practical method for administering heparin. It is painless, allows the patient to be fully ambulatory and permits him the use of both arms. A 4-hour interval between injections is usually used, though some studies have used a 6-hourly injection. A flatter dose response curve with lower peaks may be achieved with a 2-hour interval. By contrast, a constant intravenous infusion of heparin has practical disadvantages, since it requires keeping the patient immobilized, without the use of one arm, and necessitates purchase of costly infusion equipment. Nevertheless, in treatment of certain clinical states, this route of administration may be preferable.

The subcutaneous route is generally reserved for nonacute clinical situations, such as the prophylaxis of postoperative venous thromboembolism or the long-term administration (at times, self-administration) of heparin. It requires a concentrated solution (10,000–20,000 u/ml) which is injected vertically with a 26

gauge needle into the subcutaneous tissue over the iliac crest or lower abdomen. The needle should be wiped clean of heparin prior to injection in order to minimize hematoma formation.

Laboratory Control

When heparin dosage is low, as in prophylaxis, or when dosage is high, as in the initial treatment of pulmonary embolism, no laboratory control is indicated. In all other situations, some laboratory control of therapy is useful to ensure that sufficient heparin is being given and to provide a guide for modifications in the dosage as heparin requirements change. Dose requirements are usually higher in the early phases of treatment.

1. *Whole Blood Clotting Time.* The standard method described by Lee and White [22] has undergone several modifications [23]. Uncoated glass test tubes are used and prolongation of the normal clotting time by 1½–2½ times is generally considered adequate therapy. The method is reliable but has the disadvantage that is must be performed at the bedside immediately after the blood is collected.

2. *Activated Partial Thromboplastin Time (PTT).* The only advantage of this method over the above is that it can be performed by the hospital laboratory on anticoagulated blood. The same therapeutic range is used (1½–2¼ × normal PTT). It is reliable providing the following principles are observed: (1) The blood should be collected into citrate and not oxalate [24]. (2) A clean venipuncture must be obtained in order to avoid specious prolongation of the PTT [25]. (3) A reagent system should be used that gives a straight-line response to increasing concentrations of heparin. Not all of the commerically available products have this characteristic.

3. *Recalcification Time.* The recalcification time of activated blood collected into citrate may be used in place of the PTT [26].

4. *Thrombin Time.* This test is not as reliable a measure of heparin effect [27] and probably should not be used for this purpose.

In summary, until methodology and reagents become standardized, it is up to each laboratory to establish that its own method accurately reflects heparin effect. This can be readily accomplished *in vitro* by plotting the test results against a range of heparin concentrations added to a reference plasma.

Side Effects

1. *Hemorrhage.* Although laboratory monitoring of heparin therapy provides a reliable index of antithrombotic effect, it is of less value in predicting bleeding [28]. A clotting time of infinity, such as occurs after an initial large bolus of heparin, is usually well tolerated for short periods of time. The duration of heparin therapy may be as important as excessive dosage in the cause of bleeding.

Spontaneous bleeding with heparin is relatively rare, and most hemorrhagic complications arise as a result of unsuspected lesions, invasive procedures or errors in management. The following precautions should be observed:

(1) Heparin in the standard therapeutic dosage is dangerous in the immediate

postoperative period, the duration of the risk period depending on the type of surgery.

(2) Certain antiplatelet drugs, such as aspirin, phenylbutazone or indomethacin, are contraindicated during heparin therapy. The effect of aspirin is prolonged and its ingestion within 48 hours of initiating therapy warrants some modification of heparin dosage, providing the clinical circumstances permit; e.g., major pulmonary thromboembolism requires a large dose.

(3) Patients over 60, especially women, have a higher risk of heparin-induced bleeding [29], and in these patients some modification of dosage as well as duration of heparin therapy is indicated.

(4) Patients with liver disease or renal failure clear heparin less rapidly and, therefore, have reduced dose requirements.

(5) All intramuscular injections must be avoided in patients receiving heparin.

The half-life of heparin is short and, depending on the dose, normal clotting will be restored within 3–6 hours after the last intravenous administration. For this reason, antidotes are almost never necessary. Among these, however, protamine remains the drug of choice. It is given slowly in a dilute solution at a dose equivalent in milligrams to the milligrams of heparin estimated to be present in the blood.

2. *Thrombocytopenia.* Heparin appears to cause some aggregation of platelets both *in vitro* [30,31] and *in vivo* [32]. This effect is modest and probably not of clinical significance, and may be dose related [33,34]. However, on rare occasions an extreme heparin-induced thrombocytopenia is encountered which requires discontinuation of the drug [35]. Two well documented examples of this have been personally encountered [36]. Paradoxic arterial embolization which has been reported to occur in patients receiving heparin [37,38] may be related to this effect of heparin on platelet aggregation.

3. *Osteoporosis.* The development of osteoporosis has been established but appears to occur only when heparin is given for periods of six months or longer at doses of at least 10,000 units daily [39].

Use of Heparin in Specific Clinical Conditions (Table 1)

1. *Acute Pulmonary Thromboembolism*

(a) Efficacy: Since the time when heparin therapy became possible, numerous reports of its efficacy in venous thromboembolism have appeared. A dramatic reduction in deaths due to pulmonary embolism was first recorded more than 35 years ago [40]. Jorpes concluded in 1947 that the results of heparin treatment were "as striking as any hitherto reported following the introduction of a specific therapy in medicine" [41]. Bauer reported no deaths due to pulmonary embolism out of 59 patients with the disease treated with heparin [42]. This impressive but uncontrolled clinical experience was confirmed by a prospective trial in 1960 by Barritt and Jordan [43]. In this trial, a fourth of the untreated patients died and an additional fourth suffered nonfatal recurrent emboli. There were no deaths from pulmonary emboli in the treated patients (heparin followed by oral anticoagulants). In a review by Thomas, the reported mortality from pulmonary embolism after anticoagulant treatment was found to range from 0 to 4% [44].

TABLE 1. Dosage Regimens for Administration of Anticoagulants

HEPARIN
Acute Pulmonary Embolism:
10,000–15,000 units I.V. q. 4 hours for 8–24 hours, then dose adjusted to keep clotting test at 1½–2½ X normal for at least 5 days, then for another 2–3 days while oral anticoagulation is begun.
Deep Vein Thrombosis:
5,000–10,000 units I.V. q. 4 hours to maintain clotting time at 1½–2½ X normal for at least 2–5 days, then overlapped with oral anticoagulation for 2–3 days.
Prevention of Postoperative Thromboembolism:
5,000 units subcutaneously 2 hours before surgery, and every 8–12 hours thereafter until fully ambulatory.
Arterial Embolization:
Initial dose of 5,000–10,000 units I.V., then q. 4 hours to maintain clotting time at 1½–2½ X normal. (If embolus to brain, delay heparin for at least 48 hours.)
WARFARIN
All indications (see text): 10–15 mgs/day X 2–3 days, then sufficient dose to maintain prothrombin time at 1½–2½ X control. (Postoperative patients, elderly patients, patients with heart failure, and certain others require much smaller doses—see text.)

(b) Dosage: A number of authors have emphasized the importance of a high dosage regimen (10,000–15,000 units every 4 hours) in the initial treatment of pulmonary embolism [41–46]. High dose heparin therapy has been associated with the best results published. Clinical experience suggests that an initial bolus of 10,000–15,000 units of heparin (the precise dose depending on the condition, age and weight of the patient) should be given promptly when embolism is suspected and not delayed by time-consuming diagnostic tests. Experimental studies have shown that airway constriction and pulmonary vasoconstriction which accompany thromboembolism in animals [20,47,48] and probably in man [47,49–52] are inhibited by a large dose of heparin probably by interferring with thrombin-platelet interaction [19,20,53]. Smaller doses do not have this effect [20]. In major embolism, this dose should be repeated every 4 hours for at least 12–24 hours [45,46]. If the patient's clinical state is not acute, the dose can be reduced, using an appropriate clotting test as a guide to achieve a value approximately 1½–2½ times the *normal* (*not* the patient's control value which may be shortened) after 1 or 2 large doses. Prior to tapering heparin dosage, laboratory testing is valueless, since the clotting time is apt to be markedly prolonged.

(c) Route of Administration: There is general agreement that heparin should be given intravenously, but controversy exists as to whether this should be by constant infusion or intermittent injection. The latter has substantial practical advantages (see above), so that advocates of constant infusion therapy must prove that it is either more efficacious or safer. Until this evidence has been presented, the intermittent, intravenous injection of heparin is recommended. An initial large bolus of heparin should be given in any event.

(d) Duration: The duration of heparin therapy can be tailored to some extent

to the clinical condition of the patient. In general, it is given for at least 5 days prior to initiating treatment with oral anticoagulants. A period of overlap is then required for at least 2–3 days after a therapeutic level of anticoagulation is achieved with the coumarin drug, bearing in mind that the sensitivity to heparin may be somewhat increased during this time. Heparin is then discontinued, usually gradually (1,000 units every 4 hours), though the presence of a true "rebound" effect after abrupt termination of therapy has not been established.

Based on empirical observations, oral anticoagulant therapy should be maintained for around 3–6 months, the longer period being reserved for idiopathic thromboembolism. If thromboembolism follows a specific precipitating event, such as surgery, obstetric delivery, estrogen administration, etc., 2–3 months is usually adequate.

(e) "Heparin Failures": Evidence of recurrent embolization after initiation of heparin therapy is usually interpreted to mean that heparin has failed to control the thrombotic process and that venous interruption is mandatory. This interpretation of such an event should be carefully considered since it may well be incorrect. Providing that therapeutic prolongation of clotting has been achieved, there is substantial experimental [54–56] as well as clinical [43–45,57] evidence that clot propagation or new thrombus formation will not occur. Recurrent embolization under these circumstances is apt to be due to dislodgement of an already present venous thrombus or fragmentation of a hilar embolus, resulting in embolization to more peripheral pulmonary vessels. A thromboembolus may also be temporarily trapped in the chordae of the right heart before proceeding to the lungs. These causes of recurrent embolization are apt to be confined to the initial 1–5 days of treatment. They do not represent a "heparin failure" in the usual sense of that term, and it has not been established that they constitute an indication for surgical intervention. In any event, vein ligation or plication should not be done without venographic demonstration of a threatening thrombus.

2. *Deep Vein Thrombosis.* The objectives of therapy are to prevent propagation and embolization and to minimize the development of venous incompetence. These goals can be achieved by maintaining a level of anticoagulation in the usual therapeutic range [57], though some venous insufficiency is apt to persist. Clinical experience and experimental studies have indicated that initial dosage need not be as great as for pulmonary embolism. This has been attributed to the fact that thrombin-fibrinogen interaction is effectively inhibited at lower concentrations of heparin (2× normal clotting time) than is thrombin-platelet interaction [20,58]. Usually 5,000–10,000 units are given intravenously at 4-hour intervals, the dosage being regulated according to the results of daily laboratory tests. The duration of heparin therapy depends on the extent and severity of disease. Oral anticoagulants may be started within 2–5 days and then maintained for about 3–6 months according to the criteria described above.

3. *Thromboembolism during Pregnancy.* The initial treatment is the same. However, subsequent therapy is complicated by the fact that all oral anticoagulants cross the placenta and have been known to induce fetal hemorrhage. Heparin, because of its molecular size does not cross the placenta. Although no ideal method for long-term anticoagulation during pregnancy exists, subcutaneous heparin is probably the method of choice. It is practical since the drug can be self-

administered by injection over the iliac crest or the lower abdominal wall. A 12-hourly interval is usually adequate. Heparin should be promptly discontinued at the first sign that labor has started.

4. *Prevention of Postoperative Thromboembolism.* It was first observed by DeTakets that much less heparin is required to prevent thrombosis than to treat it [59]. Sharnoff subsequently reported that the administration of small amounts of heparin subcutaneously resulted in a reduction of thromboembolism, providing the therapy was started prior to surgery [60]. The development of the ^{125}I-labeled fibrinogen technic for the identification of deep vein thrombosis has permitted rather precise validation of this initial experience. The prospective, controlled trials of Kakkar et al. [61,62] Williams [63], Nicolaides et al. [64] and Gallus et al. [65] have all demonstrated a highly significant reduction in ^{125}I-fibrinogen detectable thrombosis after major surgery. Lahnborg et al. [66] also demonstrated a significant reduction in postoperative embolism, as demonstrated by photoscanning. In patients undergoing hip replacement surgery, a controversy regarding the efficacy of subcutaneous heparin remains [66,67].

The mechanism of action of small doses of heparin has been discussed previously in this chapter and is thought to be related to its potentiation of the naturally occuring inhibitor in plasma variously known as heparin cofactor, antithrombin III or anti-activated factor X.

The usually recommended dosage consists of 5,000 units of heparin administered subcutaneously 2 hours before surgery and every 8 or 12 hours thereafter. Heparin therapy should probably be maintained until the patient is fully ambulatory and is ready for discharge from hospital. Laboratory monitoring of therapy is not considered necessary.

5. *Disseminated Intravascular Coagulation (DIC).* DIC represents a potentially lethal complication of many disease processes, including infections, heat stroke, severe trauma, abruptio placentae, malignancies, cirrhosis, etc. There is general agreement that successful treatment is predicated on reversing the underlying disease with appropriate measures. If this is done promptly, heparin therapy may not be necessary. However, often attention is not drawn to the presence of DIC until extensive intravascular fibrin deposition has already taken place. This may lead to respiratory or renal failure as well as to a hemorrhagic diathesis due to a consumption of clotting constituents and to vascular injury secondary to fibrin deposits. Since intravascular thrombin elaboration is generally considered to be the cardinal feature of DIC, there is a compelling logic to administer heparin and arrest the process before irreversible organ damage has occurred. This should be started before a hemorrhagic diathesis develops or irreversible organ damage due to fibrin deposition has occurred.

Unfortunately, the literature contains no controlled clinical trials of heparin therapy in DIC and there is a wide range of opinions as to when, whether, how and how much heparin should be given. No consensus exists and the therapeutic experience to date has been largely disappointing. However, if our current concept regarding the pathophysiology of DIC is correct, it may be argued that the therapeutic failures of heparin are attributable to giving the drug too late and perhaps in the wrong dosage. It is necessary to use a therapeutic approach and

guidelines that are different from those used in the heparin treatment of thromboembolism. The following recommendations represent a personal viewpoint:

(a) Dosage and Route of Administration: The usual "therapeutic" dose of heparin tends to cause major hemorrhage in DIC, not only because of the consumption of clotting factors and platelets but probably also because of intimal damage secondary to intravascular fibrin deposition. This has resulted in an understandable reluctance to use the drug for this indication except as a last resort. However, small doses are often effective as well as safer. Heparin is given at a dose of 5–10 units/kg/hr by constant infusion. A dose of 5 units/kg/hr was recently recommended by Mulcare et al. [68]. If objective evidence of persistent thrombin elaboration or consumption is found, the dose should be increased gradually. After heparin has been started, fibrinogen and platelets may be replaced if necessary.

(b) Laboratory Control of Heparin Therapy: The objective of therapy in DIC is to prevent intravascular thrombin elaboration. Dosage should be adjusted according to laboratory evidence that this has been accomplished and *not* on any arbitrary prolongation of the clotting time or PTT. When thrombin acts on fibrinogen, it forms fibrin monomer (Fig. 1) which is found as a soluble complex in blood and is readily detected by protamine sulfate paracoagulation [69,70] or ethanol gelation [71]. These tests are simple, and when performed together provide a means for distinguishing fibrin monomer from early fibrin degradation products [72]. The serial dilution protamine sulfate test has recently been shown to be highly correlated with the more elaborate chromatographic method for measuring fibrin monomer complexes [73]. The clearance of fibrin monomer is sufficiently rapid so that if heparin dosage is adequate, little or no fibrin monomer will be detectable within 8–12 hours. This provides proof that thrombin elaboration has been inhibited and may be accomplished with a dose of heparin that causes little or no prolongation of the clotting time.

Secondly, fibrin degradation products should be determined quantitatively [74,75]. High levels are invariably present in DIC, and their concentration in the blood tends to fall rapidly (within 12–24 hours) after initiation of adequate heparin therapy. This provides a second laboratory guide to heparin dosage.

Finally, the effect of therapy may be determined by measurement of specific blood constituents whose further consumption is prevented by adequate doses of heparin. These constituents include fibrinogen, whose concentration usually increases after 24 hours of adequate therapy and platelets which increase at a somewhat slower rate.

In summary, it is our present view that DIC should be treated with a constant infusion of low doses of heparin which is not monitored by clotting time or PTT but rather by specific laboratory evidence that thrombin elaboration and factor consumption have been inhibited.

6. *Arterial Embolization.* Prompt intravenous administration of heparin is indicated in the medical treatment of arterial thromboembolism in order to prevent propagation of the clot and to minimize the likelihood of recurrence. In the event of a brain embolus, heparin should be delayed for at least 48 hours; otherwise there is a high risk of local bleeding into ischemic brain tissue. An initial dose of

5,000–10,000 units is usually given, with subsequent adjustment of dosage according to the results of laboratory tests. Unless the source of the thromboembolus is removed, long-term anticoagulation with oral anticoagulants is usually indicated.

7. *Acute Myocardial Infarction.* Although heparin therapy of acute myocardial infarction is still used in some institutions, no convincing evidence of its efficacy has been published [76]. Under these circumstances, its continued use in this condition should be discouraged.

ORAL ANTICOAGULANTS

Campbell and Link isolated the hemorrhagic factor in the spoiled sweet clover disease of cattle more than 30 years ago [77]. Since that time, the antithrombotic property of this "hemorrhagic agent" has been well established experimentally and clinically. Although certain clinical indications for oral anticoagulants remain controversial, dosage and control of therapy are more standardized than for heparin.

Oral anticoagulants can be divided into four groups on the basis of chemical structure. The anticlotting properties of all of them are alike, but there are differences in absorption, excretion, duration of action and toxicity. In this country, the mono-coumarols (warfarin) are used almost exclusively. The following discussion will, therefore, be confined to warfarin.

Pharmacologic Properties

Warfarin is rapidly and completely absorbed from the intestinal tract. Almost all of the drug seems to be bound to plasma proteins, primarily albumin. The onset of action occurs 8–12 hours after administration, reaching a maximum effect in about 36 hours. The duration of action is approximately 3 days.

The anticoagulant action of warfarin is indirect, being dependent on its antagonism to vitamin K. The precise mode of action has not been firmly established, but it does not appear to be a simple competitive inhibition between warfarin and vitamin K [78,79]. As a result of this interaction, the activity of the four vitamin K-dependent clotting factors, II (prothrombin), VII, IX and X, is reduced. Although a direct relationship between anticoagulant effect and plasma concentration of warfarin has been demonstrated [80], dose requirements vary significantly among individuals and cannot be reliably estimated on a milligram per kilogram of body weight basis.

The rate of decrease in the activity of each of the four clotting factors is considered to be a function of their half-life. Following the administration of warfarin, Factor VII activity is the first to be effected followed sequentially by Factor IX, X and II. After the first week of therapy, the degree of depression in the clotting activities of all four factors is comparable. Therefore, Quick's one stage plasma prothrombin time [81] may be used as a reliable measure of warfarin effect, even though it is insensitive to factor IX.

Both the intrinsic and extrinsic clotting systems are effected by warfarin (Fig. 1). Factors IX and X are involved in the elaboration of blood thromboplastin,

whereas factors VII and X are required for the conversion by tissue thromboplastin of prothrombin (II) to thrombin. All four factors are generally considered of equal importance in hemostasis. The likelihood of bleeding may be reliably assessed by an appropriate coagulation test, e.g., prothrombin time (PT). Spontaneous bleeding is rare if the PT is 2 times the control value or less. However, the PT at the outset of warfarin therapy may be a less reliable measure of antithrombotic effect. For example, in experimental animals, inhibition of venous stasis thrombi was not found until one week after the initiation of coumarin therapy, several days after a "therapeutic range" of PT prolongation had been achieved. [82]. A similar delay in the onset of antithrombotic effect was found when thrombosis was induced by vascular injury [83]. It is believed that the antithrombotic effect of warfarin is related to the depression of factors IX and X activity. Therefore, during the induction of warfarin therapy, at which time factor VII is depressed primarily, PT prolongation and hemostatic impairment may not be accompanied by significant protection against thrombosis.

Warfarin therapy has been reported to have some effect on certain measures of platelet function, though it has not been shown that these changes are clinically significant. Inhibition of platelet aggregation has been demonstrated in several *in vitro* test systems [84,85]. A therapeutic range of anticoagulation has been reported to be associated with prolongation of platelet survival and decreased adhesiveness [86]. On the other hand, inadequate doses of warfarin may have the opposite effect [87]. It is unlikely that warfarin therapy causes any significant suppression of platelet-induced thrombosis.

Warfarin crosses the placenta and appears to reach a concentration in the fetus comparable to that in the mother. It also appears in the breast milk, where it occasionally is found in sufficient concentration to cause some anticoagulant effect in the nursing infant [88].

Factors Influencing Dose Response

The anticoagulant effect of a standard dose of warfarin is under the influence of a number of variables. An enhanced effect requiring smaller doses of warfarin occurs in the following conditions: after surgery, in the aged, congestive heart failure, liver disease, inadequate intake of vitamin K and the suppression of vitamin K-synthesizing bacteria by antibiotics. It is not unusual for dose requirements to be 1–2 mg of warfarin daily in postoperative patients or older individuals. Women tend to require somewhat smaller doses than men. On the other hand, the presence of hyperlipidemia [89] or hyperuricemia [90] may be associated with resistance to warfarin, and patients with these conditions may require larger than average doses. Hereditary resistance to oral anticoagulants has also been reported [91].

Laboratory Control

Regular blood tests by a reliable laboratory are necessary in order to ensure maintenance of a safe and effective level of anticoagulation. The PT using Quick's one-stage technic [81] is conventionally used to monitor therapy. Al-

though a few other methods have been advocated, none has been shown to have any significant advantages. The test measures clotting via the extrinsic system (Fig. 1) and, therefore, is sensitive to Factors VII, X, V, II and fibrinogen. A commercial preparation of thromboplastin plus calcium is added to citrated plasma, and the time required for fibrin formation to occur is measured ("prothrombin time"). Since fibrin is the endpoint, the test will be prolonged by heparin (>0.75 u/ml).

The PT of the patient's plasma is compared with that of normal, control plasma. The latter should give a time of 11–14 seconds. A longer control time indicates that the thromboplastin used was of insufficient potency to produce reliable results. The final result should be recorded as the patient's versus the control PT. The reporting of results as "per cent prothrombin activity" should be discouraged. The latter is based on a dilution curve whose shape is significantly influenced by the diluent, which varies among different laboratories.

The problem of standardization of the laboratory control of anticoagulant therapy has been taken up by the British Committee for Standardization in Hematology [92] and a similar effort is underway in this country [93]. The adoption of a uniform thromboplastin and perhaps a standard reference plasma would eliminate much of the variability in the intensity of anticoagulation practiced at different centers. It is generally agreed that some of the discrepancies in the results observed in the numerous clinical trials of anticoagulant therapy may be due to variations in the laboratory control of therapy.

Laboratory testing must be done at regular intervals. A normal PT should be established before starting warfarin. Then warfarin may be given for two consecutive days and a test performed before the third dose is prescribed. Thereafter, tests should be performed daily until a therapeutic range is achieved and the maintenance dose requirements can be estimated. In patients on long-term therapy, it is unwise to allow more than 2–3 weeks to elapse between tests, since dose requirements are subject to a number of unpredictable variables, e.g., emotional factors, dietary changes, including alcohol, and climate (moving from one to another).

Therapeutic Range, Administration and Dosage

The optimum therapeutic level may be defined as the minimum depression of the prothrombin complex required to give an antithrombotic effect. This level is apt to vary somewhat with the clinical condition being treated. It is generally defined as being within range of PT prolongation 1½–2½ times the control value. Spontaneous bleeding is rare when the PT is 2 times control or less. Careful diagnostic studies to uncover an occult bleeding site are indicated in the event of bleeding at this level of anticoagulation. The incidence of spontaneous bleeding rises precipitously when the PT exceeds 2½ times the control value.

The antithrombotic effect of oral anticoagulants with respect to venous thromboembolism was established by the careful studies of Sevitt and Gallagher [94] and Sevitt and Innes [95]. They showed that both clinical as well as autopsy-proven deep vein thrombosis in patients with hip fractures was prevented if the PT was maintained above 2 times the control value.

A loading dose for the induction of therapy is unnecessary and increases the

risk of bleeding. O'Reilly and Aggeler demonstrated several years ago that the rate of depression of factors II, IX and X is not accelerated by a loading dose [96]. Instead, 10–15 milligrams of warfarin are given on a daily basis (less in postoperative or aged patients) until a therapeutic range of PT prolongation is reached. In adjusting dosage, it should be recalled that peak effect of the drug occurs at about 36 hours.

Drug Interaction with Warfarin

Numerous reports have appeared in the literature on the many drugs which potentiate or inhibit the anticoagulant effect of warfarin. A number of different mechanisms are involved which are beyond the scope of this article to describe. The literature on this subject was recently reviewed by Koch-Weser and Sellers [97] and a list of the drugs implicated to date is given (Table 2). Since the number of drugs appears to be growing, it is a wise policy to instruct patients on anticoagulants not to add or subtract any drug without notifying their physician. Any such changes should be accompanied by more frequent laboratory testing of anticoagulant effect.

Drug Toxicity

1. *Hemorrhage.* Bleeding is by far the most common side effect. The genitourinary tract is the most common site, and microscopic hematuria may occur even

TABLE 2. Drug Interactions with Warfarin

Drugs Contraindicated in Patients on Anticoagulants

Acetyl Salicylic Acid
Phenylbutazone
Oxyphenbutazone
Indomethecin

Drugs Which May Potentiate Effect	*Drugs Which May Inhibit Effect*
Anabolic Steriods	Barbiturates
Broad Spectrum Antibiotics	Corticosteroids
Chloralhydrate*	Cholestyramine
Chloramphenicol	Ethchlorvynol (Placidyl)
Clofibrate (Atromid)	Glutethimide (Doriden)
Disulfiram (Antabuse)	Griseofulvin
Ethacrynic Acid	Haloperidol (Haldol)
Glucagon	Meprobamate
Mefenamic Acid (Ponstel)	Oral Contraceptives
Methylphenidate (Ritalin)	Rifampin
Quinidine	
Quinine	
Vitamin E	

Drugs Whose Action May Be Enhanced by Warfarin

Diphenylhydantion
?Chlorpropamide (Diabenese)
?Tolbutamide (Orinase)

*Clinically insignificant (Ann. Int. Med. 81:341, 1974).

within the therapeutic range of PT prolongation. Otherwise, bleeding due to warfarin-induced impairment of hemostasis is unusual in normotensive patients whose PT is below twice the control value. The presence of occult disease should be suspected if bleeding occurs within the therapeutic range.

Many of the bleeding episodes which occur in patients on anticoagulants are avoidable. They are often related to insufficient care or knowledge on the part of the physician, improper performance or reporting of the laboratory test, or inadequate education of the patient. Every patient must be carefully instructed on the importance of taking the precise dose prescribed at regular intervals, the importance of regular blood tests, the need to avoid aspirin-containing compounds and certain other drugs (Table 2). A well-informed patient is an essential feature of responsible anticoagulant management.

2. *Rebound Thrombosis.* Some studies have shown an increased incidence of thrombotic episodes following discontinuation of long-term anticoagulant therapy [98], especially if anticoagulants are stopped because of hemorrhage [99]. Others have failed to demonstrate this phenomenon [100]. No firm conclusions are possible on the basis of published studies which relate primarily to long-term therapy. Where possible, it is customary to discontinue warfarin gradually (over a period of a few weeks), though the necessity for doing this has not been established.

3. *Idiosyncratic Reactions.* Untoward effects not related to prothrombin complex depression are very rare. Feder and Auerbach reported 6 cases of "purple toes" due to bishydroxycoumarin (Dicumarol)-induced vascular lesions occurring 3–8 weeks after starting the drug [101]. This complication is reversible.

Bishydroxycoumarin [102] and warfarin [103] have been reported to induce skin necrosis due to a drug-induced vasculitis associated with microthrombi.

Management of Bleeding

Vitamin K_1 is the specific antidote to warfarin, and after parenteral administration some restoration of coagulation activity occurs in about 6 hours; a full effect may require 1 or 2 days. Furthermore, its administration may render a patient refractory to warfarin therapy for 1 or 2 weeks.

For these reasons, bleeding is generally treated with the administration of 250–500 milliliters of bank plasma. This results in immediate reversal of the anticoagulant effect by restoring adequate levels of factors II, VII, IX and X. Since these factors are stable, bank plasma may be used.

Most cases of minor bleeding do not require any special treatment other than temporarily stopping the anticoagulant.

Conversion of Anticoagulant Therapy from Heparin to Warfarin

Warfarin is often used as an extension of heparin treatment. As already indicated, a period of overlap of the two drugs is necessary since the antithrombotic effect of warfarin may be delayed. At the outset, warfarin is given at a dose of 10–15 milligrams daily for 2–3 days and then adjusted according to the results of the PT. Since at a certain plasma level of heparin (>0.75 u/ml) the PT will be

prolonged, blood for testing should be drawn at a time just prior to the next dose of heparin. At this point, heparin plasma levels will be at their lowest point. Alternatively, when heparin is given on a 4-hourly schedule, a dose may be delayed an extra 1 or 2 hours to ensure that a reliable PT reflecting warfarin and not heparin effect is obtained.

After prolongation of the PT beyond 1½ times the control value, the patient's sensitivity to heparin may increase. It is usually wise to reduce the dose of heparin slightly at this, i.e., by about 1,000 units. Heparin may then be continued for another 2–3 days until an antithrombotic effect of warfarin is likely.

Specific Clinical Indications (Table 1)

1. *Acute pulmonary embolism* (see section on Heparin)

2. *Deep Vein Thrombosis.* Although warfarin is usually used to follow up heparin therapy (see section on Heparin), in certain subacute clinical situations, especially when the thrombotic process does not extend above the knee, warfarin may be used as primary therapy. With this approach, effective therapy will be delayed, but it has the advantage of not requiring hospitalization of the patient.

3. *Arterial Embolization*

(a) Mitral Valve Disease: In the presence of atrial fibrillation, the incidence of crippling or fatal arterial embolization is high [104,105]. Embolism often occurs in patients whose rheumatic heart disease is otherwise well compensated. The effectiveness of anticoagulants in preventing arterial embolization from this site is well established [105,106]. In light of these facts, long-term anticoagulant therapy is indicated in all patients with mitral valve disease and atrial fibrillation. Therapy should be initiated before an embolic event has taken place. More than half the emboli from this site go to the brain.

(b) Prosthetic Heart Valves: At the present time, warfarin is recommended in patients with prosthetic aortic or mitral valves. The manufacture of a more thrombosis-resistant material or the development of effective antiplatelet therapy may change this indication in the forseeable future.

(c) Mural Thrombosis: Arterial emboli arising in patients with evidence of myocardial infarction should be given anticoagulant therapy. There are no firm guidelines regarding the duration of such therapy, but unless a contraindication arises, anticoagulants should probably be maintained indefinitely.

4. *Transient Ischemic Attacks (TIA's).* The studies of Millikan and associates have provided convincing data that anticoagulants reduce the incidence of strokes in patients believed to be suffering from TIA's [107,108]. There is considerable current interest in the use of antiplatelet drugs in the treatment of this condition, but at the present time, long-term anticoagulation with warfarin remains the medical treatment of choice.

5. *Acute Myocardial Infarction.* After 25 years of experience and innumerable studies, the use of oral anticoagulants, short or long-term, in this disease remains controversial. Although the published findings have often been contradictory, they may be fairly summarized as indicating a lack of proof that anticoagulants reduce mortality, reinfarction or strokes in patients with acute myocardial infarction [109,110]. It is generally agreed that anticoagulants have no effect on the

thrombotic events which may occur within the coronary vessels and do not influence the electrical or mechanical events which are the major causes of death from this disease.

However, virtually all studies have shown that anticoagulants reduce the incidence of thromboembolic complications. The fact that their beneficial effect has not been reflected in a significant reduction in mortality is probably due to an insufficient size of the populations studied, as recently pointed out by Wessler et al. [111]. There is, therefore, evidence that anticoagulants will benefit selected patients—namely, those at risk of either venous thromboembolism or mural thrombosis.

The selection of this small group of patients by present technics is difficult. The current practice of early ambulation and discharge of patients with uncomplicated disease tends to exclude them from consideration. Among the remainder, the decision to use anticoagulants should probably be made on an individual basis. It is difficult to offer anything more concrete in the way of a recommendation.

6. *Cancer.* Anticoagulants have been shown to reduce the growth and spread of malignancies in experimental animals [112]. The literature on this subject was recently reviewed by Millar and Ketcham [113]. Anticoagulants may interfere with malignant cell lodgement, a process which is believed to require fibrin formation [114]. Improved clinical survival in warfarin-treated patients suffering from a variety of malignancies has been reported [115]. These animal studies and preliminary clinical findings appear to be sufficiently promising to warrant additional clinical trials.

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