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Clinical Considerations for the Anesthesiologist Whose Patient is on Anticoagulant Therapy

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BOTH HEPARIN [1] and coumarin [2] ‡ have been in use for more than 30 years. As many as a million patients may receive anticoagulants annually, and any practicing anesthetist is likely to encounter such patients.[3] This paper reviews the pharmacology necessary for safe, reasoned anesthetic management of these patients.

Indications for Anticoagulant Therapy (Table 1)

Anticoagulant therapy for the treatment of venous disease is based on much convincing data. Barrett and Jordon, in a well-controlled prospective study in 1960, clearly showed that anticoagulant therapy reduced mortality from pulmonary embolus.[5] Additionally, in those patients predisposed to thromboembolism (table 2), prophylactic administration of anticoagulants is justified [6] unless clear-cut contraindications exist (table 3).

Anticoagulant therapy for atherosclerotic coronary-artery disease is based on less solid data. There is a remarkable number of well-controlled studies yielding equivocal results. The first controlled prospective study of anticoagulants for coronary thrombosis, published in 1948, reported a striking improvement in prognosis when anticoagulants were used. The study recommended that "anticoagulant therapy should be used in all cases of coronary thrombosis unless a definite contraindication exists." [7] Unfortunately, subsequent studies of similar quality and magnitude have not confirmed these original findings.[8] The most recent large study of anticoagulants in coronary-artery disease showed that treatment lowered long-term mortality in men less than 55 years old only, and even in this report the authors called for still further clinical trials.[9] Studies in coronary care units have clearly shown that the major causes of death in myocardial infarction are arrhythmia and shock, and these are not influenced by anitcoagulants.[10]

Patients in congestive heart failure do benefit from anticoagulant therapy, largely because such therapy reduces their propensity towards thromboembolic phenomena. However, digitalis, diuretics, and early ambulation are more important, since they correct the sluggish circulation that is in underlying problem. Lyon and De Graff point out that since the advent of effective oral diuretics, severe chronic congestive heart failure has been rare. Nevertheless, when congestive cardiac failure with edema does occur, especially when strict bed rest is prescribed, anticoagulant therapy is logical.[11]

It is generally agreed that the morbidity of acute or chronic cerebrovascular disease is not improved by anticoagulation and that such

TABLE 1. Indications for Anticoagulant Therapy*

1. Phlebitis, phlebothrombosis and pulmonary embolism[5, 6]
2. Atherosclerotic heart disease[7, 8, 9]
3. Congestive cardiac failure[11]
4. Cerebrovascular disease[12]
5. Rheumatic heart disease[13, 14]
6. Prosthetic cardiac valves[15–18]
7. Disseminated intravascular coagulation[19]

* Modified from Borden CW.[10] (Numbers refer to the references in the present paper.

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‡ Coumarin will be used as the family name for the related anticoagulants taken orally and similar in structure and function to Link's original toxic compound.[4]

TABLE 2. Conditions Predisposing to Thromboembolism

1. Atherosclerosis of coronary, cerebral, aortic or peripheral vessels
2. Malignancy, especially pancreatic, pulmonary or prostatic
3. Sepsis
4. Pregnancy and the puerperium
5. Trauma and burns
6. Obesity
7. Dehydration
8. Polycythemia vera or hemoglobinopathy
9. Advanced age
10. History of prior thromboembolic phenomenon
11. Immobilization or bed rest

TABLE 3. Relative Contraindications to Anticoagulant Therapy

1. Bleeding diathesis (except for consumption coagulopathies)
2. Ulcerative lesions of the gastrointestinal, genitourinary (especially prostate), or respiratory tract
3. Recent central nervous system or eye surgery
4. Severe hypertension
5. Recent cerebral hemorrhage
6. Subacute bacterial endocarditis or pericarditis
7. Uncooperative patient or inadequate laboratory control
8. Pregnancy, first trimester and near term (for coumarin only)[17]

anticoagulation may, indeed, be harmful.[10] The value of anticoagulation for transient ischemic attacks remains controversial.[12]

The patient with mitral-valve disease plus atrial fibrillation or a history of systemic emboli may benefit from anticoagulants.[13] The relatively low risk of systemic emboli in elective cardioversion may be even further reduced by the use of anticoagulants.[14] Long-term use of anticoagulants in patients with prosthetic heart valves is believed to reduce the incidence of systemic emboli.[15-16] The combination with dipyridamole, which inhibits platelet adhesiveness, has been reported to be more effective than coumarin alone.[17] However, improvement in prosthetic valve design has reduced thromboembolism so much that some centers do not routinely prescribe anticoagulants.[18]

A relatively new indication for heparin therapy is disseminated intravascular coagulation. Therapy is intended to prevent further intravascular clotting and allow the liver to replenish circulating coagulation factors.[19]

Available Anticoagulants

The "ideal anticoagulant," which does not exist, has been described [20] (table 4). However, virtually all the ideal characteristics are present in one or the other of the anticoagulants currently available, heparin and coumarin.

Heparin was discovered in 1916, but it was not used clinically until 1939.[1] Heparin inhibits coagulation at four places: 1) Factor XIa activation of Factor IX; 2) action of Factor IXa; 3) action of thrombin; 4) action of Factor Xa.[21] The discovery that protamine was a heparin antidote was by a most fortuitous accident. Chargaff and Olson attempted to produce a long-acting anticoagulant by combining heparin and protamine in a manner analogous to the combination of protamine and insulin. Of course, they found that the protamine neutralized, rather than prolonged, the heparin effect.[22]

Because of its immediate onset of action and the rapidity with which its effect can be reversed, heparin is the anticoagulant of choice when rapid or highly controllable anticoagulation is necessary. However, heparin must be given intravenously by continuous drip or intermittently every two to eight hours, or subcutaneously every 12 to 24 hours, to remain effective. Wessler and Alexander believe intravenous administration every four to six hours is at least as satisfactory as, if not superior to, any other regimen.[23]

TABLE 4. Characteristics of the Ideal Anticoagulant*

1. Equally effective orally and parenterally
2. Onset of action within one hour
3. Duration of action greater than 24 hours
4. Prompt reversal with administration of a nontoxic antidote
5. No cumulative effect during long-term therapy
6. No toxic side-effects
7. Predictable relation between dose and effect
8. Simple, rapid, inexpensive monitoring test
9. Low cost

* Adapted from Levine WG.[20]

The U.S.P. unit of heparin is the quantity that will prevent 1.0 ml of citrated sheep plasma from clotting for one hour after addition of 0.2 ml of a 1:100 $CaCl_2$ solution; each milligram of heparin must contain between 90 and 110 per cent of the potency on the label (*i.e.*, 1.0 mg heparin contains 90–110 units of heparin). Since there are variations in potency among different heparin preparations, it has been suggested that doses be prescribed in units of anticoagulant activity rather than in milligrams.[23] Nevertheless, many practitioners continue to use miligrams, equating 1.0 mg with 100 U of heparin.

Coumarin is effective either orally or parenterally. However, since the onset of therapeutic effect is delayed for 12 hours, coumarin cannot be used in acute situations. Depending on the preparation, duration of action may be as long as four or five days. While it is well known that coumarin depresses prothrombin formation, it is less well known that Factors VII, IX, and X formation are even more sensitive to coumarin. These four factors together are known as the "prothrombin complex." The effective dose of coumarin varies tenfold among patients because of variations in nutritional state, vitamin K intake, genetic factors, and rate of hepatic synthesis of clotting factors.[6, 24] Oral antibiotics may reduce the available vitamin K by decreasing intestinal bacteria, a major source of vitamin K. Any systemic disease which produces severe hepatic dysfunction may increase sensitivity to coumarin. A most important cause of altered sensitivity to coumarin is the intake of other drugs.[25]

With respect to coumarin, drugs may decrease requirements, as with salicylates, or increase requirements, as with griseofulvin.[26] Both barbiturates and chloral hydrate decrease the plasma half-life of coumarin, but they affect coumarin's anticoagulant properties in opposite ways. A metabolite of chloral hydrate, trichloroacetic acid, displaces coumarin from its binding sites on plasma albumin, making more free drug available and increasing the anticoagulant effect while at the same time causing an increased rate of metabolism and renal excretion. On the other hand, barbiturates induce hepatic microsomal enzymes, resulting in a decreased coumarin half-life and decreased anticoagulant activity.[27] The possibility of drug interaction with coumarin requires frequent checks of the prothrombin time when any additional drug is added to or subtracted from a patient's regimen.

Monitoring Therapeutic Levels of Anticoagulation

Adequate therapy, as demonstrated with proper monitoring of anticoagulant therapy, is most important. Friedli *et al.* showed that the incidence of systemic emboli was significantly less when the prothrombin time was consistently kept in the therapeutic range.[16] Similar reports have been published for venous thromboembolic disease [28] and atherosclerotic coronary-artery disease.[29]

The Lee-White whole-blood coagulation test (WBCT) and the activated partial thromboplastin time (APTT) are commonly used to monitor heparin therapy, and the prothrombin time is commonly used to monitor coumarin therapy. Detailed descriptions of our techniques for performing the WBCT and APTT have appeared in this journal.[30] The importance of rigid adherence to a standard method for performing tests of coagulation cannot be overemphasized if results are to be meaningful. The variation in "normal values" from lab to lab are usually due to slight differences in technique. However, such variation within a given lab must be eliminated.[31]

Our prothrombin time test is performed with equal adherence to a standard method. Nine volumes of blood are mixed with one volume of 0.1-M sodium oxalate solution. One-tenth milliliter of the oxalated plasma and 0.1 ml of human brain thromboplastin are pipetted into a test tube. Then, 0.1 ml of 0.02-M calcium chloride solution is added and the tube tilted rapidly until gel formation occurs. The prothrombin time is the time from addition of calcium chloride to final gel formation.

Figure 1 shows the currently accepted scheme of coagulation. The reagents added for the prothrombin time (tissue thromboplastin) and the APTT (kaolin for surface contact and cephalin for phospholipid) are indicated in boxes. Obviously, the two tests will detect deficiencies only in their portions of the cas-

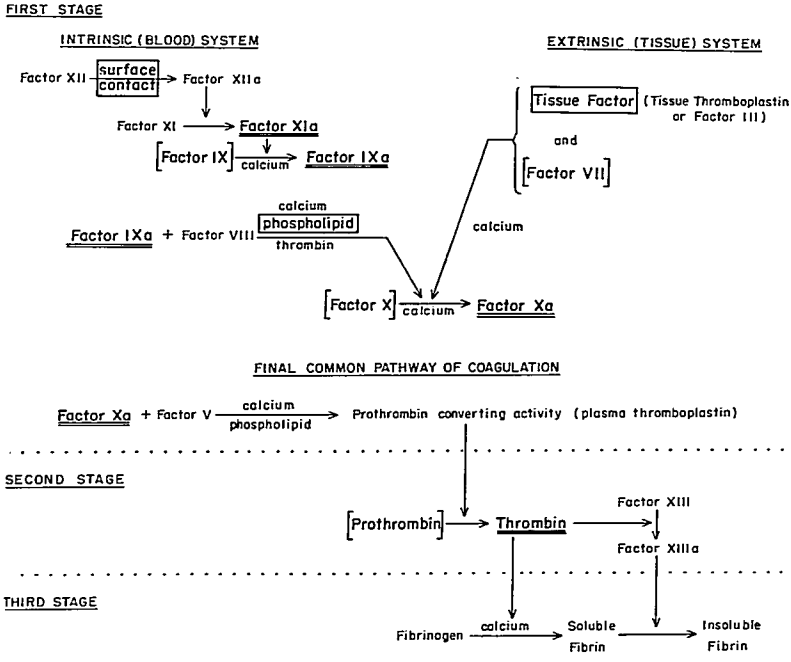

FIG. 1. Detailed scheme for coagulation of blood. Reagents added for activated partial thromboplastin time (kaolin = surface contact and cephalin = phospholipid) and prothrombin time (tissue thromboplastin) are in boxes. Factors whose production is inhibited by coumarin (prothrombin, VII, IX, X) are indicated by brackets, and factors whose action is inhibited by heparin (thrombin, IXa, Xa, XIa) are indicated by double underlining.

cade or the final common pathway of coagulation.

Coumarin affects coagulation factors in the following order of decreasing sensitivity: VII, X, IX, prothrombin. Thus, small doses of coumarin initially produce changes in the prothrombin time, which measures the extrinsic system of coagulation, due to Factor VII depression.

Heparin inhibits coagulation at four places: 1) Factor XIa activation of Factor IX; 2) action of Factor IXa; 3) action of thrombin; 4) action of Factor Xa.[21] Thus, small doses of heparin would initially produce changes in APTT, which measures the intrinsic system of coagulation, due to inhibition of Factor XIa and Factor IXa.

Large doses of coumarin may likewise affect the APTT through Factor IX depression within the intrinsic system or through Factor X or prothrombin depression in the final common pathway of coagulation. Similarly, large doses of heparin inhibit the conversion of both prothrombin to thrombin and fibrinogen to fibrin, and this might be reflected in prolongation of the prothrombin time.

The development of a cheap, rapid test for the quantitation of the anticoagulant effect of

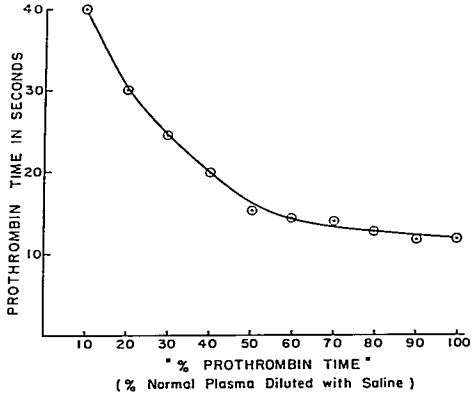

FIG. 2. Prothrombin time (in seconds) versus per cent prothrombin. With values greater than 50 per cent little anticoagulant effect is seen. Below 50 per cent small changes in percentage produce marked changes in prothrombin time.

coumarin was vital to its safety in clinical practice.[2, 32] While this need was met by the Quick prothrombin test, one of the continuing problems of coumarin therapy is the lack of a standard test acceptable to all labs and the fact that a given result obtained by one method is not readily compared with the results of another method.[33] To date there is no evidence that any test is superior to the Quick one-stage prothrombin time test for monitoring patients on coumarin therapy.[6] The loyalty of each proponent to his own test has been a major handicap in the standardization of coumarin therapy on a national basis.[34] Preferably, the prothrombin time of the patient should be reported in seconds along with the time for the control plasma. The object of therapy is to keep the patient's prothrombin time 2.0 to 2.5 times that of the control. There is not a linear relation between "per cent prothrombin time" and anticoagulant activity. Indeed, prothrombin times of more than 65 per cent represent essentially no anticoagulant activity, and times of less than 50 per cent are necessary before any appreciable anticoagulant activity is seen (fig. 2).

The usual aim of heparin therapy is to prolong the WBCT to two to three times normal or the APTT to twice normal in blood taken half an hour prior to the next dose of heparin.[10, 35] The WBCT is one of the oldest and most commonly performed tests of coagulation. Many authorities have been critical of both its sensitivity and its reliability and have, therefore, recommended monitoring heparin therapy with the APTT.[35] Our experience in the operating room, however, suggests that the WBCT, if properly performed, is a most useful and convenient method to monitor heparin therapy and its reversal. We believe criticism of the WBCT arises from improper performance which commonly results from the apparent simplicity of the test. If the many variables affecting WBCT are rigidly controlled (table 5), the test has a precision that compares favorably with that of the APTT.[30] The major advantages of the WBCT are its simplicity and the ready availability of the results in the operating room without the delay required with the APTT. Furthermore, the clot can be directly observed in the operating room for lysis or retraction.

Reversal of Anticoagulants

The advisability of operating on patients who are receiving anticoagulants remains controversial.[36-39] We believe that except for surgery of the eye, central nervous system, or large raw surfaces such as the liver bed, and in the absence of other contraindications, major surgical procedures can safely be carried

out in patients who are receiving anticoagulants.

A potential hazard of anticoagulant reversal is the possibility of a rebound hypercoagulable state, resulting in exacerbation of the original conditions for which anticoagulants were prescribed. Sise *et al.* reported that thromboembolism increased when anticoagulants were stopped abruptly.[40] Other clinicians recommend that the dose be gradually reduced to decrease the hazard of rebound hypercoagulability and resultant embolism.[41] However, no reliable data presently support this recommendation.[42] More recently, Michaels has reported that cessation of anticoagulant therapy because of hemorrhage carries no greater risk of recurrent embolism than elective discontinuation [43] and that the manner of termination (gradual or abrupt) does not affect the incidence of thromboembolic relapse.[44]

Since the removal of polybrene from the market because of the inability of the manufacturer to produce a substance of the desired molecular weight [45] and because of the drug's toxic renal effects,[23] protamine has been the only drug available for reversal of heparin. Just as heparin has immediate effects on anticoagulant activity, protamine is immediately effective in reversing heparin activity. The dose of protamine for a given dose of heparin may be calculated on the basis of the heparin dose previously administered or, preferably, may be based on a protamine titration in which the micrograms of protamine needed to neutralize the heparin in 1.0 ml of blood are measured.[30] This value is then multiplied by the patient's estimated blood volume and the appropriate amount of protamine administered at a rate which does not exceed 50 mg/70 kg/min. Confirmation of return to a normal coagulation mechanism should be confirmed by a repeat protamine titration. Unlike coumarin-induced anticoagulation, heparin-induced anticoagulation is not altered by transfusion with blood or plasma.

Even small amounts of unneutralized heparin can produce anticoagulation. We have previously shown that protamine is not a clinically important anticoagulant *in vivo* and, therefore, recommend that more than the minimal amount of protamine be administered to insure re-establishment of normal coagulation. Following extracorporeal circulation, more than adequate neutralization can be achieved by the following doses of protamine: for pumps with small primes, an amount equal to the total dose of heparin (including that in the prime); for pumps with large primes, an amount equal to half the total dose of heparin.[30]

TABLE 5. Laboratory Variables Affecting the Whole-blood Coagulation Time*

1. Size of test tube
2. Quality of glass
3. Temperature
4. Volume of blood
5. Frequency, degree and vigor of tilting
6. Definition of endpoint
7. Number of test tubes (*i.e.*, one-, two- or three-tube test)

* From Ellison N, Ominsky AJ, Wollman H.[30]

Three alternatives for the reversal of coumarin-like effects are available: 1) vitamin K, 2) blood transfusion, and 3) Factor IX concentrate. Vitamin K is a specific antidote to correct the hemostatic defect. However, after oral or intravenous administration, at least three to six hours are required before the prolonged prothrombin time will shorten.[34] The dose of vitamin K needed varies with the indication for its use. In the absence of bleeding, simply withholding one dose of coumarin may raise the prothrombin level sufficiently over the next 24 hours. If one wishes to reduce the level of anticoagulation without discontinuing treatment, only small doses of vitamin K_1 (0.5 to 1.0 mg) should be used to insure that the patient does not abruptly become relatively refractory to coumarin.[23] On the other hand, when complete reversal of coumarin is desired, vitamin K_1 in doses of 50 mg should be used to insure an adequate response, because of the considerable individual variability in response.[46-47] Since the action of coumarin may last four to five days, it is advisable to repeat vitamin K daily for three days or, alternatively, to follow the prothrombin time daily.

The second way to reverse coumarin-induced anticoagulation is to use blood or plasma transfusion. This method has the advantage of

being immediately effective when such reversal is urgent. Unfortunately, there is no formula for the volume of blood or plasma needed to achieve reversal. Both the degree of depression of the patient's sensitive coagulation factors for a given prothrombin time and the amount of the coagulation factors present in each unit of blood or plasma are extremely variable. Since the four factors in the prothrombin complex are all present in banked blood, fresh whole blood or fresh frozen plasma is not necessary.

The third theoretical method for reversing coumarin effect would be to use a Factor IX concentrate. Unfortunately, this concentrate is prepared from blood from large pools of donors and, therefore, carries a high risk of hepatitis.[48] Thus, its use is reserved almost exclusively for patients who have congenital deficiencies that necessitate administration of large doses of Factor IX concentrate.

Anesthesia for the Patient on Anticoagulant Therapy

In the previous section we discussed the advisability of reversing anticoagulation. Assuming that it has been elected to operate on the patient who is still receiving anticoagulants, this section discusses methods of anesthetic management.

Whenever possible, intramuscular injection should be avoided in the patient with a coagulation defect. Premedication, if necessary, should be given orally or intravenously. Furthermore, any necessary intramuscular or subcutaneous injections should be given in the arm so that local hemorrhage may be more easily detected and treated.

Regional anesthesia should be avoided for the same reasons. It may seem paradoxical that an operation can be performed on a patient receiving anticoagulants while regional anesthesia is relatively contraindicated. However, the surgeon can see injured blood vessels and tie them. The anesthesiologist, because he must infiltrate blindly, lacks this advantage. Nevertheless, not all anesthetists regard anticoagulation as a strong contraindication to local anesthesia. Indeed, Moore, in his textbook on regional anesthesia, states that stellate ganglion and lumbar sympathetic blocks may be used for patients who are anticoagulated.[49]

In our institution we are frequently called upon to place epidural catheters in patients with peripheral vascular disease of the legs who are to receive anticoagulants. Bromage cautions against the use of epidural catheters in patients who are to be anticoagulated, and three recent reports have brought to six the total case reports of epidural hematoma in association with epidural catheterization.[50-53] Others argue that the use of anticoagulants in patients with epidural catheters is associated with such a low incidence of bleeding that it is safe to use such catheters.[51] We do not place epidural catheters in patients who are receiving anticoagulants. Furthermore, if a patient has been on anticoagulants, we confirm that the prothrombin time or the WBCT, depending on which anticoagulant the patient was receiving, is normal before placing such a catheter. We have placed an epidural catheter in more than 500 consecutive patients, who were then started on anticoagulant therapy an hour later. We have had no epidural hematomas. If this practice is followed, Bonica recommends flushing with saline solution and aspiration to diagnose bleeding, as well as frequent neurologic examinations to diagnose immediately the development of a hematoma in the epidural space.[54] For similar reasons, Cousins suggests that a continuous epidural block be permitted to wear off long enough to assess motor and sensory function at some time during the first 24 postoperative hours.[55] It should be pointed out that spontaneous epidural hematomas have been reported as far back as 1867, and that epidural hematomas have occurred in patients on anticoagulants but without epidural catheters in place and with no history of trauma. However, a fourth of the patients with spontaneous epidural hematomas had some coagulation defect.[56]

In a patient who is already receiving anticoagulants or who has a hemorrhagic diathesis, we avoid regional anesthesia unless there are truly urgent indications for it. As a general rule, in the management of any patient with a coagulation defect, be it congenital or iatrogenic, we feel general anesthesia does offer advantages if no strong contraindications for general anesthesia exist. Of course, gentleness in everything from starting the intravenous

infusion to intubating the trachea is especially important.

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(*Continued from page 327.*)

manner. It should prove, therefore, useful as a short textbook for anesthesiologists and obstetrician–gynecologists in training. Used in this way, it serves another need extremely well by providing an overview of the subject, with the more complete Bonica text serving as a reference work.

Diagrams could be used to advantage in many places throughout the text; illustrations are far too few, there being only five tables and 13 figures in the entire volume.

Often the reader is referred to another section for additional information, but specific page references are seldom given.

Of minor annoyance are the frequent typographical errors, which detract from the author's eloquent prose.

The author seems unjustly critical of paracervical block in the conduct of labor. No mention is made of the submucosal injection method, which has been shown to decrease the incidence of fetal bradycardia substantially. Also, when the block is appropriately timed, neonatal depression is minimized, a fact not brought out in the text.

It is also interesting to note the differences between the American and British approach to analgesia and anesthesia for the laboring gravida. The narcotic doses described are much larger than those customarily used in the United States, and, of course, Entonox, so commonly used in the United Kingdom, is unavailable at this time in U. S. hospitals.

These criticisms, however, do not detract from this textbook, which may be most highly recommended for its ability to provide a solid framework upon which to hang new information. It should be widely read in the United States, for it has much to offer the student of Obstetrical Anesthesia.

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