Anticoagulant Therapy in Peripheral Vascular Disease

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During the past decade the anticoagulant drugs, heparin and dicumarol, have been found to be of considerable value in the treatment of many of the peripheral vascular diseases in which there is intravascular thrombosis. It is obvious that these drugs are used for the sole purpose of preventing thrombosis. To date there is no conclusive evidence to indicate that they have any effect on thrombi or emboli which have already developed. The use of both heparin and dicumarol requires careful medical supervision and involves a small calculated risk of bleeding even under the supervision of physicians who have had considerable experience with the drugs.

In various types of peripheral vascular disease the stimulus to thrombus formation varies considerably depending upon the degree of damage to the endothelium of the blood vessels, impairment of blood flow, and hypercoagulability of the blood. From a purely theoretic standpoint it seems that the only way that thrombosis can be prevented with certainty by interfering with the process of coagulation would be to make the blood totally incoagulable, a difficult and dangerous procedure if maintained for any considerable period of time. Anticoagulant therapy as carried out at present only attempts to inhibit the tendency to thrombosis by partially interfering with the coagulation mechanism. Again from the theoretic standpoint it is obvious that such anticoagulant therapy may fail if the stimulus to thrombosis is too great. However, a number of reports of experimental studies and clinical statistics indicate that, when properly given, heparin and dicumarol have prevented thrombosis in a large number of cases of peripheral vascular disease. An extensive review of anticoagulant therapy has recently been written by Marple and Wright.1

The statistical studies at the Mayo Clinic have indicated that among patients who have had postoperative thrombophlebitis or pulmonary emboli,2-4 or both, the incidence of recurrence or extension of venous thrombosis and further pulmonary embolism has been reduced almost to nil by carefully supervised anticoagulant therapy. Since the tendency to thrombosis exists for only a limited period during the immediate postoperative convalescence, it is only necessary to use anticoagulants for a few weeks at the most in these cases. Furthermore, there is reasonable evidence to show that postoperative thrombosis and embolism can be almost entirely prevented if dicumarol is used prophylactically beginning 48 hours after the operation has been performed. Prior to the use of dicumarol the incidence of fatal pulmonary embolism at the Mayo Clinic after abdominal hysterectomy and after resection of the colon was 0.7 per cent. During the past nine years more than 3,000 patients who have had abdominal hysterectomy have been given dicumarol prophylactically without any instance of fatal pulmonary embolism. During the same period among the patients who underwent resection of the colon and did not receive prophylactic anticoagulant therapy, the incidence of fatal pulmonary embolism has continued to be approximately 0.7 per cent.

Wise, Loker and Brambel5 have reported on two parallel series of patients who had undergone major surgery during a four-year period. Among 3,304 who were given dicumarol as a
prophylactic measure, there was only one death which could possibly be due to pulmonary embolism, and among 2,030 who were not given dicumarol there were six deaths due to pulmonary embolism. To date, however, the routine use of dicumarol for the prevention of thrombosis and embolism after operations has seemed somewhat impractical because of the statistically small risk of these complications after all operations and because of the potential danger of bleeding which also is small but cannot be ignored. However, situations are encountered, particularly among patients who have a history of previous venous thromboembolic disease, in which the risk of further thrombosis is sufficiently great to justify the prophylactic use of dicumarol following a surgical operation. In these situations it has been the practice at the Mayo Clinic in recent years to begin administration of dicumarol approximately two days after the operation and to use somewhat smaller initial doses of the drug than are employed in patients who have acute thrombophlebitis or pulmonary embolism. There have been recent reports in which it has been stated that dicumarol has been administered safely starting on the day before operation. The rationale of starting administration at this time is that therapeutic prothrombin deficiency does not develop until two or three days after the first dose of the drug has been given. For practical purposes it would seem that assuming an increased risk of bleeding by such early administration of dicumarol is unnecessary since clinically detectable venous thrombosis or pulmonary embolism rarely occurs before the sixth postoperative day. There are still variable opinions as to which surgical patients should be selected for prophylactic dicumarol postoperatively.

When postpartum thrombophlebitis or pulmonary embolism or both develop, the situation is comparable. Although information concerning sufficiently large series of treated and untreated patients is not available on which to base a statement that the use of anticoagulants has certainly reduced the incidence of further thrombosis and embolism in postpartum cases, reports of small series of cases have indicated that this is probably true. A recent report by Brambel, Hunter and Fitzpatrick gives the comparative incidence of thrombophlebitis and pulmonary embolism in two parallel groups of postpartum patients. Among 3,318 untreated patients there were 16 who had thromboembolic complications with one death due to embolism. Among 3,284 postpartum patients who were given dicumarol prophylactically, there were only two thromboembolic complications and no deaths due to embolism. In the untreated group, 12 had postpartum hemorrhages, and in the treated group, 17 had postpartum hemorrhages. There were no fatalities due to hemorrhage in either group. At first it was feared that the incidence and severity of postpartum hemorrhage might be greatly increased if anticoagulant drugs were given, but with proper dosage and control the risk of such hemorrhage, although it is present, appears to be very small. To date there is no evidence to indicate that nursing infants have prothrombin deficiency or bleeding while their mothers are receiving dicumarol in therapeutic amounts. Such infants are usually given synthetic vitamin K during such a period although the necessity for this is doubtful. The risk of bleeding is increased for both mother and fetus if anticoagulants are used during pregnancy, particularly in the late months.

Among patients in whom venous thromboembolic complications develop after severe injuries, such as fractures, with prolonged periods of enforced rest in bed, the situation can be closely compared to that which exists after surgery and childbirth. Experience to date does not warrant the definite conclusion that anticoagulants have prevented further thromboembolic complications, but in the experience at the clinic such recurrences have not been noted when patients so affected have been treated with anticoagulants. Because of prolonged hospitalization and rest in bed it is usually necessary to maintain anticoagulant therapy for longer periods in cases of post-traumatic thrombophlebitis and pulmonary embolism than in cases of thrombophlebitis and pulmonary embolism after operations and childbirth.

Patients who have had thrombophlebitis and pulmonary embolism in the course of acute infectious diseases have been treated successfully with anticoagulants although comparative
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statistical studies concerning treated and untreated groups are not available. The rationale has been that in these cases there is a definite risk of recurrence of thrombosis and embolism similar to that noted during the postoperative period. A few instances of failure to prevent recurrent thrombosis when both heparin and dicumarol in the usual therapeutic doses have been used have been noted in patients with chronic ulcerative colitis.

It is well known that peripheral venous thrombosis and pulmonary infarction may complicate congestive heart failure and there is justification for the use of anticoagulants in all cases in which such complications develop, since they may be forerunners of more extensive and serious venous thromboembolic disease. Wishart and Chapman even stated that it would be justifiable to treat all patients with congestive heart failure with dicumarol to prevent peripheral venous thrombosis. For patients with congestive heart failure, the duration of therapy is always contingent on the course of the disease, and it is hoped that the treatment can be discontinued when compensation is restored. Peripheral thromboembolic complications not infrequently develop in cases of polycythemia vera. When these complications are encountered, it is rational to use anticoagulants until the polycythemia can be brought under satisfactory control, particularly with the use of radioactive phosphorus, which seems to be an effective agent for inhibiting the tendency to thrombosis as well as controlling the erythrocytosis in this disease. The anticoagulants have been used in an attempt to prevent the recurrent venous thrombosis which has complicated inoperable carcinoma, particularly carcinoma of the pancreas. In several instances the treatment has appeared to be effective for a while but ultimately thrombosis has occurred in spite of adequate anticoagulant therapy. The incidence of failure in this group of cases has been considerably greater than in venous thromboembolic disease complicating any other type of condition.

In recurrent idiopathic thrombophlebitis (thrombophlebitis migrans), anticoagulants have been used with variable results. The irregular spacing of the episodes of activity of the disease and its variable course make it difficult to know in any individual case whether recurrences have been prevented and also how long to continue treatment. Some of these patients are somewhat resistant to anticoagulants. There have been some recurrences during treatment with dicumarol and not all of these can be explained by lapses in what is usually considered to be adequate therapeutic prothrombin deficiency. At present it seems more likely that the stimulus to thrombosis is strong and that, in some cases at least, the coagulability of the blood must be greatly impaired if thrombosis is to be prevented.

Adequate rationale and some statistical evidence are available which indicate the advisability of the use of anticoagulants in acute peripheral arterial occlusion. Such cases are medical emergencies, and the success of any type of treatment is contingent on early diagnosis and early institution of therapy including anticoagulants. When the occlusion is due to arterial embolism, the source of the embolus is usually an intracardiac thrombus. There is adequate statistical evidence to show that the prophylactic use of anticoagulants following acute myocardial infarction has been very effective in preventing the peripheral arterial embolisms which not infrequently complicate this type of cardiac lesion. One of the common causes of peripheral arterial embolism is thrombosis in a fibrillating left auricle. The seriousness of the prognosis for patients with auricular fibrillation who have had one or more emboli has been emphasized by many authors. Wright and Foley have reported success with the prolonged use of dicumarol in the prevention of more intra-auricular thrombosis and subsequent arterial embolism in such cases.

In the specific treatment of acute arterial embolism in an extremity, heparin should be administered intravenously immediately along with measures to produce as much vasodilatation in the extremity as possible. If the circulation does not improve within a few hours and an embolectomy is considered necessary, the effect of heparin can be stopped before surgery and administration can be resumed soon after surgery. At this time dicumarol also may be given and the administration of heparin discon-
continued as soon as the prothrombin time is adequately elevated. In the chronic occlusive arterial diseases,\textsuperscript{11} thromboangiitis obliterans, arteriosclerosis obliterans and simple (essential) arterial thrombosis, anticoagulant therapy has not been used commonly. In thromboangiitis obliterans episodes of arterial occlusion occur usually at rather widely spaced intervals, and cessation of the use of tobacco is almost always sufficient to prevent these recurrences. In arteriosclerosis obliterans there may be episodes of acute arterial occlusion due to thrombosis in situ and during the immediate period following such episodes, anticoagulants are of value. In simple arterial thrombosis, which is a relatively rare condition, prolonged anticoagulant therapy may be advisable unless an underlying cause of the disease, such as polycythemia vera, can be brought under control.

The Use of Heparin

Heparin is a valuable anticoagulant and has the advantage of producing a rapid effect. If heparin is given intravenously, the effect can be terminated within a short time by discontinuing administration and even more quickly by administering protamine sulfate intravenously.\textsuperscript{12} Disadvantages of heparin are its cost and difficulty of administration. Numerous studies have indicated that tolerance to heparin varies considerably among different individuals.\textsuperscript{13, 14} Increased tolerance to heparin, manifested by less marked effect on the coagulation time after standard doses, is frequently observed among patients with various types of thrombosis. However, some such patients have normal tolerance for heparin and a few have decreased tolerance. This variability of response to fixed doses of heparin has not been sufficiently appreciated in efforts to simplify administration by standardization of dosage. The coagulation time of whole venous blood has been generally used as the guide to the anticoagulant effect of heparin.

It is not generally appreciated that this test of the blood is a very crude one and is subject to numerous errors which may impair its value greatly. The errors increase when the coagulation time is prolonged by heparin. Some of the factors which influence the results of the test are the cleanliness of the tube, the amount of blood tested, the size of the tube and the frequency and vigor with which it is tipped to determine the end point. A difficult venipuncture with considerable probing for the vein will greatly shorten the time, as compared with that after a clean, quick venipuncture. Such shortening of the coagulation time is due to the introduction of greater amounts of tissue thromboplastin into the needle. Differences in the environmental temperatures at which the tests are done may greatly affect the results. If careful attention is paid to all these factors and they are rendered as nearly constant as possible, and if the same individual does the tests, a reasonable degree of accuracy and comparability of results may be obtained. Although a number of good coagulationists have concluded that the test is subject to too many errors to be of any value whatsoever, it is the most practical test of the effect of heparin available at present.

The degree of prolongation of the coagulation time by heparin which is sufficient to inhibit intravascular thrombosis has never been definitively established but it is generally considered that it should be at least twice normal, or more than 15 minutes. Some observers have noted that even with minimal prolongation of coagulation time by heparin, the clot is softer and more friable. They have stated that this indicates that heparin may exert some antithrombotic effect when there is only slight prolongation of the coagulation time.

The method of administration of heparin first recommended by the Toronto group of investigators was to give the heparin in dilute solution, 200 mg. in 1000 cc. of diluent, continuously at a regular rate, usually starting with 25 drops per minute. The rate of administration was varied to produce the desired effect (coagulation time 15 to 25 minutes). This method was effective and individualized the dosage for each patient but it required frequent tests of the coagulation time and careful supervision of the apparatus to make sure that the desired number of drops per minute of the solution was always delivered. The method is not practical for continuous use for periods of more than 10 days.

The Swedish method of administration of
heparin, which largely supplanted the Toronto method, was to give a fixed dose of concentrated solution intravenously at stated intervals, such as 50 to 100 mg. every four to six hours. This was modified at times by increasing the dose to 150 mg. at 10:00 p.m. and omitting the 2:00 a.m. dose. Clinically this method has seemed to be effective, but it ignores entirely differences in heparin tolerance among different individuals. Also there is frequently no demonstrable effect on the coagulation time at the end of two to three hours after each injection. It is possible that the antithrombotic effect of heparin may persist for a longer period than the measurable effect on the coagulation time but there is no positive evidence of this, and it seems reasonable to assume that thrombosis is not prevented unless coagulation, as measured by this test, is impaired. Thus the intermittent intravenous injection of heparin permits frequent lapses in measurable anticoagulant effect. It has the further disadvantage of requiring many venipunctures.

The administration of heparin in a slowly absorbed medium by intramuscular or deep subcutaneous injection has gained in favor but opinion is divided as to its efficacy and safety. The biggest problem has been the determination of dosage, and there is lack of agreement regarding optimal dosage schedules, probably because differences in heparin tolerance among different patients have been ignored. The method has the advantage of simplicity, and there is no doubt but that sufficient heparin can be introduced to produce an anticoagulant effect lasting a number of hours by this route. The earlier solutions frequently produced persistent pain and occasionally considerable ecchymosis at the site of injection. More recent preparations appear to have minimized these disadvantages. If it becomes desirable to stop quickly the effect of heparin administered subcutaneously, this can be accomplished by applying an ice bag to the site of injection and by giving protamine intravenously. The dose of protamine may have to be repeated.

The degree and duration of prolongation of the coagulation time vary greatly among different patients when heparin is given intramuscularly or subcutaneously in a slowly absorbed medium. Possibly the best trial dose is 200 mg. every 12 hours but in some individuals 200 mg. produces only a minimal effect lasting less than six hours. In some individuals 200 mg. may produce an excessive effect lasting more than 12 hours. In some individuals as much as 400 or 600 mg. may be required to produce an adequate effect for 12 hours. When large doses are employed, there is always the hazard of an extreme and dangerous coagulation defect lasting as long as 12 hours after injection. Whatever initial dose is used, it is advisable to test the coagulation time one to four hours and 12 hours after administration to determine roughly the intensity and duration of effect. Results of this test then can serve as a guide to the amount and frequency of subsequent doses for the particular patient under treatment. Tolerance to heparin may fluctuate from time to time in the same patient, and to maintain an optimal anticoagulant effect it is advisable to check the coagulation time at similar intervals after the injection every few days if this type of heparin therapy is continued and to vary the amount and frequency of the dose if necessary.

Heparin produces a much more profound effect on the coagulation mechanism than does dicumarol. Even in the therapeutic range of activity there appears to be a greater tendency to bleeding from operative wounds or other potential bleeding lesions when heparin is used than when dicumarol is used. If an excessive prolongation of coagulation time is produced and maintained by heparin, the danger is obviously greater. If the hemorrhage is external and detected, the effect of the heparin can be stopped quickly, but if it is internal, a dangerous situation may develop before it is recognized.

The Use of Dicumarol

As an anticoagulant dicumarol has the advantage of being cheap and easily administered. Disadvantages are delay in adequate effect for one or more days following administration and delay of subsidence of effect for several days after administration has been discontinued. Another disadvantage which has been recognized and emphasized by all who have had experience with the drug is the great difference in response
among different patients to fixed doses. Some factors which influence this sensitivity to the drug are known and some are unknown or unpredictable. In treatment with dicumarol, the aim is to produce and maintain a moderate but not excessive deficiency of prothrombin activity. The dosage must be individualized for each patient on the basis of his reaction to certain fixed amounts of the drug which are given initially. The dosage must be varied as necessary during the entire period of administration and it depends on the response of the particular patient being treated. Nothing has developed in recent years which alters the often repeated dictum that the Quick prothrombin time test is the essential guide to dicumarol therapy and that, unless it is possible for the physician to receive accurate and comparable results of this test at daily or at even more frequent intervals if necessary, the use of dicumarol may be futile or dangerous.

In discussing "therapeutic levels" of prothrombin deficiency and dosage schedules for dicumarol, one is always handicapped by the fact that thromboplastins of variable potency are used in different laboratories and institutions for the Quick prothrombin time test. Hence, it is difficult to discuss therapy or optimal effects in terms of prothrombin time in specific numbers of seconds. An attempt has been made to discuss the optimal therapeutic range of prothrombin deficiency in terms of percentages of prothrombin activity, but this has given rise to considerable confusion because of the use of different formulas for expressing the prothrombin time in terms of percentages of prothrombin activity. For the most part it is considered that prothrombin activity between 10 per cent and 30 per cent of normal is the optimal therapeutic range when dicumarol is given. Some investigators, notably Brambel and his co-workers, have concluded that for purely prophylactic purposes the therapeutic range of prothrombin activity can be 30 per cent to 50 per cent of normal.

In order to avoid confusion which exists in attempts to use percentages instead of seconds, the following scheme has been devised and can be carried out with the cooperation of any physician and any laboratory where the prothrombin time test is done regardless of the source and method of preparation of the thromboplastin. Each time a new batch of thromboplastin is prepared, $T_{30}^0$, $T_{30}^0$, and $T_{10}^0$ should be determined. $T_{30}^0$ = average prothrombin time, in seconds, of 30 per cent plasma in 0.9 per cent sodium chloride solution from three normal persons. $T_{20}^0$ = average prothrombin time, in seconds, of 20 per cent plasma in 0.9 per cent sodium chloride solution from three normal persons. $T_{10}^0$ = average prothrombin time, in seconds, of 10 per cent plasma in 0.9 per cent sodium chloride solution from three normal persons.

The prothrombin time, in seconds, of the patient under treatment with dicumarol should be kept between $T_{30}^0$ and $T_{10}^0$. Three hundred mg. of dicumarol are given on the first day and 100 mg. on each subsequent day that the prothrombin time is less than $T_{30}^0$. No dicumarol is given on days when the prothrombin time is greater than $T_{30}^0$. If the patient is found to be resistant to the drug, the dose is increased to 200 mg. on each day that prothrombin time is less than $T_{20}^0$. If the prothrombin time is greater than $T_{10}^0$ on two successive days, 30 mg. of menadione bisulphite is given intravenously. If it is desirable to continue treatment with dicumarol for a number of weeks, a daily dose of dicumarol which will keep the prothrombin time between $T_{10}^0$ and $T_{10}^0$ may be determined after the first week of treatment. This dose will usually be between 50 and 100 mg. a day and the amount can be calculated roughly on the basis of whether the patient's original response to the first few doses was average, excessive or inadequate. If the patient's prothrombin time stays in the region of $T_{30}^0$ or slightly higher rather consistently on the daily dose, the frequency of determinations of the prothrombin time can be gradually reduced from once a day to once a week.

Nichol has suggested a somewhat simpler formula based on his observation that in a number of institutions the optimal therapeutic range of prothrombin deficiency for dicumarol therapy was expressed by a prothrombin time between two and two and one-half times normal prothrombin time in seconds. In using Nichol's formula, the normal prothrombin time should
be determined each day by taking the average of results obtained by testing two or more normal individuals who were not receiving anticoagulants. The formula, moreover, is only applicable if this normal is less than 20 seconds. Three hundred mg. of dicumarol are given the first day and 100 mg. on each subsequent day until the prothrombin time is greater than twice the established normal time in seconds for that day. Then 75 mg. are given each day if the prothrombin time is in the therapeutic range (between two and two and one-half times normal). If the prothrombin time goes above the therapeutic range, doses are omitted until it returns to the therapeutic range and then continued at the rate of 50 mg. a day. If with administration of 75 mg. a day the prothrombin time drops below the therapeutic range, the dose is increased to 100 mg. a day. Further observation may indicate that variations in dosage by increments of 25 mg. on certain days may be necessary in some patients to keep the prothrombin time within the therapeutic range.

The contraindications to the use of dicumarol have not been changed, namely renal insufficiency, hepatic insufficiency, purpuric states and recent operation on the brain or spinal cord. In general, hypersensitivity to dicumarol may be noted among patients with congestive heart failure and patients whose nutritional status is impaired owing to inadequate diets or gastrointestinal disease. After operations, those patients who have never had evidence of thromboembolic phenomena as a group are somewhat more sensitive to dicumarol than those who have had recent thromboembolic manifestations. Dicumarol should be used somewhat more cautiously and with a somewhat reduced original dosage among patients who are considered to be potentially hypersensitive to the drug, among patients who have potentially bleeding lesions, such as ulcers of the gastrointestinal tract, open surgical wounds or granulating surfaces and among patients who have drainage tubes in wounds or body orifices.

The only important untoward effect which has been noted in patients who have received dicumarol is bleeding. Much of the serious bleeding which has been encountered has been due to gross overdosage with the drug due to error or to disregard for the importance of daily determinations of prothrombin time; however, even with adequately supervised therapy there is a small risk of serious local hemorrhage. Nichol recently reviewed the cases of serious and fatal hemorrhage during administration of dicumarol in a number of institutions since the drug was first introduced. He found that the mortality attributable to hemorrhage was 0.18 per cent among 15,500 patients. A number of the fatalities occurred in the early years after dicumarol was introduced; similar situations would probably not occur now that the contraindications to the use of the drug are known more generally and the prothrombin time is determined with greater accuracy. Among patients who do not have recent surgical wounds or known ulcers of the gastrointestinal or urinary tract and present no contraindications to the use of dicumarol, the incidence of major bleeding is very low and the risk of fatal hemorrhage can be considered as practically nil providing the prothrombin time is not allowed to exceed the therapeutic range. The incidence of major bleeding, particularly bleeding from operative wounds, is higher among surgical patients in the immediate postoperative period. However, it is less than 3 per cent among those surgical patients who have not had previous thrombosis and less than 1 per cent among those who have had previous thrombosis. Among the last 2,000 postoperative patients treated with dicumarol at the Clinic no fatal hemorrhage has occurred. Wise, Loker and Brambel have reported that 3,304 patients were given dicumarol after major abdominal and pelvic surgery without any deaths due to bleeding and with only three instances of bleeding sufficient to require blood transfusion. The statements in the medical literature that dicumarol is a “dangerous” drug are unjustified if the drug is properly given.

Three situations may be encountered during dicumarol therapy for which it is desirable to increase the prothrombin activity. If major bleeding is encountered, the prothrombin time should be brought down to normal as rapidly as possible. It may be advisable to stop the effect of dicumarol even when there is no bleeding if a surgical operation or some other proce-
dure involving a risk of bleeding is contemplated or when renal insufficiency develops during treatment with dicumarol. If the prothrombin time goes above the therapeutic range at any time during treatment, it is usually desirable to bring it back into the therapeutic range in order to reduce the risk of bleeding. The use of water-soluble preparations of synthetic vitamin K, such as menadione bisulfite, has been found to decrease the prothrombin which has been elevated by dicumarol in many cases. The most striking results have been noted among patients who are hypersensitive to the drug and who have excessive prothrombin deficiency after the usual initial doses of dicumarol. Several studies have indicated that vitamin K₁ and vitamin K₃ oxide given either orally or intravenously are more potent dicumarol antagonists than are the water-soluble synthetic menadione preparations. Regardless of the degree of prothrombin deficiency, the prothrombin time starts to fall within four hours and is usually normal or very near normal in 8 to 24 hours after the administration of a single dose of 500 mg. of vitamin K₁ either by mouth or by vein. Those who have used both vitamin K₁ and synthetic vitamin K seem to have no doubt but that vitamin K₁ is the preparation of choice in any situation where it is desirable to reduce the prothrombin time elevated by dicumarol to normal as rapidly as possible. However, when it is merely advisable to reduce an excessively elevated prothrombin time into the therapeutic range, the synthetic preparations are preferable. For practical purposes, a single dose of 500 mg. of vitamin K₁ given orally appears to be almost as rapidly and completely effective as the same dose given intravenously, except for patients who are vomiting or who have external biliary fistula or external biliary drainage. Following a single dose of 500 mg. of vitamin K₁, patients are usually refractory to the usual doses of dicumarol and similarly acting drugs for one to two weeks. Among patients who receive vitamin K₁ to stop the effect of dicumarol because of the development of renal insufficiency, the prothrombin time may become elevated again after it has returned to normal and subsequent doses of vitamin K₁ may be necessary. In almost all other cases, however, the prothrombin time remains normal after vitamin K₁ has been given. For control of excessive prothrombin deficiency due to dicumarol, transfusion of blood is of some value but is rarely necessary unless there has been major bleeding. In this situation the main purpose of transfusion is to restore lost blood rather than prothrombin. The effect of one transfusion on the prothrombin time is usually transient.

CHOICE OF ANTICOAGULANTS AND COMBINED THERAPY

At present if anticoagulant therapy is desirable in cases of peripheral vascular disease, heparin alone should be used if the patient has definite hepatic or renal insufficiency or if adequate tests of Quick prothrombin time are not available. If such tests are available, dicumarol alone is preferable when the risk of thromboembolic complications is increased but there have been no recent acute thromboembolic complications. The preferable plan of treatment from the standpoint of effectiveness of treatment, safety and economy for patients with acute peripheral thrombosis or embolism including pulmonary embolism is the combined use of heparin and dicumarol; this statement again is based on the assumption that adequate prothrombin time tests are available and there are no contraindications to the use of dicumarol. In this plan, doses of heparin are discontinued when the prothrombin time reaches the therapeutic range, and treatment is continued with dicumarol alone. Since heparin also affects the prothrombin time, the blood samples for prothrombin time tests to determine the effect of dicumarol alone should be drawn after the effect of heparin has been allowed to lapse.

Many observers have noted that patients with acute iliofemoral thrombosis or severe pulmonary embolism have a more rapid subsidence of symptoms and manifestations if heparin is started soon after the onset.

Dicumarol is the anticoagulant of choice for long-time anticoagulant therapy because it is so much less costly than heparin.

NEWER ANTICOAGULANT DRUGS

Tromexan, which is a trade name for 3,3'-carboxymethylene bis (4-hydroxycoumarin)
ethyl ester, is a new anticoagulant drug having a dicumarol-like action. Chemically it is very similar to dicumarol. This drug was developed in Switzerland and in Czechoslovakia where it is known as Pelantan. Preliminary observations on the clinical use of Tromexan have been reported by Burt, Wright and Kubik in England and Burke and Wright in this country. Tromexan is approximately one-fifth as potent as dicumarol milligram for milligram and therefore the dosage in milligrams is approximately five times as great. The only essential differences between the action of Tromexan and the action of dicumarol are that the effect of Tromexan develops somewhat more rapidly after administration has been started and disappears somewhat more rapidly after administration has been discontinued. Individual differences in sensitivity to Tromexan are similar to those noted with dicumarol, and when the drug is given, it is equally necessary to establish the correct dosage on the basis of daily determinations of prothrombin time. An original dose of 1200 to 1500 mg is recommended and the usual daily dose for maintaining prothrombin deficiency in the therapeutic range is considered to be 600 to 900 mg.

It has been stated that there may be a greater safety factor in using Tromexan than in using dicumarol because of the more rapid subsidence of effect after administration of the drug has been discontinued. However, the prothrombin time of some individuals has not returned to normal for as long as four or five days after the last dose of the drug was given. In the few cases in which synthetic vitamin K has been given to patients with markedly elevated prothrombin times due to Tromexan, the return to normal seemed to be somewhat accelerated and in any event has been rather rapid (within 12 to 36 hours). The only disadvantage of Tromexan over dicumarol appears to be a somewhat greater difficulty in maintaining the prothrombin deficiency within the therapeutic range during the trial period or first week or two of administration because of the tendency to more rapid fluctuations of the prothrombin time. It is said that splitting the daily dose tends to reduce these fluctuations. To date an insufficient number of patients have been treated to determine whether the drug is as effective as dicumarol in preventing thrombosis and whether the risk of bleeding is less than when dicumarol is used. It can be anticipated, however, that if similar levels of prothrombin deficiency can be maintained, Tromexan will be equally as effective and safe as dicumarol. The more rapid development of prothrombin deficiency after the drug is given would appear to be a slight advantage in some situations.

Another drug with action similar to dicumarol which has been used recently in human beings as an anticoagulant is 4-hydroxycoumarin anticoagulant No. 63 or 2-methyl-2-methoxy-4-phenyl-5-oxodihydropyran-o-(3, 2-c) (1) benzopyran. This compound was developed in the laboratory of Dr. Karl Paul Link and first reported on by Scheel, Wu and Link. It is less soluble than dicumarol and two to three times as potent milligram for milligram. Therefore, the doses recommended for producing the same levels of prothrombin deficiency are one-half to one-third those for dicumarol. It has been stated that when severe and prolonged prothrombin deficiency has been produced and maintained in animals by this drug, less tendency to bleeding has been noted than when a comparable degree and duration of prothrombin deficiency were produced by dicumarol. Clinical observations on the effects of anticoagulant No. 63 have been reported by Battle, Capps, Orth and Meyer. After an original dose of the drug is given, it appears that the prothrombin deficiency develops as rapidly as or slightly more so than when dicumarol is given. Following cessation of the use of anticoagulant No. 63 the prothrombin time remains elevated for a somewhat longer period than is noted with dicumarol. In my limited experience some patients who were resistant to dicumarol developed satisfactory prothrombin deficiency when given anticoagulant No. 63 and it has seemed to be a little easier to maintain relatively constant levels of prothrombin deficiency with this drug. Rotter and Meyer have stated that synthetic vitamin K (menadione bisulfite) is ineffective in restoring the prothrombin time to normal after it has been elevated by anticoagulant No. 63 but that vitamin K$_1$ is just as effective as it is in patients who have received
dicumarol. To date clinical experience is inadequate for satisfactory appraisal of whether the drug has any definite superiority over dicumarol, but further trial and study seem indicated. Another new drug which has been investigated as an anticoagulant is phenylindanedione, which also has an action like that of dicumarol on the prothrombin time. A preliminary report of the effects of administering this drug to 20 patients has been made by Blaustein and co-workers.\textsuperscript{21} Phenylindanedione is said to have a more rapid and more evanescent action than dicumarol, both in animals and man. The effect of phenylindanedione seems to be even more evanescent than that of Tromexan. The usual initial dose which was used by Blaustein and co-workers\textsuperscript{21} was 150 mg., and the daily maintenance dose averaged 50 mg. Interruption of sustained therapy was followed by return of the prothrombin activity to normal levels in from 48 to 72 hours. The more rapid subsidence of effect apparently increases the difficulty in maintaining the prothrombin deficiency within the so-called therapeutic limits. In some patients maintenance of relatively constant levels of prothrombin deficiency in the therapeutic range seemed to be difficult even when doses were given more frequently than once in 24 hours.

Sorenson and Wright\textsuperscript{22} have reported studies on human beings with a polysulfuric acid ester of polyanhydromannuronic acid called Paritol. This drug has a heparin-like action and its manufacture is said to be less costly than that of heparin. Paritol acts only when it is administered intravenously, and its action consists in prolongation of the coagulation time of venous blood similar to that produced by heparin. Apparently there are differences in response to the administration of various fixed amounts of Paritol among different individuals, just as have been noted with heparin. Sorenson and Wright\textsuperscript{22} have noted that approximately seven times as much Paritol as heparin was required to increase the coagulation time to the same degree. However, the effect of such doses lasted considerably longer, often 8 to 12 hours. A slight prolongation of the prothrombin time, similar to that produced by heparin, was noted. Of 35 patients to whom Paritol was given, one had a severe reaction with vascular collapse but recovered after administration of epinephrine; two had transient swelling of hands and feet, and one patient with renal insufficiency had a further rise in the blood urea nitrogen. Bartholomew has recently shown that the effect of Paritol can be stopped rapidly by the intravenous injection of protamine sulfate. One of Bartholomew's patients had nausea, vomiting and pains in the muscles after administration of Paritol and in a few cases, pain in ischemic extremities was aggravated without objective evidence of increased ischemia. Sorenson and Wright\textsuperscript{22} have stated that when some of the material was injected outside the vein local pain and soreness but no necrosis developed. They concluded that the material is unsuitable for subcutaneous or intramuscular administration. The potential advantages of Paritol over heparin would seem to be its somewhat more prolonged action and possibly its decreased cost. The chief disadvantage would seem to be the uncertainty about the question of untoward reactions. Further studies of this drug regarding the toxicity would seem to be indicated before it is released for clinical use.

Some other sulfated compounds of high molecular weight are being investigated as anticoagulants having a heparin-like action. Recently Ochsner, DeBakey and DeCamp\textsuperscript{23} have reported on the use of a different type of anticoagulant therapy for the prevention of postoperative thrombosis and embolism. They have used alpha tocopherol (epsilond M), 200 international units orally every eight hours, or alpha tocopherol phosphate, 100 mg. intramuscularly every eight hours, and calcium gluconate, 10 cc. of a 10 per cent solution every 24 hours intravenously. This type of treatment is predicated on the observations of Kay, who found that a test for plasma antithrombin showed decreased amounts of this factor in cases in which postoperative thromboembolic complications developed. This observation lacks confirmation to date. A previous study\textsuperscript{24} of antithrombin in the plasma of patients with thrombosis occurring in a variety of conditions showed that the antithrombin of some was less and of
some greater than in a series of normal individuals but that the mean for patients with thrombosis was the same as the mean for the normals. Ochsner and co-authors\textsuperscript{22} have reported results in a series of 290 patients who received alpha tocopherol and calcium during the postoperative period. Apparently, presumptive venous thrombosis developed in three patients and fatal pulmonary embolism in two. That this indicates a significant reduction in occurrence of thromboembolic complications can be seriously questioned, and it seems that a much larger series of treated patients must be studied before the value of the combination of alpha tocopherol and calcium as an anti thrombotic regimen can be established.

**SUMMARY**

The anticoagulant drugs, heparin and dicumarol, have been of great value in the prevention and treatment of peripheral thromboembolic disease. The use of both drugs requires individualization of dosage based on the results of the appropriate tests of their effect on coagulation. The risk of bleeding is very small if heparin and dicumarol are properly used. New anticoagulant drugs are being studied and evaluated clinically in an effort to increase even further the effectiveness and safety of anticoagulant therapy.

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