The Use of Anticoagulant Drugs in Ambulatory Patients

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SOMEWHAT paradoxically this Conference is emanating from a place where “armchair medicine” is generally frowned upon as a solution to problems. The justification for it rests in the fact that speculation says that the proper use of anticoagulant drugs may well be life-saving to several varieties of patients right now.

The use of anticoagulant drugs has become a more controversial matter in recent years. There has come to be some doubt in the minds of some excellent clinicians about the wisdom of using these preparations routinely in frank cases of acute myocardial infarction. To the experienced cardiologist this is difficult to understand. Here we are not relying on impressions, for our opinion is backed up by the cooperative study of the Committee on Anticoagulant Therapy of the American Heart Association. This group showed that the immediate mortality from acute coronary occlusion was approximately cut in half by anticoagulant treatment. Furthermore, the experienced physician knows that although one can separate “probably good risk” from “probably bad risk” patients with myocardial infarction, it is utterly impossible to pick an individual from among the so-called “good risk” patients who may not have a fatal attack at any moment during his first three weeks of recovery from an acute cardiac accident. These fatalities are brought about by one of several mechanisms. For example, one is the development of ventricular fibrillation, and this obviously cannot be prevented by anticoagulant treatment. However, there are at least three mechanisms of death which are theoretically and demonstrably preventable by these means. One is an extension of the existing thrombus proximally in the coronary tree and a resulting occlusion of an increasing number of branches with a wider and wider area of infarction. A second is the development of a new thrombus at another site in the arteries supplying the heart with blood. A third is the formation of a mural thrombus over the infarcted area on the inside of the heart with subsequent production of embolic accidents of sufficient magnitude to cause death when they happen to hit the brain. We can, therefore, say with great assurance that the treatment of any patient with a fresh coronary thrombosis should include the use of anticoagulant drugs.

It is safer to use heparin alone if one has the slightest doubt about his laboratory control of the doses of other anticoagulants. When adequate facilities are available, anticoagulant drugs which can be given by mouth are to be preferred. It should be stressed that in com-
petent hands there is very little danger in the use of these materials. Even when the patient has a history of bleeding from a peptic ulcer, it is important to protect him in this way when he develops a clot in a branch of a coronary artery. Other entities about which much the same may be said include embolic accidents in the presence of auricular fibrillation or a fresh thrombophlebitis or phlebothrombosis with or without pulmonary emboli.

A more controversial situation with respect to short-term anticoagulant treatment involves the patient with recently developed congestive heart failure. It was shown several years ago at the Mayo Clinic that more pulmonary emboli which complicate congestive heart failure arise from the veins in the legs than from the auricles, and that these are more frequent than is generally supposed. Whether one should use these drugs routinely in the care of patients with congestive heart failure is debatable, and no figures are known to us which settle the point. As the years pass and our experience grows, together with our feeling of security about the use of these admittedly dangerous drugs, we are inclined to use them more freely in this situation.

At the present time, without doubt, there is a very large and honest difference of opinion concerning the indications for the long-term use of anticoagulants in an ambulatory, prophylactic way. The theory, of course, is that by such use recurrences of thromboembolic accidents can be prevented. Figures which will bear statistical analysis supporting this theory are presently unavailable and probably will be for years to come. This is in part because the natural histories of the diseases for which such figures might be used are so variable from person to person, and in part because it will take years to accumulate such figures in any event. The best one can do, therefore, is to speculate and to base one's judgment as objectively as possible on the procedure one would like to have applied to oneself in such a controversial situation. It would seem that in theory these drugs would represent insurance against repetitious trouble. This has to be balanced against the difficulties inherent in their use. To us it has seemed for the past five years, and still does, that the advantages outweigh the disadvantages. We have each had a few patients in whom a succession of thromboembolic accidents was apparently brought to a halt by these means, and we are continuing their use in this way.

We may say that our impressions are based on a review of the histories of 115 patients who had received anticoagulant therapy while they were ambulatory. Their average age was 53.8 years, and there were 84 males and 31 females in the series. They had received treatment by July 1, 1953, for a total of 6,572 weeks, or an average of 57.1 weeks per patient. Sixty-eight patients were placed on long-term anticoagulant therapy because of a recent myocardial infarction and 47 for other reasons. There were hemorrhagic complications in 12 patients, or 10.5 per cent. Of these, six were so minor that the anticoagulants were not discontinued. There were recurrent thromboembolic accidents in four patients, or 3.5 per cent.

We would like, however, to present some of the difficulties we have encountered, rather than emphasize what must remain our impressions of our successes. Perhaps the most frequent problem has to do with the dosage requirement of a few individual patients from time to time. We have one patient, for example, whose Dicumarol dosage has varied during the past four and a half years from as little as five 50 mg. doses of Dicumarol per week to as much as 150 mg. alternating with 100 mg. daily. This, of course, means that the patient has to have a prothrombin time test at least once a week. It may be said in passing that this patient is the most convinced of any of our patients that this treatment is very important to her. She has an old rheumatic mitral stenosis and insufficiency with auricular fibrillation and had had three major arterial emboli in the six months preceding the onset of ambulatory anticoagulant treatment. Two of these involved the extremities and one the brain. Embolec-
tomy was performed soon after the onset of the last of these when she first came here with a cold, pulseless leg. A strikingly similar case, with respect to the clinical picture, is presented by another woman who had essentially the same anatomic diagnoses with respect to her heart and had had three embolic accidents in a period of about one year. Incidentally, she was the only patient we have ever seen where we felt genuine confidence in a diagnosis of embolism in a coronary artery. Her Dicumarol dosage has been among the most constant through four years of any that we have encountered. She is now able to go four weeks between tests and her dosage rarely varies by more than two pills in each four-week interval.

Another patient was placed under treatment with Dicumarol after two episodes of myocardial infarction. (See fig. 1) The figure shows the "prothrombin ratio," which was measured once a week, and the average daily dose of Dicumarol during each week of the ambulatory therapy.* This patient required approximately 50 mg. a day for the first 12 weeks after discharge from the hospital. At the end of this time his prothrombin ratio fell below 33 and reached a low point of 22. The dose of Dicumarol was progressively reduced and eventually was reduced to a level of 14 mg. a day for one week, after which his prothrombin ratio rose and his maintenance dose was approximately stabilized at a level of 40 mg. a day although definite fluctuations persisted. The patient was comfortable during this entire period. He had no angina and no definite symptoms of heart failure. The reason for his episode of sensitivity to Dicumarol was not elucidated. Although he did not have any hemorrhage or other untoward symptoms while his prothrombin ratio was low, it seems very probable that he would have had trouble had the dose been continued through this phase at a level of 50 mg. a day. This patient provides strong evidence for the necessity of frequent testing of prothrombin time during the administration of this drug.

Many patients seem to be easily controlled under hospital conditions during convalescence from their myocardial infarctions, but the dose established from this experience almost always has to be altered when they resume living at home. One reason for this could be the difference between home and hospital diet, though efforts to evaluate vitamin K intake in the two diets have not been rewarding. Aspirin is well known to have a Dicumarol-like effect on the prothrombin time. One of our patients receiving 4 Gm. of aspirin per day for the treatment of acute rheumatic fever had a prothrombin ratio of 52, though no anticoagulants were being administered. Consequently, our patients are advised to take salicylates sparingly for upper respiratory infections. They are likewise advised to adhere to as constant a diet as possible in the hope that we may at least control this factor. Intercurrent illness itself may affect the prothrombin time, apart from any effect of the diet or medication, but this is unproven. There is little doubt that alcoholic indulgence may

* The prothrombin time ratio as it is used here is the control prothrombin time in seconds times a hundred divided by the patient's prothrombin time. The prothrombin ratio 50 represents a prothrombin time twice the normal control, and the figure 33 three times the normal. These figures are used here as the therapeutic range. It should be noted that there is no rectilinear relation between this prothrombin time ratio and prothrombin activity, nor between either of these and prothrombin concentration or content.
also affect the dosage stability. The explanation for this is not clear, but certainly patients who drink, especially when they drink erratically and excessively, are very difficult to manage on Dicumarol. Antibiotics, too, because of their effect on intestinal flora, may influence dosage requirement.

One other factor which may play a role both in upsetting dosage regulation and creating an additional hazard of hemorrhage is the menstrual cycle. Fortunately, most patients with myocardial infarctions are not menstruating women. However, one female patient, aged 56, suffered a myocardial infarction and was started on Dicumarol therapy some six months after her last menstrual period. She also had had hot flashes and a few other minor symptoms of the menopause. On starting Dicumarol she had a resumption of the menses which was both erratic and excessive in its extent, even though her prothrombin levels were within what we consider the therapeutic range. Dicumarol finally was discontinued after three episodes of vaginal bleeding, the final one lasting for a period of two weeks. She had no more menstrual bleeding in the subsequent two years.

A younger woman, aged 41, was placed on anticoagulants because of embolic phenomena consequent to auricular fibrillation and congestive heart failure. She seemed to have a tendency to go below the therapeutic range late in each menstrual cycle so that on three successive occasions her menstrual period came at a time when the hemorrhagic tendency was most marked. Her hemoglobin fell to 9 Gm. per 100 cc. and had to be restored by transfusion on the last occasion. It was impossible to be certain whether the menstrual cycle was responsible for this woman’s cyclic prolongation of the prothrombin time or whether it was simply due to the vagaries of Dicumarol administration, but it was deemed inadvisable to continue the medication. This same sort of cyclic variation seems to be present in another menstruating patient now on Dicumarol therapy for thrombophlebitis. However, her fluctuation does not seem to be as great and may yet permit successful control of prothrombin time without hemorrhage. In any event we feel that the use of anticoagulants in ambulatory menstruating women can be very hazardous and requires close observation; it may in some cases be virtually impossible.

We have encountered the rare patient, usually during the treatment of an acute situation, but sometimes during chronic care, in whom overdosage of Dicumarol has led to a prolongation of the prothrombin time beyond the three times normal which we regard as the therapeutic level for as long as seven or eight days after the drug was stopped. In none of these patients has any demonstrable bleeding occurred during the protracted period of hypoprothrombinemia.

As was indicated earlier, the problem of accurate laboratory control of Dicumarol dosage has been a major concern of all of us from the very beginning. Determination of the prothrombin time, no matter what method is used, seems relatively simple in theory and surprisingly difficult in practice. Among other things, we have learned that it is important to have the same person draw all the bloods so that he will know of the possibility of a vitiated test because of a difficult venipuncture. We have learned that we have to sharpen our own needles to guard against excessive tissue damage at the time of the withdrawal of blood. We have tried to make the test more objective by various means, the latest being the use of a recording milliammeter and a motor-driven tilting tube. This last gives some promise of being useful but is not yet in the stage where we wish to recommend it to others.

A factor in the test which has only recently come to light is the effect of severe emotional stress upon the prothrombin time. This is well illustrated by one of our patients who has been on ambulatory Dicumarol therapy for about four years. His dosage stability was such that he usually required a test every two weeks to keep him within the therapeutic range. Since he lives 180 miles from Chicago, we made an effort to find a laboratory nearer his home which could perform the test accurately. For the first five times the test was performed near his home, and, three hours later, in Chicago with strikingly good duplication of results. Thereafter he was double-checked only once every three months, always with satisfactory comparisons.
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until the occasion about to be described. This
time he had the test made near his home about
8 a.m. and then drove to Chicago. It was during
the month of January; the weather forecast had
been faulty, and the hazardous driving condi-
tions that obtained had not been predicted. On
entering the city limits on a major boulevard,
with his wife driving, the car went into an
alarming skid but, miraculously, did not collide
with any parked cars nor with oncoming traffic.
However, being in the automobile business, the
patient was all too well aware of what might
have happened and was, as he later said, as
"scared as he ever had been in his life." He was
still weak and trembling when he had his pro-
thrombin test in Chicago. For the first time
there was a sharp disagreement between values
found by the two laboratories. Subsequent
checks were again in accord. While this is an
extreme example of the effect of fear upon the
results of the prothrombin time test, it is quite
possible that, in those patients who dread
needles, similar, though less dramatic, effects
might be encountered.

We have seen a fairly large number of very
minor hemorrhagic tendencies in ambulatory
patients on long-continued Dicumarol therapy.
Most frequently these have been small ec-
chymoses of the skin or microscopic blood in the
urine or epistaxis. A few have had bleeding
gums. Of slightly greater moment was a hema-
toma of the soft palate. We have had six in-
stances of more massive hemorrhage. Three of
these have been from the gastrointestinal tract,
one consisted of gross hematuria, one was a
hemorrhage into a joint, and one resulted in a
large hematoma of the thigh. All were quickly
brought under control by whole blood transfu-
sions and large doses of vitamin K. The case of
greatest interest in this category was one in
which there was a known history of bleeding
peptic ulcer on two occasions before the patient
had his first myocardial infarct. He was treated
with anticoagulant therapy during the acute
phase with no untoward results. He was not
placed on anticoagulant treatment in an am-
bulatory fashion because of the history of
massive gastric hemorrhages. He had a second
coronary thrombosis about four months after
the first one and again received anticoagulant
therapy successfully during the acute phase.

The question of the use of anticoagulants over a
long period of time in the presence of a history
of bleeding ulcer was a difficult one. The prob-
lem was explained to the patient, and it was
suggested that he take a calculated risk and try
them. He took Dicumarol with surprisingly lit-
tle variation in his maintenance requirements
for over a year when he had his third massive
gastric hemorrhage. His prothrombin time was
just slightly over twice the laboratory's control
value for that day at the time the hemorrhage
occurred. The hemorrhage was readily treated
with whole blood transfusions and he was ad-
vised not to attempt to continue on ambulatory
anticoagulant treatment. However, he remem-
bered the intense pain of his two episodes of
coronary thrombosis so vividly and he had so
little fear of gastric bleeding since he had had
it three times with no prolonged convalescence,
thanks to the use of multiple transfusions, that
he insisted on taking Dicumarol again and
stated that he would find some doctor who
would give it to him if we would not. Our own
impressions of the efficacy of this form of pre-
ventive treatment were so encouraging and by
this time our dread of hemorrhagic complica-
tions was so allayed, that we acquiesced. He
has been on anticoagulants ever since with no
thrombotic complications nor any hemorrhagic
ones.

An interesting patient illustrated the fact
that Dicumarol may be extremely valuable in
situations where its use seems very dangerous.
He was 46 years old when we first saw him in
1944. At that time he gave a history of having
had rheumatic fever at the ages of 13 and 19
years, which had caused him no trouble until
the age of 45 when symptoms of heart failure
began. He also gave a history of having had a
peptic ulcer which began at the age of 30 but
had caused no symptoms for the five years
preceding our contact with the patient. He was
successfully treated for heart failure from 1944
until 1946 when his ulcer again became active.
Although partially disabled, he did rather well
until 1949 when he had the first of a series of
acute illnesses which were at first thought to be
severe upper respiratory infections. Between
1949 and March of 1951 he had seven severe
recurrences of a febrile illness accompanied by cough and diffuse radiographic density in the lungs. He had several minor episodes which were not recorded. In March of 1951 a particularly severe episode was accompanied by hemoptysis and a localized density in the lung which was typical of pulmonary embolism. This possibility had been considered on several previous occasions, but a satisfactory diagnosis had not been established. In March of 1951, because it was concluded that most, if not all, of these episodes had in fact been pulmonary embolism, he was placed on Dicumarol and maintained on it until January of 1953. During this time he had no recurrences of the acute febrile episodes associated with respiratory symptoms. On Jan. 8, 1953 he suffered a massive hemorrhage from the stomach originating in his gastric ulcer. He was brought into the hospital, treated for the hemorrhage and the anticoagulants stopped. The prothrombin ratio returned rapidly to normal as a result of several transfusions. His stools had become negative for blood by the end of the month. On February 13 he developed a pulmonary embolism with an acute febrile illness similar to those which he had had before anticoagulant therapy was introduced. Because of the obvious danger to the patient’s life, Dicumarol was started again and the prothrombin ratio maintained within therapeutic range. After it had been in therapeutic range for a week the stools again became positive for blood although there was no gross hemorrhage. At this time he began to complain of severe epigastric pain. Anticoagulant medication was continued and in spite of this the stools became negative for blood on February 26. They remained negative until March 1 when, because of the intractable ulcer disease, he committed suicide. It is almost certain that this patient’s life was prolonged by the use of anticoagulants although they were dangerous because of the ulcer and there were two episodes of hemorrhage, one of which was severe.

In one of the patients who had massive gastrointestinal hemorrhages no lesion could be demonstrated in the gastrointestinal tract by any of the usual techniques of examination. The patient who had gross hematuria was known to have had bilateral renal calculi for many years. He suffered a coronary thrombosis which was an extensive one in that he had mild, but real, objective evidence of some congestive heart failure. Even though he was on anticoagulant treatment and was within the therapeutic range of prothrombin time determinations, he suffered an embolic accident to the right leg about two and a half weeks after the onset of his coronary thrombosis. He had had microscopic hematuria for years but did not show any increase in this during his anticoagulant treatment for the acute phase of his illness. Again the difficult decision had to be made as to whether to advise the use of Dicumarol in an ambulatory fashion. It was felt that his cardiac reserve was so seriously reduced that if there was any hope of preventing a recurrence of myocardial infarction it was worth the risk. He was continued, therefore, on anticoagulant treatment successfully for about seven months when he had a gross hematuria for the first time. However, this was readily treated successfully, and the fact that his hemoglobin and red blood cell count were hardly altered by this episode suggests that he did not lose very much blood. However, the drug was stopped. He died a few weeks later at home, the cause of death being uncertain since he was found dead in the morning. The presumption was high, however, that he had another thrombotic episode involving either the coronary or the cerebral vessels. Of course, he could have had ventricular fibrillation, but this is not so likely as either of the other two entities.

An example of an embolic accident occurring during Dicumarol administration was the case of a 66 year old man who was hospitalized in September 1951 for an acute myocardial infarction and started on Dicumarol therapy. He was maintained with “ambulatory Dicumarol” after the initial convalescence with some difficulty, presumably because of his drinking habits. On Oct. 25, 1952, approximately one year after his myocardial infarction, he was re-admitted with a history of pleuritic type of right-chest pain which had developed suddenly 12 hours previously. Although there was no hemoptysis or cough, there was some dyspnea and fluoroscopy revealed a wedge-shaped shadow in the right anterior lobe of the lung where a
friction rub could be heard. The morning after this occurrence his prothrombin activity was still within the therapeutic range (46 per cent) where it had been for some weeks. There was no evidence of congestive heart failure, recurrent myocardial infarction, or any of the usual acute factors predisposing to intravascular thrombosis.

Some stubborn questions remain which have no easy answers: When should patients on long-term anticoagulant therapy discontinue their medication? Should patients with auricular fibrillation and embolic accidents ever have Dicumarol discontinued? How long after an acute myocardial infarction dare we stop ambulatory anticoagulant therapy, if it is to be stopped at all? Embolic accidents usually occur in patients with auricular fibrillation, either when the fibrillation is uncontrolled by digitalis or when there are other manifestations of congestive heart failure. Consequently, some of us have been willing to discontinue Dicumarol in such patients when both failure and auricular fibrillation were unequivocally controlled for periods of several months. Some evidence has been introduced to indicate that the likelihood of recurrence of a myocardial infarction falls considerably after the first two or three years, and it has been suggested that the life expectancy of a patient who is still ambulatory two or three years after a myocardial infarction approaches that of the rest of the population of the same age and sex. This gives us a logical basis for stopping anticoagulants in anyone who is ambulatory and essentially asymptomatic, except perhaps for occasional bouts of angina pectoris, sometime between two or three years after the initial episode. Because of the hazard which cold weather brings to these people, it would seem preferable to discontinue the drug in the late spring. This, of course, is still an arbitrary pattern based on slender evidence which is an effort to compromise with those who would continue ambulatory anticoagulant therapy indefinitely and those who never use this form of treatment. There is a difference of opinion among the authors on this point but complete agreement on the wisdom of using these drugs in selected ambulatory patients for varying lengths of time.
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