SYMPOSIUM ON CORONARY HEART DISEASE

The Use of Anticoagulants in Coronary Heart Disease
Progress and Problems: 1960

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While anticoagulants in the treatment of coronary heart disease are now widely accepted throughout the civilized world and they are used daily in the treatment of many thousands of patients, some problems relating to their use still remain to be resolved. The purpose of this paper is to review some of these problems and to suggest methods by which they may be met. It is not necessary to present new evidence for the use of anticoagulants in the treatment of myocardial infarction. The original findings of the Committee on Anticoagulants of the American Heart Association have been confirmed by workers in many countries on both sides of the Iron Curtain. Cardiologists and internists as well as many well-trained general practitioners carry out anticoagulant therapy satisfactorily. Treatment is easier with the patient in a hospital, but is possible while the patient is home provided accurate laboratory facilities are readily available. The question whether it is desirable to give all patients with acute myocardial infarctions anticoagulant therapy is one that each physician must decide for himself. Most leading cardiologists state that they are unable to differentiate during the early stages of an attack between patients who will continue as "good risk" and those who will become "bad risk" patients. The result of not administering anticoagulants to some of the so-called "good risk" cases has too often been the development of severe complications of a thromboembolic nature. Under most circumstances anticoagulants are given if clinical and laboratory facilities are readily available.

The Technic of Therapy

There are many anticoagulants available for use by the physician. Heparin still remains the choice when rapid anticoagulant action is desired. Usually it is given in dosages of 75 to 100 mg. intravenously or subcutaneously. (U.S.P. XVI minimum potency is proposed as 120 units per mg.) Intravenous action is somewhat more rapid but results in a brief but marked prolongation of the clotting time with restoration to normal within 4 to 8 hours or less. Subcutaneous or intramuscular injections of heparin are now widely used in dosages of 75 to 100 mg. given at intervals of 8 to 12 hours, depending on the clotting time. In some areas heparin is used throughout the acute stages of the attack. The Lee-White clotting time, although a crude test, still remains the choice for the control of heparin administration. It is desirable that the clotting time, which may increase to 3 or 4 times the control level, return to approximately twice the control time just prior to the next injection. For example, if the clotting time by the test performed is normally 8 minutes, a test performed prior to the next injection should not be shorter than approximately 16 minutes. If it is shorter, it indicates that the time space between the 2 injections should be decreased or the dosage increased. If it is much longer than twice normal, the time spacing should be spread in an effort to avoid overdosage. Many physicians now give from 1 to 4 doses of heparin during the initial period of anti-
coagulant therapy for myocardial infarction. There is, however, little valid evidence that this is necessary in patients who are not obviously very ill at the time. Given at intervals of 24 hours or more, it has not proved successful. The long-acting preparations of heparin are used less frequently than formerly. Sublingual or oral administration of heparin is of no value for anticoagulation.

Coumadin (Warfarin sodium, Liquamar (phenprocoumon), Dicumarol (bishydroxycoumarin), or phenylindanedione are usually started at the same time the heparin is begun. All these anticoagulants and other equally effective derivatives of similar compounds are now in common use. They should be administered in an initial large dose. The second day the patient should receive approximately one half the starting dose and thereafter the dose that is considered to be average for the drug. By this time the prothrombin time will be found to be prolonged; with daily determinations of prothrombin times, it is possible to establish a stabilizing dose. The most satisfactory initial dose of coumadin is between 35 and 45 mg. daily, and the second dose 15 to 20 mg. Beginning with the third day the patient receives 5 to 10 mg. daily. For Liquamar the initial dose is usually 15 to 21 mg., the second dose 9 to 12 mg., and the daily dose thereafter 3 or 6 mg. When the effect of the prothrombin time is considered to be at therapeutic levels, heparin is discontinued. A satisfactory prothrombin time should be between 1½ and 2 times the normal control prothrombin time. For example, if the control prothrombin time is 15 seconds, the treatment level should be between 22.5 and 30 seconds, preferably dividing this figure about in half (26 or 27 seconds).

The contraindications have been reported many times, and must be well understood by all who prescribe anticoagulants. Occasionally the physician is confronted with the fact that his patient has had a duodenal ulcer and may even have suffered a hemorrhagic episode in the past. This presents a calculated hazard, but it is usually more likely that the patient will die or suffer severe complications from his myocardial infarction than from the duodenal ulcer, which may have been relatively quiescent for months or even years. Under such circumstances, antacid or neutralizing preparations are administered and the patient receives an ulcer diet. He is carefully watched for evidence of bleeding, but otherwise anticoagulant therapy is carried on in the usual manner. Many other examples might be given in which special care is essential.

The Value of Long-Term Anticoagulant Therapy

Once the value of the administration of anticoagulants during the first month after an acute myocardial infarction was well established, the question arose as to how long anticoagulant therapy should be continued. Series of cases were compiled to evaluate the effect of continued treatment on the complications or on the longevity of patients who had suffered one or more myocardial infarctions. Many reports have appeared, notably by Nichol,3 Borg, Keyes, Drake, and Smith4 Tolloch,5 Askey,6 Waaler,7 Suzman,8 Owren,9 and Manchester.10 These studies have been developed in a variety of ways, and some have justifiably been criticized from a strictly statistical viewpoint. The consistency of their results could not be ignored, however, and as the results accumulated they presented fairly strong evidence in favor of long-term anticoagulant therapy. Friedberg11 recently compiled a table that included in summary the sum of 2,253 control cases and 735 treated cases. The mortality for the treated cases was consistently reduced to between one third and one quarter of that of the control cases and the recurrences of myocardial infarction to between one quarter and one sixth of the control cases.

One of the more comprehensive studies was that reported by Bjerkelund12 of Oslo, Norway, in a comprehensive monograph based on experience with 251 patients in a well-controlled clinical trial. With patients under 60 years old on long-term treatment with Dicumarol, he found a statistically significant reduction both in the incidence of recurrent infarction and in the mortality during the first 12 months after an acute infarct. The
incidence of recurrent infarction and mortality in patients over 60 years of age during the first 12 months was also considerably lower in the treated than in the control group, but the difference was not statistically significant. Attacks of severe retrosternal pain in which the presence of recurrent infarction was suspected but not verified were observed about half as frequently in the treated group as in the control group. The morbidity from cardiovascular disease judged by the frequency and duration of admission to hospitals during the observation period was considerably lower in the treated than in the control group. Severe heart failure developed less often in the treated than in the untreated group. The electrocardiogram returned to normal more often after the recorded infarct in the treated than in the control group. The evidence of thrombosis in the coronary arteries shown at autopsy was significantly lower in the treated than in the control group. In his investigation as a whole, treatment during the observation period resulted in a reduction of the incidence of recurrent infarction by about 45 per cent and in the mortality from cardiovascular diseases by about 37 per cent. Because of the less striking effects of anticoagulants after the first 12 months, he raised the question whether it would not be advisable to consider discontinuing therapy at the end of 12 months. Our experience\textsuperscript{13} and also that of Owren,\textsuperscript{14} however, has demonstrated a rather sharp increase in thromboembolic complications following cessation of treatment; therefore, this should be undertaken with considerable hesitancy and caution. This position has been recently confirmed in a report by Sise and his co-workers.\textsuperscript{15}

The most recent comprehensive study of this nature was published in a report of the working party of the British Medical Research Council entitled "An Assessment of Long-Term Anticoagulant Administration after Cardiac Infarction."\textsuperscript{16} This Committee was headed by Sir George Pickering and was made up of outstanding cardiologists. It functioned under the critical statistical guidance of Dr. D. D. Reid of the London School of Tropical Medicine. Cases were studied in 15 of the leading medical institutions of Great Britain. The purpose of the investigation was to determine whether long-term anticoagulant therapy following myocardial infarction is worthwhile. This report is commended to the reader for detailed study. The analysis was based on experience with 383 patients who had recovered from the acute phase of a cardiac infarction of defined severity and who were thereafter divided in an unbiased selection into "high dosage" or "treated" and "low dosage" or "untreated" groups. Actually the "low dosage" or "untreated" group did receive one milligram of phenindione per day, a token dose that had no measurable effect on the coagulation of the blood. The "high dosage" group received the amount of phenindione necessary to affect the clotting mechanism properly for therapeutic purposes. The conclusions at the end of 2 years were as follows:

1. Although the death rate was higher in the low dosage series there is just the possibility that the difference could have occurred by chance. No difference was apparent in females but the numbers were too small to exclude such a difference.

Actually the death rate decreased one third in men, from 18 to 10 per cent. This is approximately of the same order as the decrease in the death rate during the first month of therapy originally reported by the Committee on Anticoagulants of the American Heart Association,\textsuperscript{1} and it also corresponds with the decrease in death rate of one third following the use of anticoagulants for thrombotic strokes as reported by Groch, McDevitt, and others from our laboratory.\textsuperscript{17} Thus, it seems that the thrombotic tendency in both these conditions produces about one third of the subsequent deaths and that if this is successfully prevented, one can anticipate a mortality decrease in approximately that amount.

2. When the infarcts serious enough to cause permanent withdrawal from the trial were added to deaths as a combined index from prophylactic failure, there was a significant reduction in their frequency among the males receiving high dosages, and there was a suggestion of better result in males under the age 55.

3. The same trends appear even more clearly
when the total reinfarction rate is used as a basis of comparison. Under the age of 55 males on high dosage suffered recurrent infarction at only one-fifth of the rate of those on low dosages. These differences are statistically significant.

4. The proportionate reduction in the risk of reinfarction achieved by the high dose regimen is slightly greater among patients with a previous history of one or more infarcts, but the difference is not statistically significant.

5. The difference in the death rate is most evident in the first six months of the follow-up period, but the disparity and the reinfarction rate is maintained for at least two years in the follow-up period.

Two years was the duration of the study up to the time of the report, so that information regarding what may have happened after that was not included.

6. More men given the higher dosage returned to work during the period and they were more often free from angina.

7. There were 15 withdrawals from the high dosage series because of the onset of conditions actively or potentially associated with hemorrhage. Four major cerebral vascular accidents, three causing withdrawal and one death were reported among the high dosage series. Only one patient on low dosage suffered a cerebral hemorrhage, but embolism was a major complicating feature in the terminal illness of three of them. There were 48 minor hemorrhagic incidents in the high dosage group compared with eight among those on low dosage.

These studies have been compared with studies previously reported and were found in close agreement in many respects. As has been pointed out, there is an apparent decrease in the benefits after the first year although benefits are measurable in subsequent years. This has not been reported in all series, but there is an explanation for its occurrence and it may be expected. A certain selection takes place as more of the control cases die. The anticoagulant therapy keeps alive an increasing number of what might be termed "border-line" patients. The "control" group gradually loses these by death, and, therefore, is made up of patients who might be considered those with the best natural prognosis. The "treated" group accumulates the corresponding patients by keeping them alive and, therefore, the series becomes increasingly weighted against the "treated" group. These patients will begin to die at a later date as their atherosclerosis progresses and from other complications, but it is well worthwhile to keep them alive for 2 to 5 years or longer if possible, as it now seems to be. One may conclude that the value of long-term anticoagulant therapy following myocardial infarction is now reasonably well established.

The main challenge that confronts us at present is the provision of such service to patients on a large scale. This is a matter of considerable concern to all, but especially to the British Medical Research Council because of the responsibility to provide care under the National Health Act. It does raise a serious question about the number of patients who might be expected to benefit and therefore to require this form of treatment. A. S. Douglas,18 Secretary of the Working Party Committee, has reported a survey of patients who might require or be deserving of anticoagulant therapy. Strictly on the basis of coronary artery disease and without consideration for the other indications for long-term anticoagulant therapy, it was determined that 1 per 380 of the population, including all from infancy to old age, had suffered an infarction within the previous 2 years and was still alive, and an additional 1 per 170 was suffering from angina. One in a hundred of the population might be a candidate for long-term anticoagulant therapy. If only the population over 40 years of age was considered, the number of candidates was 1 in every 35 of the population. Based on these figures, he concluded, that there were in the population in the west of Scotland, about 30,000 patients to be treated. Similar figures were developed for Scotland, England, and Wales, which amounted to approximately 500,000 persons. On the basis of cost it was estimated that this would amount to something in the neighborhood of 6 million pounds during the first year. In terms of American currency, this would be $16,800,000. If this were to be thought of in terms of the United States, it would be necessary to include consideration of the vastly greater population and also the
greater distances involved. In addition, in neither country are there sufficient technicians, well-trained physicians, or laboratory facilities available to carry out such a program. These figures do not have complete validity, since many of the patients because of contraindications, inconvenience, temperamental unsuitability, and other reasons could not be introduced into such a program. Nevertheless, the magnitude of the problem and the need for planning for the future become obvious. This should be of increasing interest not only to practicing physicians but also to public health officials, since the public health services could well play a leading role in providing better standardization of laboratory tests and in the training of technicians. It is a major challenge to the medical-school faculties. No longer should physicians be graduated without a sound understanding of the basic principles of anticoagulant therapy.

Anticoagulants in the Treatment of Angina

Another facet of this interesting problem is the question whether patients should be given anticoagulant therapy who are suffering from angina without having had definite evidence of myocardial infarction. This will be made the subject of additional study by the Working Party Committee. Reports by Owen,19 Beamish,20 Nichol,21 and others indicate that the death rate of patients on anticoagulant therapy because of angina due to coronary artery disease is approximately one half of those not on anticoagulant therapy over a period of years of observation. This possibility is certainly worthy of further careful study, since true angina is undoubtedly of serious importance to very large numbers of patients. The Working Party of the Medical Research Council is interested in such a study. However, the determination of criteria for angina due to coronary artery disease is fraught with considerable difficulty and in itself will constitute an engaging study.

The Use of Anticoagulants during Surgical Procedures

A question that frequently arises in the course of long-term anticoagulant therapy is whether it is safe or advisable to proceed with surgery while the patient is on anticoagulant therapy, or whether it is necessary to discontinue the anticoagulant prior to the surgical intervention. This has become more sharply focused by the reports of Carter and others13 from our laboratory and also of Siso15 and his co-workers from Boston, which indicate that cessation of anticoagulants is associated with increased risk of thromboembolism. We have seen several patients who, when anticoagulants were discontinued for such minor procedures as tooth extraction, developed serious complications such as permanent hemiplegia within a few days. Therefore, one should not discontinue anticoagulants in patients who have previously shown a definite thromboembolic tendency without good and sufficient reason. The reason for this increase in thromboembolic episodes, especially during the first 6 weeks to 3 months after discontinuing anticoagulants, is not fully understood. It has been rather loosely termed a "rebound phenomenon," suggesting that following cessation there is actually an increase in the tendency to thrombosis of the blood. This has been difficult to substantiate by means of careful laboratory tests for many clotting factors. Another factor may play a leading role.

While the long-term anticoagulant therapy does decrease the frequency of thromboembolic complications, it is not believed that it affects the progression of the deposition of cholesterol and lipid plaques in the pathogenesis of atherosclerosis. Therefore, with the passage of time more and more narrowed arterial channels develop. These would, in the normal course of events, be subject to early thrombotic closure, but when the blood is under the influence of anticoagulants, these narrowed and often roughened surfaces do present areas in which clotting may take place easily. Thus, instead of a "rebound phenomenon," one might more correctly consider this as a "catching-up process," in other words, a process by which the natural course of the combination of atherosclerosis and thromboembolism which has been delayed by anticoagulants catches up to the status that would
have been reached if they had not been used.

It has now been clearly demonstrated that major surgery can be conducted successfully with the patient on anticoagulant therapy. Storm and Hansen have reported series of patients who have had major cardiac and pulmonary surgery, even lobectomy. I had the pleasure of seeing the first 2 patients in whom Storm had performed aortic graft replacements while they were on active anticoagulant therapy. In this country, Miscall has now compiled a series of over 100 patients on whom he has performed mitral commissurotomy while they were on anticoagulant therapy. While there has been some increase in bleeding, there has been a marked decrease in the incidence of thromboembolic complications following this procedure as compared with a controlled series. It is not the purpose of this paper to evaluate the importance of this type of surgery, but rather to point out that its feasibility has now been demonstrated if the surgeon uses proper and more complete hemostatic technics. Certainly this experience suggests that one may be justified in maintaining patients on anticoagulant therapy during minor surgical procedures. We do not discontinue anticoagulants for the extraction of teeth at the New York Hospital at present. Dr. Behrman has compiled a series of more than 75 patients on anticoagulant therapy from whom he has extracted teeth without any difficulty whatsoever. These have included extractions of simple uncomplicated molar extractions, 6 teeth from 1 patient, molars with abscesses, and in 1 case 4 teeth were removed with bone trimming. Our general plan is to have the prothrombin time approximately 1½ the normal control for such procedures. While the use of this technic for major surgery is still being evaluated more completely, the risk of discontinuing anticoagulant therapy may force the issue and result in more patients being operated on during it.

**Relationship of Drugs to Anticoagulant Therapy**

It has been repeatedly emphasized that the administration of large amounts of salicylates to the patient on anticoagulant therapy may greatly prolong the prothrombin time and occasionally lead to hemorrhage. The chemical relation of salicylates to the coumarin compounds may augment their action on the prothrombin complex. In addition, the use of certain of the gut-sterilizing antibiotics such as chloramphenicol, chlortetracycline hydrochloric acid, and some of the urinary antiseptics such as sulfasoxazole and nitrofurantoin may result in marked changes in the prothrombin time. It is believed that these drugs may interfere with the production of vitamin K by changing the bacterial flora of the gastrointestinal tract. This needs further study. However, when these or other drugs are administered to the patient on long-term anticoagulant therapy, he should have more frequent prothrombin times and the physician should be alerted. The patient should be instructed regarding this risk because he may take these drugs on his own or on the prescription of another physician who may not be aware of the details of his anticoagulant therapy. Phenobarbital has also been shown to have an effect on anticoagulant therapy.

This consideration points up the importance of training each patient who is to go on anticoagulant therapy regarding various events that may be of new significance to him such as acute intestinal disturbances, alcoholic debauches, serious infections, and the use of drugs as mentioned above. If he is alerted to these factors, he may be more intelligent in his own approach to his regimen and in discussing it with other physicians whose services he may require.

**Increased Understanding of the Clotting Mechanism**

Today the most widely used prothrombin test still remains the Quick test with various modifications. This 1-stage test has been used as a guide in the treatment of many tens of thousands of patients and has served the purpose well. There are individuals who are more difficult to control or sensitive to anticoagulants. For them, more detailed studies of the various factors involved in the clotting mechanism are required. As a result of work in many laboratories a greater understanding
has been developed of the clotting mechanism and of the effect that anticoagulants of the coumarin and phenylindanedione type exert on certain factors beside prothrombin. The Quick 1-stage test not only measures factor II (prothrombin) but also factor VII (proconvertin) and factor X (Stuart-Prower) ac-globulin, and factor V to a lesser degree. Changes in factor VII, which generally precede those in the prothrombin activity, may be of the greatest importance in the therapeutic effect of anticoagulants of the coumarin or indanedione families. Factor IX may play some role in this anticoagulant action, and factor X also has a later effect. It is probable that other undiscovered factors also are active in this process. Changes in the less well recognized factors may result in unexpected episodes of bleeding or thrombosis when the patient is on apparently satisfactory anticoagulant therapy from the viewpoint of the prothrombin complex 1-stage test (Quick) alone. Therefore, other more sensitive tests have been developed. The Link-Shapiro modifications of the Quick test, especially with the use of a 12.5 per cent solution, results in a more sensitive determination of the effect of anticoagulants on the blood clotting mechanism. Owren has previously reported his work with the now widely used P and P test and has now developed a new method for the control of anticoagulant therapy, which is known as the "thrombotest."25 The theory upon which this test is based is as follows:

The normal clotting of the blood occurs through partly separate systems called the "intrinsic and extrinsic coagulation systems." Clotting factors of the first system are all present in the circulating blood. These consist of factor II (prothrombin), platelets, the Hageman factor, factor VIII (antihemophilic factor A), factor IX (antihemophilic factor B), antihemophilic factor C, factor X (Stuart-Prower factor), factor IV (calcium), and factor V (proaccelerin). The coagulation is initiated by contact with foreign surfaces. It takes several minutes depending on the type of surface.

The extrinsic system is initiated by tissue fluid containing thromboplastin. This includes tissue factor III (thromboplastin), factor VII (proconvertin), factor X (Stuart-Prower factor), calcium, and factor V (proaccelerin).

In the presence of an active tissue thromboplastin, blood clots in only 12 to 15 seconds and the activity of the slower intrinsic system cannot be detected under these conditions. During anticoagulant treatment with Dicumarol-like drugs, both the intrinsic and extrinsic coagulation systems are depressed; the former through reduction of factor IX (?), the latter through reduction of factor VII. Reduction of factor X and prothrombin influence both systems. Owren states that the new method includes a combined determination of all 4 factors that are depressed by the anticoagulant treatment. This new preparation consists of crude cephalin prepared by extraction of human brain or soybean, a thromboplastin prepared from animal organs, for example, ox or horse brain, absorbed bovine plasma that has been freed completely of the 4 factors, and calcium chloride in optimal concentration. All these ingredients are mixed into one reagent that is lyophilized and kept in vacuum in sealed ampoules. It is reconstituted with distilled water for testing in capillary blood and with weak calcium chloride solution for testing of citrated blood or plasma. The final reagent is opaque because cephalin and thromboplastin are insoluble in aqueous media and form a fine suspension. This material lyophilized and vacuum-sealed will keep for 12 months at room temperatures. The activity is unchanged after storage for 30 days at 47 C. After reconstitution the activity is constant for 12 hours at room temperature and for 3 days at 6 C. If the reagent is stored overnight in the ice box, it should be well mixed for further use. According to Owren, this material can be used for both capillary and venous blood and for citrated plasma. This technic constitutes a serious effort to provide the medical profession with a somewhat more comprehensive test that may prevent some of the hitherto unexplained complications of anticoagulant therapy. It is now under evaluation in many laboratories throughout the world.

Organization for Providing Long-Term Anticoagulant Therapy

It became clear some years ago that in order
to provide adequate and comprehensive anticoagulant therapy in large hospitals, a team should be developed consisting of members who are thoroughly versed in the intricacies and the possible complications of anticoagulant therapy. Therefore, the Long-Term Anticoagulant Clinic of the New York Hospital was established in 1946. It was at first integrated with the Vascular Clinic, but soon outgrew this status and since 1950 has operated as a separate unit with overlapping interests and staffs. Dr. Ellen McDevitt has served as Chief of this clinic at the New York Hospital as well as a similar one at Bellevue Hospital since 1951.

The present organization structure (table 1) is as follows: Most of the patients on the hospital service who require anticoagulant treatment start this therapy while hospitalized for a thromboembolic state. They may be in the wards, semi-private, or private sections of the hospital. If any problem arises in the care of these cases, or if it is decided that long-term anticoagulation is desirable, the Anticoagulant Consultation Service is notified. With private patients this consultation is at the option of the patient’s physician. Members of this service visit the patient, consult with the resident staff regarding a desirable regimen, and, if necessary, follow the patient, arranging for him to attend the anticoagulant clinic after leaving the hospital. A private patient may wish to continue with his own physician or if he and his doctor so elect, the control of his anticoagulant treatment may be assigned to a member of the anticoagulant staff in private practice. These patients may originally be seen on any service in the hospital. They may on occasion be started on anticoagulant treatment without previously being hospitalized if the indications seem clear. Patients who become part of the study group are assigned to the Long-Term Anticoagulant Clinic where they are seen at weekly intervals by a staff especially trained in this work. Some very stable patients are seen at intervals of 2 or even 3 weeks. If an anticoagulant therapy, their prothrombin tests are checked at these visits. As time goes on, each patient’s regimen evolves into 1 of 3 patterns. If he requires continuous therapy and his anticoagulant control is not difficult, and if he is not a part of some special group under investigation at the time, he is transferred to the General Medical Clinic for continued care. This decreases the ever-growing

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pressure on the Anticoagulant Clinic and it broadens the training of both students and other physicians in this technic. However, a member of the Anticoagulant Clinic is in constant attendance at the medical clinic to act as consultant and instructor and to handle any difficulties that may arise. If the patient proves difficult to control or has a condition that is under investigation, he remains assigned to the Anticoagulant Clinic under close supervision. If, as often is the case with thrombophlebitis, with a passage of a few weeks it is decided that anticoagulants should be discontinued, the dosage is gradually decreased and his anticoagulant care is terminated. He is then seen less frequently.

All patients are carefully catalogued. The natural history of these diseases is a major interest so that all patients are kept under surveillance and are included in the research and teaching program. This study also includes many patients treated for thromboembolic conditions by practicing physicians who are members of the staff. The Anticoagulant Clinic patients have their blood drawn on Tuesday mornings. About two thirds of them receive their dosage schedules for the next week or two before they leave the clinic. The others telephone Tuesday afternoons to receive their instructions. The same general routine is followed for private cases. It is important that each clinic and each physician undertaking anticoagulant therapy provide a 24-hour emergency service. Someone must always be on call. These patients are afflicted with diseases that frequently strike suddenly and brook no delay in medical care. Without anticoagulants, the stroke, myocardial infarction, or pulmonary embolus requires immediate attention regardless of the hour. While the use of anticoagulants reduces the risk of thromboembolic complications, it does introduce the need for a physician to be available at all times to advise regarding hemorrhagic manifestations. All patients carry a card of identification (fig. 1) obtained from the American Heart Association. It indicates that they are on anticoagulants and also gives the name, address, and telephone number of their physician or clinic. In addition, they are provided with a small supply of vitamin K1, 5-mg. tablets. In the event of any major bleeding, they are instructed to take 2 of these tablets and call the doctor. This has been found to be a practical way of inaugurating early treatment, since hours may elapse before the doctor sees the patient.

It has been found most useful for the anticoagulant team to have conferences with the resident staff to review the technics used. An important conference is held during the first week of July when the new interns and residents first joint the staff. The meeting helps to develop uniformity of technic and a better liaison between the resident staff and the anticoagulant staff. The incidence of preventable complications has thus been markedly reduced.

Conclusions

1. The use of anticoagulant therapy in the treatment of acute myocardial infarction is generally accepted.

2. It should be used in most cases except...
when contraindications or lack of facilities exists.

3. Heparin may be used in the initial stages of anticoagulant therapy, especially when there is need for rapid action.

4. The evidence now strongly favors long-term anticoagulant therapy after one or more myocardial infarctions in men. The evidence for its use in women is less conclusive but the available figures are too small for final evaluation.

5. The provision of adequate long-term anticoagulant care for those whose condition justifies its use is becoming a major social, economic, and technical problem. This is a challenge for the medical profession, the clinical pathology societies, the medical schools, and the public health services.

6. Evidence is accumulating that anticoagulant therapy favorably affects the incidence of morbidity and death in patients who suffer from angina pectoris due to coronary artery disease. Further studies are needed in this area.

7. It is possible to perform safely minor and even some major operations while patients are maintained on anticoagulant therapy. This reduces the risk of thromboembolic complications.

8. Patients on anticoagulant therapy should be given instruction regarding the effects of salicylates, antibiotics, other drugs, excessive alcohol, and various illnesses on the prothrombin activity.

9. The Quick 1-stage test carefully performed is satisfactory for most cases. However, many patients are sensitive, resistant, or otherwise difficult to control with anticoagulant therapy and for these more sensitive tests are indicated.

10. It is advantageous for hospitals to set up anticoagulant services in order to make available special knowledge regarding the problems that arise from this type of treatment and to help in obtaining maximum benefits from it.

11. An operating plan is presented as it functions at the New York Hospital. It is hoped that this will prove helpful to institutions considering the development of such a program.

**Summario in Interlingua**

1. Le uso de therapias anticoagulante in le tractamento de acute infarimento myocardial es generalmente acceptate.

2. Therapias de ille genere debe esser usate in le majoritate del casos, excepte in le presentia de contraindicaciones o quando le requirite equipamento non es disponibile.

3. Heparina pote esser usate durante le stadios initial del therapia anticoagulante, specialmente quando un action rapide es indispensabile.

4. Le datos usque nunc colligite argue fortemente in favor del uso prolongate de therapia anticoagulante post un o plure infarimentos myocardial in masculos. Le situation es minus clar pro femininas; le casuistics non es satis extense pro permitter un evaluation definitiva.

5. Le provision de adequate servicios de anticoagulantes a long vista pro le subjectos in qui su uso es justificate deveni gradualmente un major problema social, economic, e technic. Isto es un situation que demanda le attention del profesion medical, del societates de pathologia clinic, del scholas medical, e del servicios de sanitate public.

6. Le indicationes se accumula que le therapia anticoagulante affice favorabilmente le incidentia de morbiditate e morte in patientes qui sufre de angina de pectore per morbo de arteria coronari. Studios additional es requirite in iste area.

7. Il es possibile interprendere salvemente operationes minor e mesmo major durante que le patiente se trova sub therapia anticoagulante. Isto reduce le riso de complicationes thromboembolic.

8. Patientes sub therapia anticoagulante debe esser instruite con respecto al effectos de salicylatos, antibioticos, altere drogas, alcohol in excesso, e varie maladies super le activitate de prothrombina.

9. Le test uniphasie de Quick, si executate meticulosemente, es satisfactori in le majoritate del casos. Tamen, multe patientes es hypersensible, resistente, o alteremente difficile a regular per medio de un therapia anticoagulante, e in tal casos metodo plus raffinate es indicate.

10. Il es avantajose pro le hospitales establir servicios anticoagulante pro dispensar informationes special con respecto al problemes que resulta ab ilte typo de tractamento e pro assecutar le obtention de beneficios maximal ab illo.

11. Un plano de organisation es presentate como illo es in function al Hospital New York. Es sperate que isto va esser de valor pro institutiones que desira prender in consideration le elaboration de un tal programma.
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