ANTICOAGULANTS IN MYOCARDIAL INFARCTION

BY

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The use of anticoagulants in the treatment of myocardial infarction has greatly increased in recent years, and practically all reports have acknowledged their value. It has usually been accepted that anticoagulant therapy reduces the mortality rate in myocardial infarction by as much as a third or a half. The only serious argument in recent times about the value of anticoagulants has been whether these drugs should be used in so-called "good-risk" cases as opposed to "bad-risk" cases. Russek and Zohman (1957) define bad-risk patients as those with a history of previous infarction, who have intractable pain, extreme or persistent shock, significant cardiac enlargement, arrhythmia, or diabetic acidosis.

Russek and Zohman have been the principal proponents for the limited use of anticoagulants—that is, for giving anticoagulants to bad-risk patients only. They have shown that the mortality rate in good-risk patients, even without the use of these drugs, is very low—3.3% in a review of 1,000 cases (Russek and Zohman, 1957)—and they therefore consider that the value of anticoagulant therapy for these patients is questionable, especially as the use of anticoagulants is not without risk. Wright (1957) and many other authorities, whilst agreeing that good-risk cases have a low mortality, believe that these cases can be determined only in retrospect—that is, good-risk patients often rapidly become bad-risk patients—and therefore they advise the use of anticoagulants for all patients with cardiac infarction, unless there is some special contraindication to their use.

Russek and Zohman, whilst denying the value of the routine use of anticoagulants for good-risk patients, state that "the value of anticoagulants in properly selected patients—those with poor prognostic signs—constitutes a major advance in the treatment of acute myocardial infarction." Therefore, in view of the widely accepted opinion of the value of anticoagulants, at least for all bad-risk patients, the report by Honey and Truelove (1957) is most surprising. These authors state that the use of anticoagulants at the Radcliffe Infirmary at Oxford has not made a dramatic difference to the mortality rate in cardiac infarction, and that anticoagulants have saved lives solely by abolishing the risk of pulmonary embolism.

Honey and Truelove show in their detailed analysis of patients with myocardial infarction admitted to the Radcliffe Infirmary that there appeared to be a definite bias in the selection of patients for treatment with anticoagulants, and that a high proportion of bad-risk patients were not treated. At New End Hospital I have for many years considered the diagnosis of myocardial infarction to be a specific indication for the use of anticoagulants and have for some time been of the opinion that there is very seldom any contraindication. I believe, therefore, that it is of value to compare in detail the results of Honey and Truelove's series with mine, and that the effect of this comparison is to render their conclusion that anticoagulants are of little value in the treatment of myocardial infarction questionable.

This comparison is perhaps of particular importance in view of the editorial comments in the *Lancet* (1957) supporting the views given as a result of the review of cases treated at the Radcliffe Infirmary.

Sources of Data

All patients in the New End series were under my care and were admitted to hospital between 1951 and 1957. In all cases the diagnosis was confirmed by electrocardiograph or at necropsy. Honey and Truelove, in reviewing their 543 admissions, state that no fewer than 75 out of the total 195 deaths (38%) occurred in the first 48 hours after admission. They say: "This reflects the fact that the Radcliffe Infirmary receives a large proportion of its patients as acute emergencies soon after the actual infarction. (The results obtained in different hospitals are difficult to compare because of differences in the proportion of patients admitted in the earliest and most dangerous stage of the disease.)"

Between 1951 and 1957, 326 patients with proved myocardial infarction were treated with anticoagulants at New End Hospital. In this group there were 67 deaths. The early deaths in the first 48 hours were 26 (38%), which is the same as at the Radcliffe Infirmary. However, to show how severely and seriously ill the patients admitted to New End Hospital are, I should add that there were in this period a further 52 patients admitted with infarction, all of whom died within 24 hours and of whom all but a few died within a few hours of admission—that is, too soon for a definite diagnosis to be established and for the patient to receive anticoagulant therapy. Therefore 65% of the deaths at New End Hospital in the period under review occurred in the first 48 hours—that is, nearly twice as high a percentage as in the Radcliffe series. Not one patient was denied treatment because of any specific contraindication. This, I believe, rules out any question of bias in the selection of patients for treatment.

Age Comparison.—Honey and Truelove rightly demonstrate the well-known fact that in each sex the fatality rate increases with advancing years. Table I shows the composi-

TABLE I

Age in Years	No. of Patients	
	New End	Radcliffe
<40	8	10
40—	37	71
50—	69	149
60—	111	179
70—	80	115
80+	21	19
	326	543

tion in terms of age of the Radcliffe and New End series. It is seen that the New End series contains a higher proportion of patients in the older age groups. In the 70- and 80-year-old group, in which the mortality in untreated patients is particularly high (from 50 to 80%), the percentage of patients in the New End series is 30.9% compared with 24.6% in the Radcliffe series.

Comparison of Factors Affecting Prognosis in the Acute Attack

Before we can try to compare the results of anticoagulant therapy in the New End series of 326 treated cases and the Radcliffe group of 110 untreated cases it is essential, as Honey and Truelove state, that the various factors affecting prognosis be carefully compared in both groups—that is, that the proportion of good- and bad-risk cases in each group be carefully taken into account.

The percentage of good-risk patients in the untreated group of 110 patients in the Radcliffe series was 24.5%, while in the New End series it was 25.7%.

In assessing the various factors associated with a bad late prognosis so as to compare the Radcliffe and New End series, I have included in the bad-risk group only those patients with definite unequivocal signs related to a poor prognosis as mentioned by Honey and Truelove. I have

already shown that there is a very high proportion of patients in the earliest and most dangerous stage of the disease admitted to New End, with a rate of early deaths to late deaths nearly twice as great as in the Radcliffe series. The age composition of the two series is seen in Table I. Finally, Table II shows the proportion of patients with cardiac

TABLE II

	New End		Radcliffe	
	No. of Patients	%	No. of Patients	%
Heart failure	114	38	143	30.5
Arrhythmia	107	35.6	83	17.7
Shock and hypotension ..	35	10.7	41	7.7
Shock or hypotension ..	78	24	71	13

failure, arrhythmia, shock, and hypotension in both series. It can be seen that the percentage of patients with heart failure is much higher in the New End group—38% as compared with 30.5% in the Radcliffe group. Similarly the percentage of patients with arrhythmia in the New End series was considerably greater—35.6% compared with 17.7%.

If all the factors mentioned by Honey and Truelove in assessing good- and bad-risk patients are taken into account a valid comparison may be made between the Radcliffe and New End series, bearing in mind that all patients in the New End series were treated and that there was no bias in the selection of the patients. The late mortality rate—that is, excluding deaths in the first 48 hours—in the Radcliffe series of 110 untreated cases was 28.3%, while in the New End series it was only 13.6% (Table III). The expected mortality

TABLE III

	New End	Radcliffe
Total No. of patients	326 (treated)	110 (untreated)
Early deaths in first 48 hours ..	26	18
Late deaths	41	26
Late mortality rate	13.6%	28.3%
Good-risk patients	25.7%	24.5%

rate of the New End series, based on Honey and Truelove's calculations, was 27.8%, taking into account that the percentage of good-risk patients was 25.7%.

These results do not bear out the conclusion of Honey and Truelove that anticoagulants have little effect in reducing the mortality rate in acute myocardial infarction. The results shown here, where the expected death rate is reduced by half, is in keeping with most published results from authorities experienced in the use of anticoagulant therapy.

Control of Anticoagulant Therapy

The control of anticoagulant therapy, even to-day, with all the experience gained over many years, is not simple. For proper control it is essential for the clinician to be fully experienced in the use of anticoagulant drugs and to be conversant with the laboratory procedures. Only good team-work can achieve the best results: by best results is meant not only the avoidance of haemorrhage but, just as important, the achievement of an adequate therapeutic cover. In order to avoid the danger of haemorrhage the importance of maintaining adequate anticoagulant therapy throughout the illness is often overlooked.

Adequate laboratory control is essential for the proper maintenance of anticoagulant therapy. Perhaps the greatest single factor in effective laboratory control is the preparation of an active and reliable thromboplastin which gives constant times with normal control plasma. Quick's prothrombin time, using a reliable thromboplastin, has stood the test of time and gives very reliable results. However, with the simultaneous use of Quick's, Owren's (Owren and Aas, 1951), and Ware's modification of Owren's technique (Ware and Stragnell, 1952) in over 2,000 estimations for in-patient therapy, I have found Owren's method superior to the others (Toohey, 1958).

Choice of Anticoagulant Drug

If it is accepted that anticoagulant therapy is of value, then the more quickly an adequate anticoagulant cover is provided the better. For this reason, ideally, all patients treated with anticoagulants should be given heparin for the first 24 hours or longer, according to the type of coumarin compound also used.

There are many different coumarin-type anticoagulants available, and it has been truly said that the anticoagulant of choice is the drug that you are most familiar with. To achieve the best results with anticoagulants is not mainly, or even primarily, a question of Quick's technique versus Owren's; given adequate laboratory control, with either Quick's or Owren's method, the most important factor is an experienced clinician who prescribes a drug he is familiar with and who understands the basic essentials of laboratory control.

Because of their slow, prolonged cumulative action, which may take days to appear, the longer-acting coumarin derivatives are undoubtedly more difficult to control than the quick-acting drugs. The latter have the advantage that any change in the maintenance dose is quickly reflected in the prothrombin estimation. Because any change in dose or sign of incorrect dosage is rapidly reflected in the blood estimation, quick-acting coumarin drugs are far easier to use and the correct maintenance dose of the anticoagulant is more quickly arrived at. The quick-acting coumarin derivatives commonly used are phenindione ("dindevan") and ethyl biscoumacetate ("tromexan"). In my opinion the latter drug has too short-lived an effect, with the result that it is difficult to maintain adequate anticoagulant cover with it. Phenindione is a comparatively easy drug to control, and in my experience is one of the best drugs as yet available. The incidence of agranulocytosis with this drug is low, considering its widespread use, and should never prevent its use. The incidence of drug rashes with phenindione is about 1 to 2%; again it will be found that more often than not, when a rash develops, other drugs, especially barbiturates, are also being given.

The longer-acting anticoagulants available, such as phenylpropylhydroxycoumarin ("marcoumar"), diphenindione ("dipaxin"), and dicoumarol, are, I have found, less satisfactory to use than phenindione. Recently there have been reports that warfarin sodium ("coumadin") is the "anticoagulant of choice." This anticoagulant is very nearly as quick-acting as phenindione, but has a more cumulative effect. Because of its rapid action any change in dose is quickly reflected in the prothrombin estimation, and so the necessary adjustment in the dosage can be quickly made.

Table IV shows my results with different anticoagulants. Whether the number of patients treated with each drug is statistically significant, thus enabling any definite conclusion

TABLE IV

Anticoagulant	Patients Treated	Late Mortality Rate
Phenindione	71	8.4%
Phenylpropyl-hydroxycoumarin ..	94	21.2%
Diphenindione	73	12.3%
Warfarin sodium	35	14.2%

about their relative merits to be arrived at, is perhaps open to question. It should be noted that the number of patients treated with warfarin sodium is certainly too small to mean much.

Before leaving this question of choice of anticoagulant it is essential to point out that the above remarks apply to treatment for an acute illness where it is important to achieve and maintain an adequate anticoagulant cover as quickly as possible. For long-term prophylactic treatment the whole problem is entirely different, and long-acting coumarin derivatives such as marcoumar are, if anything, better than the quick-acting drugs. My experience of over 130 patients on long-term anticoagulant therapy has proved marcoumar

to be an ideal drug for this purpose. The control of long-term anticoagulant therapy presents many different problems from those of short-term therapy for the acute illness.

Haemorrhage in Anticoagulant Therapy and the Use of Vitamin K₁

In my opinion the danger of haemorrhage has been exaggerated. The occurrence of minor haemorrhage, such as slight epistaxis, is not uncommon when adequate anticoagulant therapy is being given. Such minor episodes do not call for cessation of treatment, but merely for a regulation of the dose of anticoagulant where necessary.

Vitamin K₁ is one of the most powerful drugs in use, and, while it is invaluable in anticoagulant control, it must be used with the greatest possible caution. It should be given only if there are very definite indications for its use. Briefly its use falls into two main categories: first, to reduce a very prolonged prothrombin time even where there is no evidence of haemorrhage; and, secondly, when more than minimal haemorrhage has occurred. For the first only very small doses of vitamin K₁ are needed, such as 2 to 3 mg., and rarely is an initial dose as large as 5 mg. required. If larger doses are given the patient may escape from anticoagulant cover with a resultant very definite risk of fresh thrombo-embolic episodes. If the first small dose does not have the desired effect the same amount should be repeated after 12 hours.

If severe haemorrhage has occurred larger doses of vitamin K₁ will be necessary, such as 10 to 20 mg. It should be realized that 10 mg. is a large dose, while it is certainly seldom necessary to give more than 20 mg. It is better, subject to the urgency of each individual case, to give small repeated doses at intervals of 8 or 12 hours, and to regulate the dosage by repeated 8- or 12-hourly prothrombin estimations, than to give a large initial dose and render the patient refractory to anticoagulants.

Use of Other Drugs with Anticoagulants.—In prescribing anticoagulant therapy particular care must be taken if oral antibiotics such as penicillin, and especially the broad-spectrum tetracycline antibiotics, are given at the same time. Oral antibiotics enhance the action of oral anticoagulants, and the dose of the anticoagulant will therefore probably have to be reduced. Phenylbutazone ("butazolidin") is known to cause haematemesis, and should never be used together with anticoagulants. Similarly, aspirin is well known for its irritant effect on the gastric mucosa and has often caused haematemesis. Aspirin and all aspirin-containing remedies must never be given to patients on anticoagulant drugs, as haemorrhage is very likely to occur. Again, large doses of salicylates, and probably quinine, reduce the prothrombin level and thus potentiate the effect of anticoagulants. Lastly, it is an impression of mine that frequent doses of liquid paraffin or similar oil emulsions interfere with the absorption of oral anticoagulants, and I therefore avoid their use.

Anticoagulants for All

There is little doubt, to my mind, that anticoagulants are a major advance in the treatment of the bad-risk patient with myocardial infarction. Even Russek and Zohman, the most severe critics of anticoagulant therapy, agree that all bad-risk patients must be treated. The problem remains whether good-risk patients should be given anticoagulants, as the mortality rate for such patients is so low: Russek and Zohman (1957) estimate 3.3% in a series of 1,000 good-risk patients. In my total series of 326 patients there were only 3 deaths among 84 good-risk patients—that is, 3.5%. With such a low mortality rate I believe that there is room for the opinion that such patients need not have anticoagulant therapy, and I certainly believe that unless skilled clinical as well as laboratory control is available it is better not to use anticoagulants for good-risk patients. With skilled clinical and laboratory facilities available, however, there is nothing to lose in giving anticoagulants, especially as there is always the problem of satisfactorily classifying patients

as good- or bad-risk patients at the time they are first seen. Of the 326 patients in this series, 12 initially classified as good-risk changed to bad-risk patients in a short period of time.

With adequate facilities at hand it is exceptional for a patient needing anticoagulant therapy to be denied such treatment. In the last five years at New End Hospital not one patient has been considered to have an absolute contraindication for anticoagulant therapy. Major surgical procedures, including intestinal surgery, have been performed while patients have continued to have anticoagulant treatment. Such minor procedures as dental extractions have been commonplace with patients on long-term treatment without the need for cessation of anticoagulant therapy.

Conclusions

As a result of an analysis of patients admitted to the Radcliffe Infirmary, Honey and Truelove recently came to the conclusion that anticoagulants are of but little value in the treatment of acute myocardial infarction. They state that in comparing treated and untreated patients it is essential to take into account the number of bad-risk patients, and the age grouping in each series.

A series of 326 patients treated at New End Hospital from 1951 to 1957 have been strictly classified according to all the bad-risk factors mentioned by Honey and Truelove, and the age groups are given to show that this series is in every way comparable to that of Honey and Truelove. In their group of 110 untreated patients there were 24.5% good-risk patients, and the mortality rate, excluding deaths in the first 48 hours, was 28.3%. In the New End series of treated patients the number of good-risk patients was 25.7%, but the mortality rate was only 13.6%. In other words, the death rate was about half. These findings confirm the view, widely accepted by most authorities experienced in the use of anticoagulants, that anticoagulants are of real value in the treatment of acute myocardial infarction.

In my opinion all bad-risk patients should be treated with anticoagulant therapy. In assessing bad-risk factors I agree fully with the criteria laid down by Russek and Zohman—previous history of infarction, intractable pain, cardiac failure, arrhythmia, significant cardiac enlargement, diabetic acidosis, and severe shock and hypotension.

The control of anticoagulant therapy calls for considerable skill, not only to avoid haemorrhage, but, just as important, to give effective anticoagulant cover throughout the whole course of the illness. In the control of treatment there are two equally important essentials—adequate laboratory technique and administration of the anticoagulant drug by a clinician experienced in its use.

In carrying out reliable laboratory control perhaps the most important factor is the availability of an active and potent thromboplastin which gives uniform results from day to day. Better laboratory techniques, such as Owren's as opposed to Quick's method, will, however, be completely offset by inexperienced prescribing of the anticoagulant drug. For adequate anticoagulant therapy the clinician must be thoroughly familiar with the anticoagulant used. For short-term treatment of the acute illness, as opposed to long-term preventive treatment, the quick-acting coumarin drugs such as phenindione and warfarin sodium are much easier to control than long-acting drugs such as dicoumarol and marcoumar. (For long-term therapy the opposite holds true.)

With experienced control serious haemorrhage is very rare nowadays, and minor haemorrhage, though not infrequently seen with adequate therapy, does not call for cessation of treatment. Vitamin K₁ is invaluable in the control of haemorrhage due to overdosage with anticoagulant drugs, but it must be used with caution, and in very small doses, as it is so potent.

Certain drugs enhance the effect of oral anticoagulants or may cause haemorrhage. As a result, the administration of oral antibiotics, particularly the broad-spectrum drugs such as the tetracyclines and to a less extent penicillin, may call for a reduction in the dose of the anticoagulant drug. Aspirin, phenylbutazone, and probably quinine should not be given at the same time as anticoagulant therapy, and liquid paraffin is also best avoided.

With skilled laboratory and clinical control, emergency surgical procedures, including major operations, can be carried out on patients still receiving adequate anticoagulant cover without the necessity for the treatment to be stopped altogether. This is particularly important in relation to long-term therapy.

In experienced hands anticoagulant therapy has proved so beneficial in thrombo-embolic disorders that everything possible should be done to ensure that the treatment is carried out to the best advantage and that adequate anticoagulant cover is maintained throughout the illness. To-day, with the increasing use of long-term anticoagulant therapy, there is perhaps justification for a special unit in large hospitals for the control of this treatment.

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A TECHNIQUE FOR INVESTIGATING THE BLOOD SUPPLY OF MUSCLE DURING EXERCISE

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One of the major difficulties in investigating problems of diagnosis and treatment in intermittent claudication has been the lack of a suitable objective test for measuring blood flow in the calf muscles during exercise. Plethysmographic studies of muscle are relatively easy to perform with the patient at rest, but such investigations do not help in patients with claudication, because resting blood flow is usually adequate. It is only when exercise leads to a demand for blood greatly above the resting flow that claudication is manifest, and during exercise plethysmography is extremely difficult to perform.

The test described in this paper is based on experimental work carried out over the last few years and has been in use by this clinic for four years, some 200 patients having been investigated. As in the case of any test, it is essential to appreciate the basic factors concerned and to be aware of the limitations of the method. It is proposed in this paper to describe the technique which has been evolved and to discuss the interpretation of the results obtained in the light of experimental findings.

In 1948 Kety published a paper reporting the measurement of the local clearance of radioactive sodium pre-

viously injected into a tissue, and suggested that this might prove to be a method for the experimental study of the peripheral circulation. As a result of an investigation of the clearance of injected radioactive sodium from muscle it was established (Walder, 1955) that with certain provisos changes in the clearance rate were linearly related to changes in blood flow (Fig. 1). The clearance rate of radioactive sodium is expressed as the "clearance constant" K.

FIG. 1.—Relationship between blood flow as measured with a conventional type of plethysmograph and radioactive sodium clearance constant K in the human gastrocnemius muscle during the immediate post-exercise period.

$$K = \frac{\log C_1 - C_2}{0.4343 (t_1 - t_2)}$$

where C_1 and C_2 are the percentage activity of the injected ^{24}Na remaining at the two times t_1 and t_2 after the first measure of activity, which is taken as 100%. Hence, by calibration of clearance rate against blood flow measured at rest, the method can be developed in such a way that it becomes easy to measure blood flow during exercise.

While the problems of measuring blood flow in muscle during exercise were being investigated it was noticed that in the case of patients suffering from peripheral vascular disease the ^{24}Na clearance curve during the type of exercise used showed a characteristic pattern such that there appeared to be no flow through the muscle during the period of exercise. This observation allowed considerable simplification of the clinical test for vascular sufficiency during exercise to be made, since it is only changes in blood flow that are required and it becomes unnecessary to measure the absolute blood flow at any stage of the test.

Object of the Test

The object of the test is to detect vascular insufficiency in human muscle. It allows such insufficiency to be demonstrated at a very early stage in its development, and in those instances where patients describe symptoms which may or may not be attributable to muscle ischaemia during exercise the test enables a firm decision to be made one way or the other. Since any one muscle can be selected for testing it enables the exact location of the ischaemic muscle to be determined, a point which opens up the possibility of performing localized neurectomies as treatment for some cases of claudication. Finally, provided that the test is performed under properly controlled conditions, it offers objective evidence of the state of the circulation in a muscle and a record which can be used for comparison later with subsequent tests following treatment. This latter point is of importance in that it provides an objective means of assessing the results of treatment for a condition where the patient's desire to be better and the doctor's enthusiasm can so colour the picture.