THE USE AND ABUSE OF ANTICOAGULANTS IN MYOCARDIAL INFARCTION

— *by R. SOLER* —

The wheel has turned a full circle with regard to the place of anticoagulants therapy in the treatment of recent myocardial infarction. Initially therapuetic enthusiasts claimed a marked reduction in the morbidity and mortality rates, especially from thromboemolism, with the result that the use of anticoagulants became widespread throughout the world. With the passage of time enthusiasm had begun to wane; but recent therapuetic trials especially one by the Medical Research Council (M.R.C.) in 1959 has again aquired to a certain degree a prominent place for anticoagulants in the treatment of myocardial infarction.

An understanding of the pathology of myocardial infarction is very helpful in explaining the need for anticoagulants. Cardiac infarction entails necrosis of heart muscle usually due to the interruption of blood supply by coronary artery occlusion. The latter may be due to coronary atheroma with or without supra-added thrombosis. However, cases are recorded where there is no evidence of arterial occlusion at necropsy. In these cases the lumen of the arteries is usually narrowed by atheromatous deposits in the intima. These cases are usually brought about by a disturbance of circulatory dynamics, as occurs in conditions such as shock or severe anaemia. Thus it can be appreciated that infarction does not necessarily imply thrombosis. In cases where the cause of the infarction happens to be arterial insufficiency, anticoagulants will be most helpful in preventing intra-luminal thrombosis of the arteries distal to the site of the infarction and so help in limiting the extension of the infarct which might prove fatal. However, evidence has been brought forward, showing, that anticoagulants can produce extravasation of blood into an atheromatous plaque, and this has been one of the arguments brought against their use in cardiac infarction.

It is agreed that the blood of patients with ischaemic heart disease is hypercoagulable because of the increased thromboplastin generation and increased platelet adhesiveness. Platelet adhesiveness is probably due to a coat of fibrin deposited on the platelets. Since heparin is known to decrease fibrin formation, it consequently reduces platelet adhesiveness. Moreover, has been suggested (Duguid 1955) that atheroma develops as a consequence of fibrin deposition on the intima. Duguid showed that mural thrombi laid down in arteries rapidly become covered with endothelium and may later appear to arise from within the vessel wall. Fat deposition and other changes convert the original lesion into an atheroma. If this hypothesis is correct then one might expect anticoagulant therapy to prevent the extension of the atheromatous process.

Another aspect of thrombotic disease in general which bears a relationship to myocardial infarction, is the physiological process of fibrinolysis. It is known that fibrinogen is continually being converted to fibrin in vivo but that the action of fibrinolysin (or plasmin) prevents the formation of thrombi by a proteolytic action on the fibrin formed. If there is any change in blood coagulation which encourages thrombosis then it might well be that it is the balance between forces for fibrin formation and those for fibrin dissolu-

tion which is the important. Hume (1958) has shown that immediately following an infarct, there is a decreased level of fibrinolysin but this gradually returns to normal levels over the succeeding ten days. Lackner & Mersky (1960) showed that heparin increased the fibrinolytic activity in vivo. This increase in fibrinolytic activity, maximal 1 hour after heparin injection, was frequently observed in patients treated with heparin. It is possible that the action of heparin in promoting fibrinolysis is due to its action on lipids; lipaemia has been proved to inhibit fibrinolysis.

From what has been said so far, it is clear that there is more than meets the eye in the use of anticoagulants for the prevention and the dissolution of thrombi. The pharmacological action of herapin in blood clotting occurs at two main sites. It prevents the interaction of thrombin with fibrinogen to form fibrin and prevents the conversion of prothrombin to thrombin by the blood thromboplastin system. The coumarin derivatives act on the liver and competitively occupy sites on the liver cell intended for the vitamin K which is necessary for the production of prothrombin. Prothrombin depletion in the peripheral blood causes impaired thromboplastin formation and so blood coagulability is reduced.

It has been argued that the use of anticoagulant therapy in acute myocardial infarction is fruitless, because, once the vessel has been occluded by a thrombus, then, the anticoagulants are of no use whatsoever. This statement does not take into account the number of infarcts due to arterial insufficiency as was mentioned above. It must be stressed at the outset that anticoagulant therapy is not curative of the condition but is of prophylactic value in the subsequent few days, following the attack. Thus it is known that retrograde growth of a thrombus may occlude further the coronary vessels and this may be sufficient to cause death from ventricular fibrillation. It may prevent mural thrombus formation in the left ventricle or thrombosis of leg-veins (from stasis of the peripheral circulation due to heart failure following the infarction), with consequent risk of embolisation. Statistics show a reduction in clinically diagnosed episodes of thrombo-embolic incidents.

Myocardial infarction may present in various degrees of severity. In the good risk cases where the prognosis is favourable and the occurrence of thrombo-embolic incidents rare, anticoagulant therapy may be safely omitted and its possible complications particularly haemorrhage avoided. A good risk patient may be considered to be a patient below 60 years, with a first attack of infarction, without history of preceding angina and who shows no major fall in blood pressure following the attack. Other criteria in favour of a 'good risk' case are the absence of cardiac failure or arrhythmias; no history of diabetes mellitus or other sign of previous arterial disease elsewhere, and in a patient who is not obese. If these criteria are fulfilled it may be fairly said that the possible complications of anticoagulant therapy far outweigh the risk of thrombo-embolic incidents. Moreover in patients with coronary artery disease of sufficient severity as to have caused a previous recognisable infarct, long term anticoagulant therapy can only make a limited type of contribution in terms of reduction in deaths and reinfarction rate. Naturally this long term anticoagulant treatment does not make a therapeutic attack on the fundamental aetiology of mycoardial infarction, but merely interrupts one of the terminal links in the chain of events leading to this lession. From the statistical evidence (which is discussed later (M.R.C.) it was found that the benefits of long term treatment were greater in angina cases than in those who had already suffered an infarction, suggesting that the earlier the disease is so treated the greater is the benefit. Moreover it was noted that in the older age group and in patients who had already suffered one or more infarcts, the contribution made by therapy was unsatisfactory.

On the other hand, the patient himself may present definite contra-indications of anticoagulant therapy of

any sort. Thus a patient, who is judged to lack sufficient intelligence to carry out the treatment or who is unreliable in attendence to the out-patient clinic, is not a fit candidate for long term anti-coagulant treatment. A patient who is a chronic alcoholic or suffers from liver dysfunction may provide a greater risk to bleeding due to the deficient prothrombin formation. A patient with an active peptic ulcer, hiatus hernia or other lesion of the gastro-intestinal tract known liable to bleed should be excluded from anticoagulants. Malignant hypertension associated with hypertensive retinopathy or any retinopathy (diabetic, renal), in which there is evidence of fundal haemorrhage, constitute other contraindications. A raised blood urea or surgical lesions of the kidney (calculus) should also be borne in mind when anticoagulant therapy is being contempalted. A patient with a known blood dyscrazia should also be eliminated from anticoagulant therapy. Finally pregnant or nursing mothers should also be taken off the list of patients for anticoagulants. Certainly the availability of a well-equipped laboratory for the necessary prothrombin and clotting time determinations is essential. From the preceding list of conditions it can be seen that the major hazard of anticoagulants is the liability to haemorrhage. However the statistical evidence does not present such a gloomy picture as one might think. Haemorrhages of a minor degree are two or 3 times as common as the casastrophic major incidents e.g. haemoptysis or haematemesis. With short term therapy, that is up to 4-6 weeks the incidence of haemorrhage is roughly 5% of cases treated. The incidence of bleeding during long term therapy is of the order of one case per 7 treatment years (M.R.C. 1959). It will be noted that the incidence of bleeding is higher in the former than in the latter. This fact can be explained by application of therapy to a case, which constitutes one the contraindications mentioned above; thus for example the development of a major haemorrhage bringing to notice an unsuspected peptic ulcer. Naturally such cases should be excluded from anticoagulant therapy. Besides this danger from bleeding, long term therapy with phenindione is liable to produce other distressing side-effects of which a sensitivity reaction is the most important. This allergic reaction takes the form of a rash accompanied by pyrexia and leucopenia. Progression to exfoliate dermatitis can occur. Other less common side-effects are serious renal damage with albuminuria, anaemia and a leukomoid blood pictures, diarrhoea, and disturbances of vision. Any signs of the development of side-effects naturally precludes the cessation of treatment. As judged by the M.R.C. trial sensitivity reactions occurred in 1.5% of patients and of the three fatalities recorded, one was attributed to agranulocytosis and the other two to a renal lesion.

The rationale behind the use of anticoagulants as an adjuvant to standard treatment of a myocardial infarct, is to prevent the extension of the original thrombus, which has caused the infarction and therefore prevent the extensin of the damage; to prevent a fresh myocardial infarct, and finally to reduce the incidence of thromboembolic episodes.

Usual sequalae of an infarct, after the preliminary state of shock has passed off, is the development of atrial fibrillation and of mural thrombi in the left ventricle subjacent to the area of infarction. Emboli shot off from the atrium of ventricle can lodge in the cerebral vessels or in any systemic artery. Pulmonary embolism from peripheral venous thrombosis, usually from the leg, is a major hazard.

Anticoagulant therapy can be instituted on a short or a long term policy. The evidence in favour of a short term anticoagulant therapy is not so favourable; even so, due to lowered mortality rate in long term anticoagulant therapy, it should be started as soon as the patient is admitted to hospital on the basis that long term therapy is likely to be obligatory. Honey and Truelove (1957) concluded that such a reduction in mortality as occurred in anticoagulated patients was

due to a lowering of the incidence of fatal pulmonary embolism. Certain physicians are still, however, hesitant in giving anticoagulants to all patients admitted with myocardial infarct; so they take the middle road and reserve treatment for patients in whom the prognosis is poor. The 'poor risk' patients, about 30% of those admitted for myocardial infarction, are considered to be those who have had a previous infarct and who suffer from shock; those with heart failure, or atrial fibrillation and flutter or a bundle branch block; and those who show signs of ventricular anuerysm, severe diabetes, thrombophlebitis, and those who are markedly obese.

The statistical evidence so far brought forward has shown that the only type of anticoagulant therapy which can claim a certain amount of success is the 'long term' treatment. Therefore, if it is decided to embark on anticoagulant, it will be of greater prognotical value if one were to adopt the long term regime. At the beginning of this paper it was stated that treatment with anticoagulants is again coming in favour with many practising physicians. How has this change of opinion been brought about? There have been three well constituted clinical trials or long term anticoagulant therapy in the last ten years. These have shown a definite improvement in prognosis in patients suffering from myocardial infarction. These trials were conducted by Bjerklund and Borchgnevink in 1957 and 1960 respectively and by the Medical Research Council in 1959 with a follow-up in 1960. May I here be permitted to digress a bit from the subject matter and say that M.R.C. report was the paper which stimulated my interest in this highly controversial subject. Whilst agreeing to the fact that some of the criticisms on the available trials are admissible, these criticisms do not in their own right completely invalidate the evidence in favour of anticoagulants. Indeed, unless a properly constituted trial should be conducted which disproves the alledged benefit, then the existing claims for its use in acute myocardial infarction must be accepted.

I propose to deal with the M.R.C. trial in a certain detail. The purpose of the trial was to determine whether, in patients who had survived at least one month after their most recent infarction, continuous anticoagulant therapy would reduce the risk of recurrence and death below the levels concurrently observed in a series of comparable patients not so treated.

Only patients with the Q wave electrocardiographic evidence of recent infact were included. The age of the patients admitted was from 40 to 69 of either sex and they were admitted to the trial at any stage from the 29th day to the 42nd day after their recent evidence of infarction. Patients who showed any of the following conditions were excluded from the trial.

a) Haemorrhage from any site within the previous 6 months.

b) Peptic ulcer on clinical or radiological diagnosis.

c) Any lesion thought likely to bleed.

d) Hepatic disease.

e) Renal disease with persistent raised blood urea.

f) Malignant hypertension.

g) Cardiac failure.

h) Previous cerebrovascular accident.

These in fact, constitue the contra-indications which were mentioned above.

The judgement on the benefit or otherwise of this therapy rests on two criteria viz. the death rate and the reinfarction rate. In the M.R.C. trial 165 patients (males) received anticoagulants and 100 patients acted as a control group receiving placebos. Of this number of patients, the deaths recorded amounted to 17 in the first group and 28 in the control group. There are some critics who are unwilling to accept the reinfarction group as valid evidence because the adjucating clinician was aware of those in

the treatment group. In the M.R.C. trial there were 17 patients with a recurrent infarction in the treatment group and 54 reinfarction incidents in the control. If these figures are given as percentages, it will be found that 20% of patients receiving anticoagulants either died or suffered from reinfarction whilst 51.3% of patients in the control group suffered from the same result. These figures suggest that there is a marked reduction in mortality and reinfarction rate in patients receiving anticoaguants than in those not so treated. It must be stressed again that the evidence in favour of long term anticoagulants is still statistical.

There is some evidence that therapy is more effective in the under 55 age group. The death rate was reduced by 50% in those under 55 years and by 33% in those over 55 years whilst the reinfarction rate in those under 55 years was 20% as compared to the 50% incidence in patients over 55 years. The deaths occurring in the test group was maximal during the first 3 to 6 months and it has been suggested that this increase in relapses during the early part of the follow-up was due to early cessation of treatment. The major cause of death in both the control and the test of groups was recurrent infarction which suggests that although anticoagulant therapy reduces the mortality rate it does not entirely prevent recurrent infarction; it does however reduce the incidence of embolism, since only one case of death was attributed to cerebral embolism in the M.R.C. trial and this occurred in the control group. On the other hand although much fuss is made about the risks of haemorrhage in using anticoagulants, the incidence of bleeding severe enough to cause death amounted to one in the treatment group. Hence, barring the presence of any lesion liable to bleed, the dangers of therapy are small indeed as long as proper check is kept on the blood prothrombin time.

The regime of treatment varies from clinician to clinician. However, they all, more or less, follow the form outlined below.

10,000 units of heparin are given intravenously every 3 hours for the first 48 hours. An oral anticoagulant, Phenindione, is started concurrently with heparin. 200mg of phenindione should be given on the first day, 150 mg on the second day and 100 mg on the third day. After 48 hours a prothrombin time is carried out. The ideal anticoagulant effect is two to three times the nomal (16 secs.) prothrombin time. The maintenance dose of phenindione can then be gauged from assessment of the initial prothrombin time. If the above regime is carried out the maintenance dose works out to be 100mg to 50mg daily.

In the short term therapy, anticoagulants are continued as long as the patient remains in bed. However, as has already been stressed, the patient is better safe guarded against reinfarction if he is put on a long term policy. Certain precautions are required if the patient is put on long-term therapy. The patient should be kept as an outpatient and regular check is kept on his prothrombin time. He should be warned not to undergo any surgical procedures, especially tooth extraction without prior consultation with the physician in charge of his treatment. He should be warned against partaking of such drugs as salicylates, cincophen phenylbutazone, oral antibiotics and ACTH all of which tend to precipitate bleeding. If after a number of years it is thought fit to stop treatment then it will be good clinical practise to taper off the dose over a 4 week period by reducing a quarter of the stabilising dose each week. This precaution is essential to avoid the rebound hypercoagulabiliay of the blood which occurs when anticoagulants are stopped suddenly and which might easily result in a recurrent thrombosis.

If inspite of all the precautions undertaken, haemorrhage develops, 5 ml. of a 1% protamine sulphate solution are injected slowly intravenously if the patient is on heparin or if he is on oral anticoagulants, the drugs should be stopped and vitamin K, 100

to 50mg, are injected intravenously. Blood transfusion should be given in all cases until the effect of oral anticoagulants wears off.

The role of anticoagulants in myocardial infarction is still undecided. From the study of the extensive literature on the subject, I have reached the conclusion that there is a place for anticoagulants in certain special cases, that is the poor risk patient mentioned above. However, one should not be dogmatic about their use, as quite a substantial number of cases present definite contra-indications to their use. On one point is there agreement among all clinicians and in that, anticoagulants are a *must* in preinfarction angina. Until our diagnostic procedures are improved to bring to light these patients before the catastrophy and the layman instructed to present to the clinician earlier, the use of anticoagulants in the established case will remain an illdefined prophylactic against re-infarction.

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