FIBRINOLYTIC TREATMENT OF CORONARY THROMBOSIS

A PILOT STUDY

BY

H. A. DEWAR, M.D., F.R.C.P.

A. R. HORLER, M.D., M.R.C.P.

AND

A. J. CASSELLS-SMITH, M.D.

The Royal Victoria Infirmary, Newcastle upon Tyne

The therapeutic use of fibrinolytic preparations in thromboembolic disease was foreseen when the dissolution by human plasmin (fibrinolysin) of artificially induced thrombi in experimental animals was demonstrated by Clifton and his colleagues in 1954. Subsequently good results were claimed for the therapeutic effect of plasmin in human subjects with a variety of thrombotic manifestations (*Angiology*, 1959). The possibility of treating coronary thrombosis in man by fibrinolytic means was foreshadowed by the experimental work of Rueggsegger *et al.* (1959). Artificial clots were induced in the coronary arteries of dogs, some of which were then infused with thrombolysin (human plasminogen activated by streptokinase). Serial coronary arteriograms showed that in the control animals the clots persisted up to 15 hours with no more than 20% reduction in size; in those infused with thrombolysin, progressive reduction in the size of the clots was evident within two hours, and by three to seven hours complete lysis had occurred in half and a reduction in size of 60% or more in the remainder. This was confirmed by post-mortem dissection, and histological examination of the infarcts showed that in the treated animals there was less oedema in the marginal areas, less fibrinous epicarditis, and less dilatation of capillaries with no microthrombi to be found in them. These findings obtained even with incomplete lysis of the primary thrombus, suggesting that the plasmin had penetrated the infarct by collateral perfusion. The possibility of a real advance in the treatment of acute coronary thrombosis thus presented itself: early administration of plasmin might re-establish the coronary circulation and minimize permanent damage to the myocardium.

Moser (1958) first reported a case of myocardial infarction treated with plasmin. The use of fibrinolytic agents in a larger number of cases has been reported by Clifton (1959), deLeon *et al.* (1959), Fletcher *et al.* (1959), Richter *et al.* (1960), and Boucek and Murphy (1960), who gave plasmin by intermittent injection through a catheter passed to the base of the aorta. Fletcher *et al.* and Boucek and Murphy claimed that the treatment caused a more rapid rise and fall in the serum transaminase levels as compared with the controls.

The Present Study

The three principal objects were to establish whether the preparation to be used in the treatment of human coronary thrombosis was safe, whether it was potent *in vivo*, and whether it had a beneficial effect on the course of the disease. The material, thrombolysin, is derived from human plasma which is rich in

plasminogen, activated by purified streptokinase, the final product consisting of plasmin and an excess of activator.

Observations were made to determine whether thrombolysin produced the same side-effects as have been reported with other streptokinase preparations—namely, fever, vomiting, and hypotension—and also whether it predisposed to excessive haemorrhage or cardiac rupture. The potency of the preparation was assessed by estimating the fibrinolytic activity of the plasma before, during, and after infusion, and by parallel estimation of plasma fibrinogen levels.

Conclusive evidence of a beneficial effect from the treatment must await the results of a prolonged study with a large number of patients. In the meantime, since it was regarded as unjustifiable to perform coronary arteriography before and after treatment, more indirect methods of assessment have been employed. Observations were made of the duration of pain, the pyrexial reaction, the clinical progress and complications, the evolution of the electrocardiogram, the mortality, and, after recovery, the degree of cardiac insufficiency. It was also thought that the transaminase curves might well provide good evidence of whether the infarct had, in fact, been modified by the treatment. Reperfusion by lysis either of the primary thrombus or of thrombi in the collateral channels might result in a more rapid liberation of enzyme in the treated patients, represented by a higher and earlier peak and a more rapid descent.

Selection of Patients

The patients studied had all been admitted to hospital within 12 hours of the onset of pain. The only grounds for exclusion were the occurrence of episodes of prolonged pain during the days or hours preceding the acute onset (suggesting that minor infarction and liberation of transaminase had already taken place) or obviously imminent death. All patients included had electrocardiographic evidence of fresh infarction at the time of admission except one in whom it subsequently developed. The presence of a Q wave as proof of infarction was not insisted upon as it is often not obtainable in early tracings even of fully transmural necrosis. After the first six, who all received thrombolysin, patients were allotted to the treated or control groups alternately in order of admission, except for a short period when, owing to a shortage of supplies of thrombolysin, successive patients were accepted as controls.

The total number of patients included was 33, of whom 17 (15 men and 2 women) received thrombolysin, and 16 (15 men and 1 woman) were controls. The average age of the treated group was 60.2 years (range 36–80) and of the controls 59.4 years (range 47–72). A history of angina pectoris was elicited from eight of the treated patients and from ten of the controls, and three in each group had had previous myocardial infarcts. The average time elapsing from the onset of pain to the beginning of treatment was 6.3 hours in the treated group (range 3.25–12) and 6.3 hours in the control group (range 2.25–10.25).

Technique of Investigation and Treatment

As soon as the patient was judged suitable for the study a sample of venous blood was collected for

baseline estimation of enzyme levels, fibrinogen content, and fibrinolytic activity (without use of a tourniquet). A wide-bore unbevelled "polythene" cannula was then inserted into a forearm vein and advanced, usually to the elbow, where the junction of a tributary permitted easy withdrawal of further samples. This cannula was kept patent by a slow drip of 3.8% sodium citrate solution. Another polythene cannula of fine bore, or a Guest-type metal cannula, was inserted into a vein of the opposite forearm, and through this the infusion was given, using a children's type of giving set with a 100-ml. cylinder. In the treated cases, 25,000 units of thrombolytic freshly dissolved in 60 ml. of 5% glucose in water were infused rapidly over a few minutes and followed by a further 25,000 units slowly over the next hour. Thereafter 50,000 units in 60 ml. were given hourly for the next 11 hours, making a total dosage of 600,000 units. In the control cases glucose solution was used without the addition of thrombolytic. At the end of the 12-hour period this cannula was withdrawn, but the wide-bore cannula was retained in the other arm until the end of the third day, for the purpose both of obtaining samples of blood and of administering heparin; it was kept patent by a slow drip of 4.1% glucose in N/5 saline.

Blood for serum transaminase estimations (S.G.O.-T.) was withdrawn every four hours for three days, then once daily (by venepuncture) for 10 days. Blood for plasma fibrinogen estimation was withdrawn every four hours for 16 hours, then daily for 12 days. Samples for determination of fibrinolytic activity were withdrawn (without use of a tourniquet) at 5, 10, 15, 30, and 60 minutes after the beginning of the infusion, then two-hourly until its completion and half-hourly for a further three hours. The above routine was modified for the later patients of the series when the estimation of fibrinolytic activity was omitted. Only one cannula (wide-bore) was used for both infusion and withdrawal of samples, care being taken not to lose dead-space thrombolytic, and in these cases citrate solution was not necessary.

Routine anticoagulant therapy was begun as soon as the last specimen for fibrinolytic activity had been obtained. Heparin was administered by drip for 36 hours, and phenindione was continued on a long-term basis. Morphine was given liberally in the event of chest pain, and mephentermine or noradrenaline was administered if shock was profound. If considered necessary, oxygen, digitalis, quinidine, diuretics, and antibiotics were also given.

Twelve-lead electrocardiograms were recorded every eight hours for the first two days, then daily for a further 10 days, and a record was kept of temperature, pulse or apex rate, blood-pressure, and fluid intake and output. The patients were normally kept in hospital for three weeks, and arrangements made for regular follow-up attendance.

Methods

Serum transaminase (S.G.O.-T) was estimated by the method of Reitman and Frankel (1957). Sigma Chemical Company reagents were used.

Plasma fibrinolytic activity was estimated by a method based on that of Fearnley *et al.* (1957) modified by Dr. A. S. Todd in order to shorten the lysis time to a more practical range and to permit the estimation

to be made at leisure. To 1.7 ml. of phosphate buffer, pH 7.4 (Billimoria *et al.*, 1959), in an ice-bath, was added 0.1 ml. of blood and mixed by inversion. To this was added 0.1 ml. of thrombin solution (Parke Davis) diluted in physiological saline at 0° C. to give 20 units per ml., and again mixed by inversion. The mixture was allowed to clot, then was deep-frozen to lyse red cells. The clots were observed in tubes in a water-bath at 37° C., and the time at which they began to disintegrate was taken as the fibrinolysis time. In nine normal subjects the range was 240 to 540 minutes with a mean of 340 minutes.

Plasma fibrinogen was estimated by precipitating the fibrinogen by the method of Harrison (1947) and measuring the protein content colorimetrically by the method of Hiller *et al.* (1927).

Results

Potency of the Preparation.—The fibrinolytic activity in 10 treated cases and six controls is shown in Figs. 1 and 2. Along the ordinates are plotted logarithmically the reciprocals of the lysis times in minutes multiplied by 10,000, so that figures above the 10,000 mark

FIG. 1.—Fibrinolytic activity in 10 treated cases.

FIG. 2.—Fibrinolytic activity in 6 controls.

represent lysis times of less than one minute, indicating intense fibrinolytic activity. Along the abscissae are plotted the times from the beginning of the infusion. It will be seen that although the levels fluctuated greatly and in all patients they were above the normal range, only one of the control patients, and on a single occasion, exceeded 2,000 units of activity. Among the treated group, however, the levels of five patients reached or exceeded 2,000 units during a substantial part of the infusion, and only one of these was receiving a pressor drug at the time. Figs. 3 and 4 show the results of plasma fibrinogen estimations. There is no striking difference between the two groups, but in five

of the treated patients levels fell below 0.2% and in two instances to zero. Correlation between these levels and the fibrinolytic activity was not close, but in one patient the fibrinogen was absent when the lysis time was under one minute.

Side-effects.—(1) *Fever*: The pyrexial reaction recorded did not differ between the two groups either in the time of onset or in the height or duration of the fever. Only one patient, a control, experienced

FIG. 3.—Plasma fibrinogen in 16 treated cases.

FIG. 4.—Plasma fibrinogen in 16 controls.

a rigor, and it was not followed by fever. (2) *Hypotension*: Although the average fall in systolic pressure in the treated group (25 mm. Hg $\pm$ 7) and the controls (23 mm. Hg $\pm$ 5) did not differ significantly, in three treated patients the fall was such as to require pressor drugs, and it cannot be stated with certainty that this was not the effect of thrombolytic. No other side-effects were encountered.

Clinical Effects.—In general, thrombolytic infusion, although well tolerated, produced no striking change. Accurate records of the severity and duration of pain were vitiated by the liberal use of morphine, but there was no obvious benefit from the treatment.

Mortality.—Details of the deaths are shown in Table I. It will be seen that five treated patients died and only one control. No important conclusions can be drawn from the necropsy findings, though it may be of interest that the thrombus in the control patient extended distally into the infarct, whereas in the two treated patients who had a fresh thrombus the vessel beyond it was in each case patent.

Post-infarction Angina and Myocardial Insufficiency.

—The number of patients in each group who suffered

from these conditions before the current infarct or developed them afterwards was too small for comparison to be valid.

Electrocardiograms.—The evolution of cardiographic changes has been studied in each patient from the tracings taken on admission, at 24 hours after the onset of pain (that is, shortly after completion of the infusion), at 7 days, at 21 days, and at the three-month follow-up visit. From the unipolar limb leads and from the chest leads V2 to V6 a measurement was made of the greatest pathological Q wave, and the number of leads in which such a wave appeared. A similar estimate was made of the ST elevation and T-wave inversion. The mean figures for each group are presented in Table II. There was very little difference between treated and controls except that the T-wave inversion at 24 hours was much less in the treated group. By seven days this difference had disappeared.

Transaminase Curves.—The transaminase levels for each patient were plotted against the time of the onset of pain, and the curves produced varied greatly from one patient to another according to the severity of the infarct. The characteristic form consisted of a steep

TABLE I.—Deaths

Age and Sex	Series	Hours after Onset to Infusion	Time after Onset to Death	Mode of Death	Necropsy Findings
78 F	Treated	5½	14 hours	Hypotension	Infarct with partial rupture. No thrombus
69 F	"	7½	6 weeks	Congestive failure	Many old thrombi. 6-week infarct and haemorrhage into atheromatous plaque
50 M	"	12	1 year	"	No necropsy
49 M	"	8½	8 weeks	"	Old thrombi in R. and L. cor. art. 8-week thrombus in interventricular branch with infarct
80 M	"	4	27 hours	Hypotension	Fresh thrombus and infarct
60 M	Control	5½	2 weeks	Bronchopneumonia and hypotension	" "

TABLE II.—Electrocardiograms (Mean Figures)

Series		Initial	24 Hours	7 Days	21 Days	3 Months or More
Q Waves						
Treated	Greatest depth (mm.)	4	6	7	5	4.1
	No. of leads involved	1.5	2	2	2	1.6
Control	Greatest depth (mm.)	3	5.5	7	5	5.6
	No. of leads involved	2	2	2	2	1.9
ST Elevation						
Treated	Greatest height (mm.)	4	2	1.3	1	0.5
	No. of leads involved	3	3	2.4	2	1
Control	Greatest height (mm.)	2	1.5	1.5	1	0.6
	No. of leads involved	2.5	3	2.5	1.7	1.2
T-Wave Inversion						
Treated	Greatest depth (mm.)	0.9	1.8	1.6	5.2	1.1
	No. of leads involved	0.8	2.3	2.4	3.3	2
Control	Greatest depth (mm.)	1	3.8	1.7	5.8	1.6
	No. of leads involved	1.4	3.2	2.5	3.8	3

and linear ascent, a sharp peak, a rapid descent to about 50% of the total fall, and thereafter a more gradual decline until the resting level was reached about the seventh day. Unfortunately in several of the patients, for various technical reasons such as haemolysis of the samples, the curves obtained were incomplete and when the deficiencies involved the peak of the curve these results could not be included in the analysis. Fully reliable curves were available from 10 treated patients, and these have been matched against the first 10 satisfactory curves from controls. They have been analysed individually in respect of a number of parameters, and the mean figures for the two groups are compared in Table III. Contrary to what has been previously reported (Fletcher *et al.*, 1959; Boucek and Murphy, 1960) the peak was not attained sooner in the treated

TABLE III

	Average Control	Average Plasmin	t_{18} df.	P
Hours from onset to peak . .	23.9	26.5	0.81	40%
Days from peak to resting level	7.7	6.6	0.94	35%
Rate of rise (units/hour) . .	11.6	16.2	0.99	30%
Peak* (S.F. units)	221	283	0.77	45%
Rate of fall from peak to halfway (units/hour)	9.1	28.2	1.35	20%
Area (unit-days)	410	381	0.32	75%
Rate of rise peak	0.050	0.046	0.36	70%
„ „ rise area	0.031	0.044	1.07	30%
Peak area	0.634	0.918	2.36	3%
Rate of fall peak	0.326	0.054	1.74	10%
„ „ fall/area	0.021	0.057	1.78	10%

* Analysis based on logarithms.
In order to be significant at 5% level, t_{18} must exceed 2.1, and at 1% level t_{18} must exceed 2.9.

cases. The rate of rise and, still more, the rate of fall were greater in the treated group but not to a significant degree. The height of the peak and the area underlying the curve likewise did not differ significantly in the two groups. When, however, the ratio of peak to area was calculated for each patient, the mean of the results was significantly greater in the treatment group. Also, when the rate of fall was similarly related to peak and area the differences between the two groups began to approach significance, though they did not attain it. It would seem, therefore, that, *provided the two populations are comparable in respect of the extent of original myocardial injury*, thrombolytic has had the effect of making the transaminase curves taller and narrower, and this is in keeping with our original concept of what might be expected.

Discussion

The object of using this treatment for coronary thrombosis was to dissolve the thrombus so that the infarct which must inevitably ensue if the artery has been occluded for more than 60 minutes (Savranoglu *et al.*, 1959) would be reperfused and consequently modified in its evolution. It must be realized, however, that the experimental conditions upon which the clinical trial was based differed in important respects from those obtaining in human disease. In the experiments on dogs a fibrin clot was produced in a segment of healthy artery, whereas in the human subject fibrin and platelet thrombi have in most instances been deposited on the surface of atheromatous plaques, which have already narrowed the vessel to a greater or less degree. Such thrombi might well be more resistant, and if lysed might leave a permanent constriction that would impede the flow of blood and even cause it to cease if hypotension should supervene. In this respect collateral perfusion of the margins of the infarct is an important possibility.

The dose of thrombolytic to be given was arbitrarily selected so as to strike a balance between the safe and the effective. Although it might have been theoretically desirable to assess the requirement of activator for each patient in relation to the level of streptokinase antibody, the time consumed would have rendered most difficult the early institution of treatment which was essential to the trial. In the event, the average time from onset of pain to commencement of infusion, 6.3 hours for both groups, is probably as short as can reasonably be expected in hospital practice. Similarly it was thought that an interrupted course of treatment on successive days, as adopted by Richter *et al.* (1960), would only make the effects of treatment more difficult to assess. Heparin and phenindione were withheld for the first 15 hours so as not to interfere with the estimation of fibrinolytic activity. Reports of the effects of these drugs upon such activity have been conflicting (Von Kaulla and McDonald, 1958; Moser and Hajjar, 1960).

Our results confirm the findings of Lackner and Merskey (1960) that most patients with acute myocardial infarction have a greatly enhanced fibrinolytic activity in the blood. In several of our treated group, however, the activity was much greater than in the controls, having risen from comparable initial levels, and it is concluded that this was the effect of the thrombolytic.

The absence of serious side-effects was gratifying, although hypotension may have been induced in a few. The temporary disappearance of fibrinogen from the blood of two patients caused some disquiet, but was not followed by further complications.

The clinical results of treatment have demonstrated no dramatic change, and although five of the treated patients have died and only one control, firm conclusions cannot be drawn from this in so small a series, and must await a more extended trial. It was hoped that the electrocardiograms might have demonstrated the effect of therapy upon the evolution of the infarct, and it is perhaps disappointing that in the development of Q waves, ST elevation, and T-wave inversion the two groups have not differed significantly.

The transaminase curves, therefore, remain in this study the sole evidence of a significant difference between the treated and the untreated. If, by extending the trial, it can be shown with certainty that the two groups are identical in respect of the extent of the original injury, then they may provide evidence of the treatment having a significant effect upon the infarct. Only many more necropsies, however, will show definitely whether this effect is obtained by removing the thrombus from the obstructed vessel, by recanalizing collaterals, or by some other process. Only further study, too, will show how important are fibrinolytic mechanisms in the natural evolution of cardiac infarction in man, and to what extent it may be possible to use artificial fibrinolytic agents as a means of treatment.

Summary

A series of 33 patients suffering from coronary thrombosis of less than 12 hours' duration have been included in a preliminary clinical trial in which 17 of them were treated with a fibrinolytic preparation and 16 served as controls.

A greater degree of fibrinolytic activity in the blood has been demonstrated in a sample of the treated

patients than in a sample of the controls. In a few of them there was also a significant fall in the level of fibrinogen.

The fibrinolytic agent did not produce any febrile reactions, but it may occasionally have caused hypotension.

The numbers included in this pilot study were too small for differences in mortality to be significant. There were no definite differences in the clinical response of the two groups, nor in the evolution of the electrocardiographic changes.

Detailed transaminase curves have been prepared and appear to differ significantly in one respect—namely, the peak area ratio, which is greater in the treated group. The implication of this is discussed.

A more extended trial is in progress.

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Reporting that more teachers are flying from England to New Zealand, *The Times* (August 31) records the following comment by one of them: "The pay here is not high enough to compensate for this land's stinking, dying attitude. My wife and I are escaping from the typical overcrowded and lethargic existence of this welfare state. We and many other teachers here are sick to death of this country. Lack of pay is certainly an important factor, but it is only one of the criticisms we can justifiably level against England to-day."

LIVER FUNCTION IN ACUTE MYOCARDIAL INFARCTION

A STUDY USING BROMSULPHTHALEIN TEST

BY

A. J. ROSIN, M.B., F.R.F.P.S., M.R.C.P.
*Lately Medical Registrar, Royal Alexandra Infirmary,
 Paisley*

The bromsulphthalein (B.S.P.) test is regarded as one of the most sensitive biochemical tests of liver function (Rosenthal and White, 1925; Sherlock, 1955). It is well known that disturbances of liver function occur commonly in cardiac disease. They range from transient abnormalities of liver function, such as occur in reversible congestive cardiac failure (Evans *et al.*, 1952b), to a true cardiac cirrhosis. In states of acute cardiac damage, such as myocardial infarction, jaundice may appear, and excess urobilinogen has been noted in the urine for several days after an attack (Evans *et al.*, 1952a; Koskelo, 1956).

It was therefore decided to investigate liver function by the B.S.P. test in an unselected group of cases of acute myocardial infarction. These results were compared with those of other methods of detecting liver dysfunction.

Material and Methods

A group of 20 patients (15 men and 5 women) aged from 40 to 72 years was studied. Each was admitted with acute myocardial infarction and was examined by me within a few hours of admission. Clinical shock was diagnosed by the following criteria: cold, pale skin, sweating, cyanosis, thready pulse, and hypotension. Blood was taken for the estimation of haemoglobin, serum bilirubin, thymol turbidity, zinc sulphate turbidity, alkaline phosphatase, and blood urea. The B.S.P. test was performed by injecting 5 mg. of B.S.P. per kg. body weight, and specimens were taken after 5 and 45 minutes. The results reported are the percentage retention of B.S.P. in the blood after 45 minutes, the normal being less than 6%. The sample was compared with a standard solution of B.S.P. at a concentration of 10 mg./100 ml., which is theoretically the level of B.S.P. equilibrated throughout the serum in the dose administered.

Results

Clinical details and results of the B.S.P. tests are shown in the Table. Fifteen patients (75%) had abnormal B.S.P. retention within a few hours of myocardial infarction. Of these, three died within three weeks. In eight patients the B.S.P. test was repeated 7–10 days after admission, and was still abnormal in four cases. One year later, B.S.P. retention in three of these patients was 3%, 10%, and 12%. In five patients (25%) it was normal at the time of admission. Shock was diagnosed in two of these patients, one of whom died a few months later. Abnormal B.S.P. retention was more marked in patients who were shocked ($26\% \pm 18.2\%$) than in those who were not ($14.9\% \pm 13.3\%$), but the differences do not reach statistical significance because of the large variance. There was no correlation between abnormality of the B.S.P. test and elevation of the blood urea, the latter being a reflection of reduced renal blood flow.