Low-molecular-weight Dextran in Acute Myocardial Infarction

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In spite of vasopressor agents, anti-arrhythmic drugs, early ambulation, and anticoagulant therapy the mortality among patients with acute myocardial infarction is almost 40%. Intensive-care units may reduce this figure, but other attempts to lower the mortality should be sought. Langsjoen et al. (1963) reported the beneficial effect of low-molecular-weight dextran (mean molecular weight 40,000) in acute infarction, the mortality being reduced from 46.6 to 17.6%. Two years later Langsjoen (1965) confirmed his favourable impression of this treatment. Lindén (1964) reported a reduction of the mortality from 33 to 15% in a small series of patients with myocardial infarction receiving low-molecular-weight dextran. Both these studies were, however, carried out without proper controls and therefore do not admit of definite conclusions.

Theoretically, low-molecular-weight dextran has many advantages. It has antithrombotic properties (Bryant et al., 1963) ; it increases plasma volume (Gelin et al., 1961) and may thus prevent shock ; it improves blood-flow (Gelin and Thorén, 1961) by reducing viscosity and may therefore improve circulation at the border of the infarction, thereby limiting its extension. It has an antisludging effect (Long et al., 1962), which will improve microcirculation. Sludging of the red cells is a frequent finding in myocardial infarction (Bloch, 1955), and it can itself produce myocardial infarction (Long et al., 1962).

Theoretically, 500 ml. of 10% low-molecular-weight dextran binds 1,000 ml. of water. The increase in plasma volume will depend on the injected amount, on the infusion-time, and on the renal function. Dextran molecules of less than 50,000-60,000 are cleared by the kidney (Arturson and Wallenius, 1963).

The effect on plasma volume, which may be beneficial by preventing shock, may have an opposite effect on the already strained left ventricle, thus causing pulmonary congestion. On the other hand, Askrog and Fossaberg (1965) used low-molecular-weight dextran in the treatment of pulmonary oedema, caused by overloading of the circulation, in patients with apparently normal hearts. Severe congestive heart failure is said by the manufacturer to be a contraindication to low-molecular-weight dextran therapy.

Weighing the possible advantages against the disadvantages, we believed treatment with low-molecular-weight dextran to be encouraging enough to warrant clinical trial. With our selection of patients and with the method of administration we have been unable to demonstrate any beneficial effect of low-molecular-weight dextran on mortality in patients with acute myocardial infarction.

Material and Methods

Low-molecular-weight dextran, Rheomacrodex, 10% in glucose was used. A study was made of patients under 75 years admitted to hospital with symptoms suggestive of acute myocardial infarction of less than 24 hours' duration. The following were excluded: those with diabetes requiring insulin and those with pulmonary oedema or definite signs of pul-

monary congestion, the decision being left to the attending physician.

Myocardial infarction was defined according to the standard rules of this department (Enger et al., 1963), requiring typical E.C.G. pattern with Q waves or ST changes. When the E.C.G. pattern was not obvious the diagnosis was made if three of the following criteria were present: a rise in the sedimentation rate, serum glutamic oxaloacetic transaminase (G.O.T.) values above 40 units, a typical temperature curve, and a leucocyte count above 9,000.

The patients admitted to the study were randomized into two groups according to a preconceived list. Separate criteria were made for the two sexes and for the patients with recognized previous infarction.

Treatment

According to Langsjoen (1963) 1,500 ml. of a 10% solution of low-molecular-weight dextran should be given daily for three days in a continuous drip. We carried out a pilot study with this procedure. Of the 13 patients so treated eight died. In some of these frank pulmonary congestion developed though there had been no previous signs of left ventricular failure. The patients felt uncomfortable with the three-day continuous drip. Rheomacrodex did not influence the clotting or the fibrinolytic mechanism, but the bleeding-time (modified Ivy method) was almost doubled (from 5 to 9.2 minutes) at the end of the three days. As the patients also received anticoagulant therapy, we felt that the effect on the bleeding-time introduced a tendency to bleed of possible clinical importance, since shock-threatened patients can hardly afford even a minor loss. When, therefore, Lindén (1964) reported encouraging results similar to those of Langsjoen with a less intensive regime we decided to follow his procedure. Rheomacrodex 500 ml. was given intravenously over five hours as soon as possible after admission. This was repeated twice during the first 48 hours. This method did not influence the bleeding-time. If frank clinical signs of pulmonary congestion developed the low-molecular-weight dextran infusion was discontinued.

Both groups received routine treatment—including vaso-pressor agents, salt-restriction, digitalis, antiarrhythmic drugs—when required. Anticoagulant therapy, without initial heparin, was given to all patients. In addition one group received Rheomacrodex as described. The study was not double-blind. We did not want to infuse the control group with glucose or saline as we were not convinced that this would be completely harmless.

Results

Of 130 patients who entered the study, 67 received Rheomacrodex and 63 did not. In 28 the original diagnosis of a myocardial infarction could not be confirmed—18 were in the control group and 10 in the treated group. Of the 102 patients with a proved infarction, 57 were treated and 45 were controls (Table I).

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Table II provides information on the comparability of the groups. There were minor differences, but on the whole there is no reason to believe that the groups differed prognostically. About half of the patients in the treated series had the Rheomacrodex infusion started within six hours after the onset of chest pain, and 75% within 12 hours.

TABLE I.—*Survey of the Total Number of Patients*

	Treated Series	Control Series
Total No. of patients	67	63
No. with coronary heart disease. Acute myocardial infarction not verified ..	8	15
No. without signs of coronary heart disease	2	3
No. with acute myocardial infarction remaining for evaluation of therapy ..	57	45

TABLE II.—*Comparison Between the Two Groups on Admission*

	Treated Series	Control Series
No. of patients	57	45
Males	44	38
Females	13	7
Age in years	60·4	59·0
No. with first infarction	43	35
„ „ previous „	14	10
„ „ hypertension	16	5
„ overweight	5	2
Mean serum cholesterol (mg./100 ml.) ..	273	311
„ „ G.O.T. (units)	66	95
„ sedimentation rate (mm.)	17	12

In nine patients the infusion had to be stopped because of clinical signs of increasing pulmonary congestion. Four of these patients died—two on the second day, one on the ninth day, and one on the 25th day. In three the infusion was not completed because of death on the first day. These patients had each received 500 ml. of Rheomacrodex ; one of them developed severe pulmonary congestion. The treatment with Rheomacrodex was thus completed in 45 of the 57 patients.

Fig. 1 gives the mean value of serum G.O.T. during the first five days. The initial transaminase value was lower in the
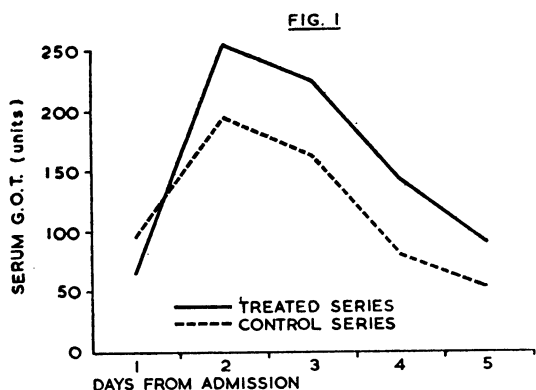
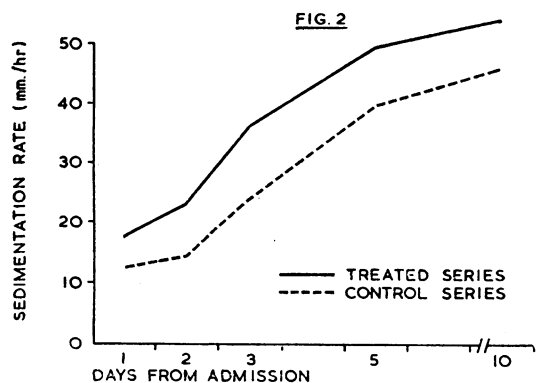FIG. 1.—Mean serum G.O.T. values in the two series.

FIG. 2.—Mean sedimentation rate in the two series.

treated group, but on the second day it was higher and remained so. The difference between the two groups in respect of the mean increase of serum G.O.T. from the first to the second day is statistically significant (P<0.01).

Fig. 2 gives the corresponding values for the sedimentation rate during the first 10 days. The small difference on the first day increased slightly during the next day, and the sedimentation rate remained higher in the treated group.

Fig. 3 gives the mean thrombotest curves during the stay in hospital. The intensity of the anticoagulant therapy was satisfactory, and the same in the two groups.
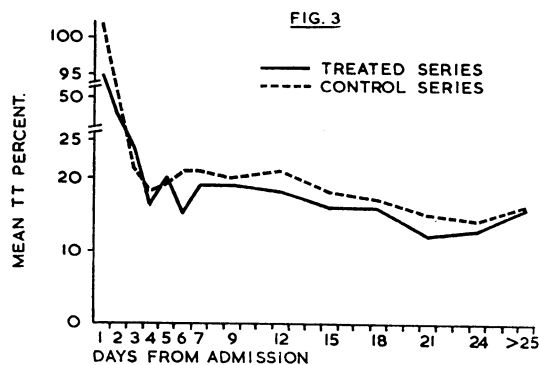
FIG. 3.—Mean thrombotest (TT) values in the two series.

Table III shows pertinent data on the patients during their stay in hospital. Congestive heart failure developed significantly more often in the treated patients than in the controls (0.01<P< 0.05). Pneumonia, post-infarction syndrome, and arrhythmia were also more frequent in the treated series, though the differences between the groups were not statistically significant. The percentage of patients needing vasopressor agents was the same. There was no thromboembolic complication in either group and only one minor bleeding episode in the control series. The mean duration of the hospital stay was slightly longer in the treated group, mainly because of the patients with post-infarction syndrome.

TABLE III.—*Comparison of Clinical and Biochemical Data in the Two Series of Patients*

	Treated Series	Control Series
Typical E.C.G. changes (%)	88	91
Serum G.O.T. = Above 40 units (%) ..	89	93
= „ 200 „ (%) ..	54	44
Increased sedimentation rate (%)	91	87
Typical temperature curve (%)	72	76
Leucocytosis (above 9,000 c.mm.) (%) ..	66	67
Pericardial friction rub (%)	18	9
Arrhythmia (%)	40	27
Shock requiring vasopressor therapy (%) ..	21	22
Congestive heart failure (%)	58	31*
Pneumonia (%)	14	2
Post-myocardial infarction syndrome (%) ..	7	0
Thromboembolic phenomena (%)	0	0
Bleeding complications (%)	0	2
Days in hospital ± S.D. (surviving patients)	30 ± 13	26 ± 6
Heart volume (ml./m.² body surface) ..	466	440

* 0·01 < P < 0·05.

None of the excluded patients died. The results in the 102 patients with proved myocardial infarction are given in Table IV, which shows a higher mortality in the treated series— namely, 14% against 8.9%. The difference is not statistically significant. A detailed description of the fatal cases and the necropsy findings are given in Table V. All 12 patients who died had an acute myocardial infarction.

TABLE IV.—*Mortality in the Two Groups*

	Treated Series	Control Series
No. of patients	57	45
„ „ deaths*	8 (14·0%)	4 (8·9%)

* Three patients died on the first day, each having received 500 ml. of Rheomacrodex.

TABLE V.—*Clinical and Necropsy Data on the Patients Who Died*

Sex and Age	Time from Admission Until Death (Days)	Clinical Cause of Death	Heart Weight (g.)	Necropsy Findings of Congestive Heart Failure	Other Necropsy Findings of Importance
		Treated	*Series*		
M 47	1	Shock	380	Severe	Acute myocardial infarction with thrombotic coronary occlusion
M 61	12	Ventricular fibrillation—shock	540	Moderate	,, ,,
M 43	9	Congestive heart failure	530	,,	,, ,,
M 70	2	Ventricular fibrillation—shock	510	,,	,, ,,
F 65	2	Shock	330	,,	,, ,,
F 70	25	Sudden death	510	None	Acute and old myocardial infarction without coronary occlusion
M 66	1	Congestive heart failure	490	Severe	Acute myocardial infarction with thrombotic coronary occlusion. Rupture of myocardium
M 63	1	Sudden death	490	Moderate	,, ,,
		Control	*Series*		
M 73	3	Congestive heart failure and shock	450	Moderate	Acute myocardial infarction with thrombotic coronary occlusion
M 65	1	Sudden death	300	Severe	Rupture of myocardium, acute myocardial infarction, and thrombotic coronary occlusion
F 75	8	,, ,,	340	Moderate	,, ,,
M 55	11	,, ,,	440	None	,, ,,

Discussion

In the pilot study we followed the procedure of Langsjoen, giving continuous infusion of low-molecular-weight dextran, 1,500 ml. a day for three days. The patients felt uncomfortable. Since we introduced a tendency to bleed, and as pulmonary congestion developed in some of the patients, we believe that this intensive treatment might be harmful. The simplified procedure of Lindén (1964) had apparently given the same striking result on mortality and was therefore adopted.

A comparison between the two groups with verified infarction showed that they were well matched, though there were more treated patients with hypertension. The course of the disease seemed to differ in the two series, as more treated patients developed congestive heart failure, post-infarction syndrome, arrhythmia, and pneumonia. The latter complication may be a consequence of the pulmonary congestion. The increase in serum G.O.T. value from the first to the second day was significantly greater in the patients receiving Rheomacrodex. This may be due to liver congestion or to more pronounced myocardial necrosis in the treated series. As we have no reason to believe that the groups differed prognostically on admission, the different clinical course suggests that Rheomacrodex had an unfavourable effect. Thus the theoretical advantages were outweighed by an increased stress of low-molecular-weight dextran infusion on the already strained left ventricle.

The number of patients needing vasopressor agents was the same in the two groups, showing that Rheomacrodex apparently did not prevent shock. It is noteworthy that there was no thromboembolic complication in the two groups; this we attribute to the anticoagulant therapy. A thrombotest level of 15 to 20% seems sufficient to prevent venous thrombosis without undue risk of bleeding.

We were unable to show any beneficial effect of Rheomacrodex on the mortality rate. In fact, the treated patients had a higher mortality than the controls. Thus the results of Langsjoen *et al.* (1963) and Lindén (1964) are not confirmed. It is remarkable that Langsjoen *et al.* found a mortality of 17.6% in their treated patients and Lindén 15%, which are very close to the 14% mortality in the present series. However, neither Langsjoen *et al.* nor Lindén had a comparable control group,

selected according to proper statistical principles. They therefore compared their results with previous experience in the same hospitals. Langsjoen *et al.* found a reduction in mortality from 46.6 to 17.6% and Lindén from 33 to 15%. If we had followed the same principle we would have found a reduction from 40%, which is the average mortality in patients with acute myocardial infarction in this hospital, to 14% in our treated series. This once again stresses the paramount importance of having a proper control group, as the mortality of 14% should, of course, not be compared with our previous experience of 40%, but with 8.9% in the present control group. The latter mortality is remarkably low. This is most probably related to our criteria of selection of patients, particularly to the exclusion of those showing obvious clinical signs of pulmonary congestion. The exclusion of old patients and of those dying on admission will further reduce the mortality in the remaining patients. Any comparison with previous experience has little meaning, as it is almost impossible retrospectively to select a comparative " control " group.

From Table I we can calculate that in the patients with coronary heart disease a diagnosis of acute myocardial infarction was maintained in 88% of the treated series against 75% of the controls. Though this difference is not statistically significant, it may indicate that in patients with impending infarction Rheomacrodex actually enhanced the development of myocardial infarction or at least influenced some of our diagnostic criteria.

Our results should perhaps be compared directly only with those of Lindén (1964), as Langsjoen *et al.* (1963) used a longer and more intensive treatment. However, our experience in the pilot study, when we copied Langsjoen's procedure, was not encouraging, and we therefore very much doubt that this regimen would have improved the prognosis in the treated series.

Our study was not double-blind, as we did not feel justified in giving placebo infusions with saline or glucose to the control patients. Therefore a bias may have been introduced when evaluating congestive heart failure. The difference in the occurrence of pneumonia, arrhythmia, and post-infarction syndrome can hardly be explained by bias. It seems highly improbable that the mortality figures, which form the basis for rejecting Rheomacrodex treatment in acute myocardial infarction, would have differed if the study had been double-blind. Therefore we believe that conclusions of general validity may be drawn from the study.

Summary

Patients with symptoms suggestive of acute myocardial infarction of less than 24 hours' duration were randomized into two groups according to a preconceived list. Both groups received routine treatment, including anticoagulant therapy. In addition, one group received low-molecular-weight dextran (Rheomacrodex) 500 ml. of a 10% solution three times during the first 48 hours after admission.

Of the 130 patients entering the study 102 had proved myocardial infarction; 57 of these received Rheomacrodex, 45 did not. The groups were well matched.

The increase in mean serum G.O.T. values from the first to the second day was significantly higher in the treated series. Congestive heart failure developed in 58% of the treated patients and in 31% of the controls (0.01<P<0.05). Furthermore, pneumonia, arrhythmia, and post-infarction syndrome occurred more frequently in the treated group.

Eight (14%) of the treated patients died, against 4 (8.9%) of the controls. The difference is not statistically significant.

It is concluded that low-molecular-weight dextran administered as described does not improve the prognosis in patients with acute myocardial infarction. The results suggest, on the

contrary, that it may be harmful. This is in contrast to previous studies.

Rheomacrodex was supplied by Pharmacia, Uppsala, Sweden.

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Life-table for Cystic Fibrosis

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Life-tables can be of value in assessing the social problem which a disease presents and in evaluating the success of different methods of treatment. Two methods of constructing a life-table are available if a hospital series is used: (1) entering the patient from the age at proved diagnosis, and (2) entering the patient from birth. The first method will probably over-estimate mortality, especially when diagnosis tends to be made shortly before death. The second will probably underestimate mortality, except in surveys of specific geographical areas in which all patients with the disease may be expected to be ascertained.

Cystic fibrosis is the commonest autosomal recessively determined disease of childhood. The best estimate of incidence in children of European stock is probably that of Danks, Allan, and Anderson (1965), which gives an incidence of approximately 1 in 2,400 live births.

Source of Case Material

A survey has been made of 498 children attending the Hospital for Sick Children between 1943 and midsummer 1964 who were coded in the hospital records as suffering or possibly suffering from cystic fibrosis. One further case was identified from a search of the post-mortem index, giving a total of 499 cases. Of these cases 399 were coded as suffering from cystic fibrosis and 100 from cystic fibrosis presenting with meconium ileus. Below are given the clinical and laboratory data resulting from the invesigation.

1. Cystic Fibrosis Not Presenting as Meconium Ileus

Examination of the case material disclosed pronounced variation in both the presence and the degree of characteristic clinical features. The diagnostic laboratory data consist of tests of tryptic activity of the duodenal juice or the sodium content of the sweat. As would be expected for cases collected over a period of more than 20 years, one or both tests had not always been carried out.

The variability both in clinical manifestation and in laboratory data is of potential importance in the construction of a life-table for the disease. Where laboratory data were not available the diagnosis was more likely to be correct in those cases in which the clinical manifestation was typical than in those in which it was not. Assay of the tryptic activity of the duodenal juice is not as reliable a confirmatory test as is the concentration of sodium in the sweat. For these reasons

the patients were divided into four primary groups, according to the presence or absence of the two laboratory tests and to the results. Each of these groups was then subdivided according to the clinical manifestations.

Classification on Laboratory Test Findings

Assay of the tryptic activity of the duodenal juice before 1952 was carried out by the method of Andersen and Early (1942). From 1952 until 1962 the method of Horsfield (1952) was used, and subsequently that of McGowan and Wills (1962). Inability to digest gelatin at a titre of 1:100 of the juice in the case of the two former methods, and a tryptic activity of the juice of less than 7 units by the latter method, were regarded as confirmatory. In all instances where the pH of the juice was stated to be below 7, or "acid," the results of the test have been excluded.

Prior to 1959 estimation of the sodium content of the sweat was determined by the method of Shwachman, Higgins, and Dooley, as quoted by Shwachman and Leubner (1955), and subsequently by the method of Gibson and Cooke (1959). By either method a sodium level of 70 mEq/K or L, or greater, was considered confirmatory.

The results of the pilocarpine iontophoresis method have been accepted only in those instances where the weight of sweat obtained was at least 100 mg. McKendrick (1962) discussed the effect of age on the sodium content of the sweat and concluded that, in infancy, levels as low as 50 mEq/l. cffer strong evidence of the disease. In the present series there were seven patients in whom the sodium content of the sweat was found to lie between 50 and 70 mEq/l. Of these, four were below the age of 1 year at the time of estimation, and their diagnosis has therefore been accepted as having been confirmed. Laboratory data obtained from tests done at other hospitals were not used in the classification of cases.

The four primary groups were as follows:

1. Diagnosis first confirmed by the sodium content of the sweat—93 cases. (In 21 the diagnosis was subsequently also confirmed by the tryptic activity of the duodenal juice. In seven cases the tryptic activity of the duodenal juice was non-confirmatory.)

2. Diagnosis first confirmed by the tryptic activity of the duodenal juice—163 cases. (In 39 the diagnosis was subsequently also confirmed by the sodium content of the sweat.)

3. Diagnosis not confirmed by either test, since neither test was done—105 cases.

4. Diagnosis regarded as not confirmed by laboratory tests—27 cases: duodenal juice confirmatory but sweat test non-confirmatory, 2 cases ; duodenal juice non-confirmatory, sweat test not done, 17 cases ; sweat test non-confirmatory, duodenal juice not examined, 6

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