Effect of Atromid-S on Fibrinolytic Activity in Patients with Ischaemic Heart Disease and Normal Blood Cholesterol Levels

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Brit. med. J., 1966, **1**, 325–327

Srivastava *et al.* (1963) have shown that in patients with hypercholesterolaemia and ischaemic heart disease the fibrinolytic activity of venous blood is very much lower than in healthy young controls, and that there is a close inverse relationship between the level of this activity and of serum cholesterol. The latter was significantly lowered by treatment with Atromid and the fibrinolytic activity was correspondingly enhanced by it.

The present study was undertaken to assess the fibrinolytic activity of patients with ischaemic heart disease in whom the serum cholesterol did not exceed 300 mg./100 ml. and then to measure the effect of Atromid-S (clofibrate) on both the cholesterol level and the fibrinolytic activity. The drug Atromid is ethyl-*p*-chlorophenoxyisobutyrate in combination with androsterone, each capsule containing 244.5 mg. and 5.5 mg. respectively. Each capsule of Atromid-S contains 250 mg. of the isobutyrate compound only. This latter drug was used in this study because the patients under observation were taking part in a therapeutic trial (to be published later) in which the preparation without androsterone was chosen because of its relative cheapness and because earlier trials had shown that there was no difference between the two preparations in their capacity to lower blood cholesterol (Howard *et al.*, 1963; Oliver, 1963).

Materials and Methods

Thirty patients (2 females and 28 males) were included in the present trial. Twenty-five had had one or more myocardial infarcts during the preceding two months to two years. The remaining five had suffered from angina for from six months to four years, and all had electrocardiographic evidence of ischaemic heart disease at rest. Eighteen of the patients had been on long-term phenindione therapy, and this was discontinued one week before the beginning of the trial in all except one patient (Case 30), who continued on anticoagulant therapy throughout the period of the trial. All patients had initial serum cholesterol figures below 300 mg./100 ml. except for one at that figure. The average of two serum estimations made fasting one week apart is taken as the initial level in the tables. The estimations were made by an AutoAnalyzer in the I.C.I. Laboratories by the same method as in the study by Srivastava *et al.* (1963). Samples of blood were collected as before (Srivastava *et al.*, 1963) for estimation of both cholesterol and whole-blood-clot lysis times. For the latter the figure taken was the average of two readings to the nearest half-hour.

The trial was conducted on a double-blind basis. Fifteen patients received Atromid-S and 15 received placebo capsules each containing 200 mg. of corn oil. The drug was given orally; those patients weighing 140 lb. (63.5 kg.) or more received eight capsules of 250 mg. a day, and those weighing less than 140 lb. received six capsules a day. The patients were reviewed at monthly intervals for the first three months and thereafter at three-monthly intervals. The subjects were tested fasting, and rested in the morning at approximately the same hour on each visit.

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Results

General.—The drug was well tolerated by all the patients. Two patients, one control and one treated, died during the trial—one (Case 13) during the second month and the other (Case 25) during the eighth month, in each case of coronary thrombosis. The remainder have been followed for periods of six to nine months.

Serum Cholesterol.—Table I shows the serum cholesterol levels in the 15 treated patients initially and during the period of treatment. Cholesterol values were reduced significantly after one month of treatment, but the maximum reduction occurred during the second month. It can be seen that five of the patients showed little response to treatment. The effect of the drug appears to be well sustained over the period of observation (Fig. 1), though there has been a slight rise of cholesterol (8%) at the ninth month in the first 11 patients who were tested up to this period. Table II shows the serum cholesterol values in the 15 control subjects. Their initial

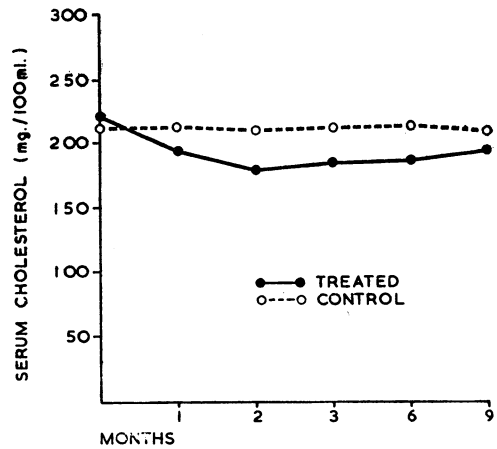

FIG. 1.—Mean change in serum cholesterol for the whole group during nine months' treatment.

TABLE I.—*Serum Cholesterol Changes in 15 Patients Taking Atromid-S (mg./100 ml.)*

Case No.	Initial Level	Trial Period (Months)				
		1	2	3	6	9
1	205	225	205	190	200	**190**
2	175	165	160	155	175	**185**
3	235	190	150	225	—	**210**
4	170	170	145	140	185	**190**
5	185	135	130	—	170	**160**
6	255	145	145	155	155	**180**
7	245	215	175	170	155	**200**
8	185	160	190	200	225	**230**
9	260	190	195	—	205	**225**
10	265	270	160	195	200	**200**
11	280	195	150	145	190	**165**
12	150	145	130	145	140	—
13	260	250	Died			
14	250	215	220	220	230	—
15	300	185	220	210	175	—
Mean	228	190	170	179	180	**194**
Mean change		−38	−58	−49	−48	**−34**
S.E.		±9·25	±10·99	±13·07	±14·41	**±10·75**
t		4·11	5·28	3·75	3·33	**3·16**
P		<0·01	<0·001	<0·01	<0·01	**<0·02**

levels did not differ significantly from the treated group, and over the nine months' observation there was no change (Fig. 1). The difference in response of the two groups is statistically significant.

Fibrinolytic Activity.—The fibrinolytic activity is expressed as units calculated as a reciprocal of the clot-lysis time in minutes multiplied by 10,000. Normal clot-lysis time as determined in 12 healthy subjects aged 18 to 39 years varied from 210 to 480 minutes, with a mean of 290 minutes, giving a fibrinolytic activity of 47.6 to 20.8 units, with a mean of 34.4 units. In the treated and control groups the fibrinolytic activity is shown in Tables III and IV respectively. All patients except one (Case 26 in the control group) had initial levels within the normal range, and over the period of observation no significant change in the levels took place in either group (Fig. 2). Among the treated patients in whom the blood cholesterol level was lowered the fibrinolytic activity, so far from rising, actually fell, though not to a significant degree. The absence of any correlation between the levels of serum cholesterol and of fibrinolytic activity is demonstrated in Fig. 3.

TABLE II.—*Serum Cholesterol Changes in 15 Patients Taking Placebo (mg./100 ml.)*

Case No.	Initial Level	Trial Period (Months) 1	2	3	6	9
16	270	265	260	245	245	225
17	205	210	210	205	210	185
18	220	265	240	215	225	245
19	210	230	215	225	230	230
20	190	175	195	185	165	215
21	170	155	135	125	—	150
22	275	240	235	235	260	275
23	200	165	165	165	135	190
24	175	195	165	175	200	220
25	215	190	225	230	225	Died
26	270	260	270	260	275	270
27	225	235	240	215	230	215
28	195	215	210	225	220	215
29	195	220	220	235	250	—
30	225	200	215	230	255	—
Mean	216	215	214	218	219	213
Mean change ..		−1	−2	+2	+3	−3
S.E.		±6·25	±4·3	±5·02	±7·83	±7·29
t ..		0·16	0·46	0·39	0·38	0·41
P ..		<0·90	<0·70	<0·70	<0·70	<0·70

TABLE III.—*Fibrinolytic Activity in 15 Patients Taking Atromid-S (Units)*

Case No.	Initial Level	Trial Period (Months) 1	2	3	6	9
1	30·3	33·3	33·3	33·3	47·6	41·7
2	37·0	33·3	37·0	33·3	41·7	37·0
3	37·0	23·8	23·8	20·8	20·8	27·8
4	37·0	33·3	33·3	37·0	47·6	41·7
5	47·6	41·7	41·7	41·7	37·0	41·7
6	47·6	30·3	37·0	37·0	47·6	47·6
7	41·7	37·0	33·3	30·3	33·3	30·3
8	33·3	23·8	33·3	33·3	33·3	33·3
9	33·3	33·3	41·7	33·3	33·3	41·7
10	33·3	30·3	25·6	41·7	33·3	30·3
11	33·3	47·6	41·7	37·0	37·0	37·0
12	30·3	37·0	33·3	47·6	37·0	—
13	30·3	30·3	Died			
14	47·6	41·7	37·0	47·6	47·6	—
15	41·7	37·0	37·0	41·7	37·0	—
Mean	37·4	34·2	34·9	36·8	38·1	37·3
Mean change ..		−3·2	−2·5	−0·6	+0·7	−0·1
S.E.		1·97				
t ..		1·6	N.S.	N.S.	N.S.	N.S.
P ..		<0·20				

N.S. = Not significant as tested by Student's t test.

TABLE IV.—*Fibrinolytic Activity in 15 Patients Taking Placebo (Units)*

Case No.	Initial Level	Trial Period (Months) 1	2	3	6	9
16	37·0	33·3	37·0	37·0	37·0	37·0
17	30·3	30·3	30·3	37·0	33·3	33·3
18	37·0	47·6	47·6	47·6	47·6	47·6
19	37·0	30·3	19·6	13·9	20·8	25·6
20	41·7	41·7	41·7	47·6	37·0	41·7
21	25·6	33·3	33·3	33·3	37·0	33·3
22	25·6	27·8	27·8	27·8	25·6	27·8
23	41·7	47·6	47·6	37·0	41·7	41·7
24	27·8	33·3	33·3	27·8	30·3	30·3
25	27·8	16·7	30·3	33·3	30·3	Died
26	15·1	13·3	13·9	15·9	17·4	—
27	41·7	41·7	30·3	41·7	41·7	47·6
28	25·6	17·4	15·2	15·2	20·8	20·8
29	47·6	47·6	47·6	47·6	47·6	—
30	55·5	47·6	47·6	47·6	47·6	—
Mean	34·5	34·0	33·5	34·0	34·4	33·9
Mean change ..		0·5	1·0	0·5	0·1	0·6
t ..		N.S.	N.S.	N.S.	N.S.	N.S.

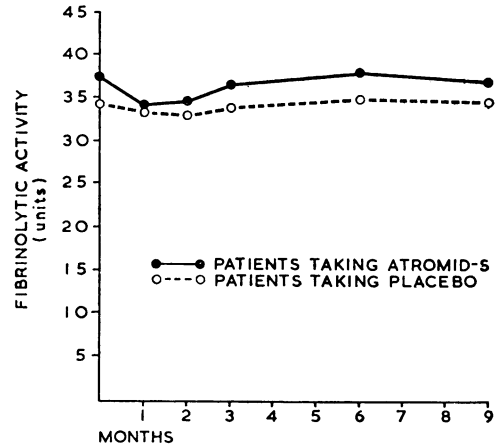

FIG. 2.—Mean change in fibrinolytic activity.

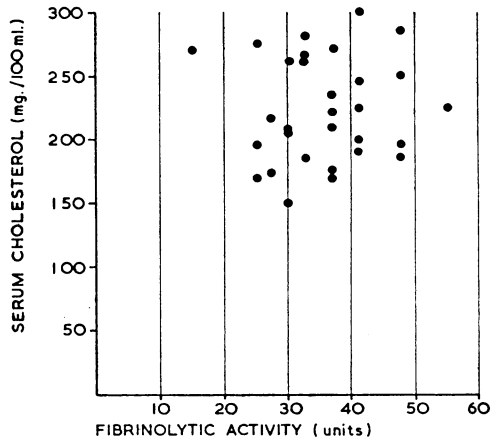

FIG. 3.—Scattergram of cholesterol values and fibrinolytic activity in 30 patients (initial levels).

Discussion

This study shows that the fibrinolytic activity of a group of patients with ischaemic heart disease and normal cholesterol values is, with the exception of one patient (Case 26), within the same range as that of a healthy group of controls. No relation between this activity and the levels of serum cholesterol was found. This finding is in striking contrast to the findings of the study by Srivastava *et al.* (1963), where the initial levels of cholesterol and fibrinolytic activity in the hypercholesterolaemic range were inversely related. In further contrast to the study mentioned the fibrinolytic activity of the treated patients did not rise as their levels of cholesterol fell.

The present findings are in line with those recorded by Merskey *et al.* (1960), Goldrick (1961), and Fearnley *et al.* (1963). If one accepts that decreased fibrinolytic activity plays a part in the pathogenesis of atherosclerosis, this work may imply that the aetiological factors in the production of atherosclerosis are somewhat different in patients with hypercholesterolaemia from what they are in those with normal blood cholesterol values.

Summary

Fibrinolytic activity has been estimated in 30 patients with ischaemic heart disease and fasting serum cholesterol levels of

300 mg. or less. The activity lay within the normal range and did not correlate with cholesterol levels.

Atromid-S (clofibrate) lowered the serum cholesterol significantly in 15 of the patients compared with 15 controls.

Fibrinolytic activity did not change significantly in either treated or control groups.

These results are in striking contrast with those of a previous trial involving patients with hypercholesterolaemia.

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Induction of Labour by Intra-amniotic Hypertonic Saline

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Brit. med. J., 1966, **1**, 327–330

Throughout obstetrics there is a conflict between conservative management and operative intervention. Nowhere is the problem of induction of labour more controversial than when the foetus is dead or deformed. The efficacy of the various methods of induction must be balanced against the inevitability of labour. Conservative management may be complicated by mental distress in the mother awaiting labour (Corbett, 1958), hypofibrinogenaemia with a dead baby (Barry *et al.*, 1955; Quinn and Harper, 1958), or dystocia at term with a large malformed foetus. These dangers may tempt the obstetrician to intervene.

On the other hand, there are undoubted maternal hazards in the conventional methods of induction. Amniotomy may introduce infection into a dead pregnancy, while rapid drainage of massive hydramnios (for example, in anencephaly) may provoke placental separation (Cunningham, 1965). Missed abortion in the first three months may be evacuated surgically, but here, too, there is a risk of haemorrhage. Various forms of medical induction with oestrogens, quinine, and oxytocin injections have been found unreliable (Martin and Menzies, 1955).

A failed induction in this type of case merely serves to increase maternal distress and frustration, so that the method used must be both safe and reliable.

Similarly in the rare cases when therapeutic termination of pregnancy is indicated it is equally essential that an induction be effective and without significant risk to a mother who may be too ill to withstand hysterotomy. Simple dilatation and curettage is practicable only before the twelfth week, and often the decision about termination has not been made as early as this. Thus there is a need for a reliable method of inducing abortion in the second trimester.

New Methods of Induction

Intra-amniotic Hypertonic Saline

Burke (1935) reported that Uroselectan B injected for amniography often induced labour, and it was used for this purpose by Playfair (1941). Hypertonic glucose was also used at this time, but the method was abandoned for normal cases because of a high incidence of intrauterine death.

Aburel (1934) first described the instillation of "a serum containing 33% sodium chloride" into the amniotic sac as a safe and reliable method of terminating early pregnancy. The increasing demand for legalized abortion in Scandinavia has resulted in renewed interest in the method (Svane, 1960; Wagner *et al.*, 1962). Such cases have been used to study the physiology of uterine action (Bengtsson and Csapo, 1962; Wiqvist and Eriksson, 1964). Fifty per cent. glucose has also been used successfully (Brosset, 1958; Wood *et al.*, 1962), but there have been two reports of maternal deaths due to anaerobic infection following this technique (Briggs, 1964; MacDonald *et al.*, 1965). Glucose favours the growth of saccharolytic organisms, and therefore saline might be safer. On the other hand, there is a theoretical risk of overloading the circulation with saline in pre-eclampsia and cardiac disease.

The method is unacceptable as a routine means of induction because the hypertonic solution often kills the baby, but it is applicable not only for therapeutic abortion but also in cases of gross foetal abnormality incompatible with life and when the baby is already dead (Csapo *et al.*, 1963b).

For therapeutic abortion the intra-amniotic injection is best performed by the abdominal route after the sixteenth week. This delay allows the obstetrician more time to consider fully the indications for the operation.

In cases of intrauterine death amniocentesis can be carried out with complete sterility, avoiding the risk of infection which accompanies conventional amniotomy. Should induction fail, therefore, one is not committed to an operative delivery.

High-dosage Oxytocin Infusion

This is effective when the baby is dead (Loudon, 1959; Liggins, 1962), but rarely cardiovascular and antidiuretic complications do occur (Reinberger and Mackey, 1958; Mayes and Shearman, 1956; Abdul-Karim and Assali, 1961).

The method is completely unsuccessful in inducing therapeutic abortion and relatively ineffective in viable pregnancies with intact membranes.

Surgical induction by amniotomy, as a prelude to oxytocin, greatly increases the efficiency and success of the method. However, on those occasions when such inductions fail with an abnormal baby, the hazards of intrauterine infection increase the longer the awkward decision to undertake caesarean section is postponed.

Though disproportion is seldom present in the group of premature inductions under discussion, rupture of the uterus

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