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PRELIMINARY COMMUNICATIONS

Combined Use of Clofibrate and Cholestyramine or DEAE Sephadex in Hypercholesterolaemia

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British Medical Journal, 1971, **3**, 25–27

Summary

A comparison was made of the effect of DEAE (diethylaminoethyl) Sephadex (an anion exchange resin) and cholestyramine (Questran) with and without the addition of clofibrate in normal and hypercholesterolaemic patients. DEAE Sephadex (12-15 g/day) alone appeared to be as effective as cholestyramine in lowering the plasma cholesterol by 12-15%. Clofibrate acted synergistically with DEAE Sephadex and increased the activity of the latter by over twofold. This combination proved superior to that of clofibrate and cholestyramine and has the greatest potential use in the treatment of type II pattern hyperlipoproteinaemia.

Introduction

The treatment of hypercholesterolaemia by means of non-absorbable bile acid sequestrants is now well established, and one such resin, cholestyramine (Bergen and van Itallie, 1963; Hashim and van Itallie, 1965), produces a lowering of plasma cholesterol of about 15% when 15 g is given daily. The mechanism of action of this class of drugs is to bind bile acids preferentially in the intestine, thus facilitating their increased faecal excretion. Since cholesterol is the precursor of bile acids the body content of cholesterol (including plasma cholesterol) is reduced provided a high enough dose is given. Cholestyramine has the disadvantages of being only moderately effective, is unpalatable to some, and causes gastrointestinal side effects in a fair proportion of patients. DEAE (diethylaminoethyl) Sephadex, which has been shown to be as active as cholestyramine in vitro and in animals (Parkinson, 1967), has the advantage of being a tasteless powder which forms a gel in water and is potentially more acceptable to the patient. Comparative experiments were therefore carried out to compare its efficacy and acceptability with cholestyramine.

The chief factor which limits the use of anion exchange resins is the large quantity needed for treatment. This is because with small quantities the body compensates completely for the removal of bile acids by synthesizing more cholesterol from acetate (Goodman and Noble, 1968). Attempts were therefore made to improve the potency of ion exchange resins by the use of clofibrate, a compound with a completely different mode of action (Grundy *et al.*, 1969).

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Experimental Design and Methods

Geriatric patients attending Chesterton Hospital were screened for plasma cholesterol and suitable subjects were chosen for study. These comprised a number of hypercholesterolaemic and normal patients.

Study 1.—Three groups of hypercholesterolaemic (Fredrickson *et al.*, 1967) patients (five per group, each containing one type IV and four type II pattern of lipoprotein disorder) were placed on a moderately low cholesterol, low saturated fat diet (saturated fats reduced, no more than three eggs a week, corn oil used for cooking, etc.) Blood was then taken after an overnight fast. After a three-month baseline period their treatment was planned as follows: group 1, a placebo consisting of an inert resin (4 g three times daily); group 2, cholestyramine (Questran 4 g active material, three times daily); and group 3, DEAE Sephadex (4 g three times daily). Each resin was well mixed with water for several minutes before taking. All patients were studied for at least six months.

Study 2.—Eighteen patients (13 hypercholesterolaemic, of whom 12 were type II and 1 was type IV, and 5 normal) were asked to continue on their normal diet. Blood was then taken weekly after an overnight fast. Their treatment was as shown in the Table. After two weeks without treatment they were given either DEAE Sephadex (5 g three times daily) or clofibrate (500 mg three times daily) or a combination of DEAE Sephadex (5 g three times daily) and clofibrate (500 mg three times daily) or cholestyramine (Questran 4 g active substance four times daily) and clofibrate (500 mg three times daily). To avoid any possibility of interference with absorption clofibrate was given half an hour before meals and the resin with meals. After each two-week or four-week treatment period there was a period of two weeks without treatment before the next treatment was started. Each sequence was carried out at random.

STUDY 2—*Effect of Clofibrate and Ion Exchange Resins (Cholestyramine and DEAE Sephadex) on Plasma Cholesterol Levels (in mg/100 ml)*

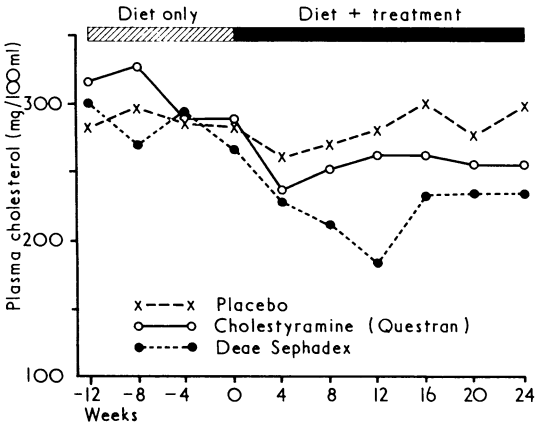
Case No.	Lipoprotein Type	DEAE Sephadex + Clofibrate					Clofibrate			DEAE Sephadex			Cholestyramine + Clofibrate		
		i	ii	Change	iii	Change	iv	v	Change	vi	vii	Change	viii	ix	Change
Time of study (weeks):		0	2	(%)	4	(%)	0	2	(%)	0	2	(%)	0	2	(%)
1	II	415	215	48											
2	IV	355	253	29	244	31									
3	II	355	241	32	273	23									
4	II	346	210	39	200	42									
5	II	336	193	43									324	244	25
6	II	318	211	34									271	183	32
7	II	310	212	32									295	216	27
8	II	289	228	21									273	252	8
9	II	296	182	39	221	25	279	267	4	308	253	15	315	259	18
10	II	279	186	33	180	35	208	182	13	200	189	6	230	209	9
11	II	272	125	54	147	46	308	236	23	218	183	16	250	227	9
12	II	278	202	27	162	42	248	183	26	262	274	+5	252	204	19
13	II	270	180	32	152	44	240	218	9	236	196	17	228	204	10
14	N	248	187	26			261	262	0	215	180	16	273	198	27
15	N	230	175	24			204	227	+11	233	204	12	244	199	18
16	N	230	162	30	120	48	245	245	0	224	184	18	238	188	21
17	N	228	142	38	170	25	253	253	0	246	186	24	247	160	35
18	N	180	125	31	141	22									
Mean change (%)	Cases 1-18			34		35									
	„ 9-17			33					7			13			
	„ 5-17			34											20

Statistical comparisons: Columns i and ii, P <0·001; i and iii, P <0·001; iv and v, N.S.; vi and vii, P <0·001; viii and ix, P <0·001; i-ii and viii-ix, P <0·01.

Plasma Lipid Determinations—Plasma cholesterol was determined by hydrolysis and digitonin precipitation (Sperry and Webb, 1950) and estimated by the ferric chloride and sulphuric acid method (Crawford, 1958). Plasma triglycerides were estimated with the autoanalyser (Lofland, 1964).

Results

Study 1.—Two patients allocated to the cholestyramine group withdrew because of gastrointestinal side effects (constipation or stomach acidity). Otherwise all subjects adhered to their treatment and complained only occasionally of constipation. Both cholestyramine and DEAE Sephadex lowered plasma cholesterol, compared with the placebo (see Chart). Though DEAE Sephadex seemed slightly more effective (15% compared with 12%) the difference was not statistically significant. Plasma triglycerides were unaffected by resin treatment.



STUDY 1—Effect of Cholestyramine and DEAE Sephadex on Plasma Cholesterol (Five Patients per Group). Statistical Analysis: DEAE Sephadex and Placebo P<0·001; Cholestyramine and Placebo P<0·05; DEAE Sephadex and Cholestyramine P = 0·5 (N.S.).

Study 2.—The most effective treatment was a combination of DEAE Sephadex and clofibrate, which produced a mean lowering in plasma cholesterol of 34% (21-54%) in two weeks and 35% (22-48%) in four weeks (see Table). The combination of cholestyramine and clofibrate was much less effective in all patients, with a mean lowering of 20% (8-35%). Of the 18 patients examined three were unable to continue treatment with cholestyramine after a few days because of gastrointestinal upsets. These three were able to tolerate DEAE Sephadex without side effects. DEAE Sephadex and clofibrate acted synergistically. Thus in nine patients directly compared the mean lowering with clofibrate alone was 7% (not significant), with DEAE Sephadex alone 13%, and 33% for the combination.

Discussion

DEAE Sephadex is a palatable anion exchange resin which is as effective as cholestyramine in lowering plasma cholesterol. Our work therefore confirms and extends the unpublished studies of Parkinson (1968). It would thus seem to be a suitable alternative for those patients who are unable to tolerate cholestyramine because of initial gastrointestinal disturbance. In our experience the acceptability of DEAE Sephadex is excellent and side effects are negligible.

Attempts to improve the efficacy of DEAE Sephadex by the additional use of clofibrate were very successful, and the mean decrease in plasma cholesterol after two weeks was improved from 13 to 33%. The combination of clofibrate with cholestyramine was less effective, and the decrease of 20% was only slightly more than that previously reported with cholestyramine alone (Bergen and van Itallie, 1963; Hashim and van Itallie, 1965). The synergistic effect of clofibrate with DEAE Sephadex is surprising but is no doubt due to the interaction of the different properties of each drug. Thus clofibrate has been shown to increase the weight of bile salts secreted into the intestine, in the dog (Horning and Horning, 1970) and in the rat (Hess, 1970) to inhibit cholesterol biosynthesis in the rat (Gould and Swyryd, 1968) and in man (Grundy *et al.*, 1969), and to increase the faecal excretion of cholesterol (Grundy *et al.*, 1969). All of these properties would tend to increase the effectiveness of bile acid sequestrants. Further work is obviously needed before the relative importance of these mechanisms can be established. Though in these experiments the two drugs were given separately our recent work has shown that DEAE Sephadex interferes very little with the absorption of clofibrate when given simultaneously, and it is therefore not necessary to give separate dosage as in the described experiments.

The most interesting feature of the use of DEAE Sephadex and clofibrate was that the combination appeared to be effective in all patients, even in those with apparently normal plasma cholesterol. With such a small study it is impossible to state

which classes of hyperlipoproteinaemia are best treated with a combination or with clofibrate alone. It is, however, quite clear that its greatest potential use is for the treatment of the type II pattern, which is, in general, affected little by clofibrate alone and only moderately by cholestyramine.

We are indebted to Dr. W. Davison for permission to study some patients under his care; Drs. M. S. Rao, G. Foubister, and A. A. Beeson, and the medical and nursing staff of Chesterton Hospital, Cambridge, for their help with the patients; and also Mr. M. Brown and Mrs. A. Bright for technical help.

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MEDICAL MEMORANDA

Ischaemic Colitis and the Contraceptive Pill

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Ischaemic colitis is a well-defined clinical, radiological, and pathological entity (Marston *et al.*, 1966). It occurs most commonly in elderly patients with arteriosclerosis. Most younger patients have had associated conditions which predispose to embolism, venous thrombosis, or vasculitis, such as cardiac disease, diabetes mellitus, or rheumatoid arthritis (Lea Thomas, 1968).

We report a typical attack of ischaemic colitis occurring in a woman taking the contraceptive pill and discuss the possible causative relationship.

Case Report

A married woman aged 39 was admitted to hospital because of sudden severe colicky abdominal pain below the left costal margin associated with bloody diarrhoea. Her bowel habit had previously been normal apart from occasional blood loss due to haemorrhoids. She smoked 10-15 cigarettes a day. She had been taking Ovulen (ethynodiol diacetate 1 mg, mestranol 0·1 mg) cyclically as a contraceptive for two years. Two weeks before admission this had been changed to Ovulen 50 (ethynodiol diacetate 1 mg, ethinyloestradiol 0·05 mg).

On examination she was found to be moderately overweight and not seriously ill. Her temperature reached 38°C intermittently over the first few days. The left side of the abdomen was tender but there was no palpable mass or sign of peritonitis. Rectal examination and sigmoidoscopy showed internal haemorrhoids, normal rectal mucosa, and bleeding from above the rectosigmoid junction. There were no signs of peripheral vascular disease or arthritis. The cardiac rhythm was regular and the blood pressure 120/70 mm Hg.

On admission the haemoglobin was 14·0 g/100 ml; W.B.C. 12,400/mm^3 (91% neutrophils); E.S.R. 12 mm/hr (Westergren); platelets were 210,000/mm^3; and serum protein electrophoresis was normal. There was no glycosuria and no pathogens were isolated from the stools or urine. Plain *x*-ray films of the abdomen showed absence of gas in the splenic flexture and descending colon.

Barium-enema examination five days after the onset of symptoms showed a narrowed segment from the splenic flexure to about halfway down the descending colon, merging gradually into normal colon at either end. The margin of the segment was irregular and showed evidence of "thumb-printing" (Fig. 1 A). An abdominal aortogram performed by flood aortic injection in the prone position showed normal origins of the coeliac axis and superior and inferior mesenteric arteries. No abnormality of their distal branches or of the marginal artery was seen.

The abdominal pain, tenderness, and fever settled within three days without specific treatment. The diarrhoea ceased after the first day and there was no further bleeding. Oral contraceptives were discontinued and she left hospital after 11 days.

A repeat barium-enema examination a month after the first showed that the segment had considerably widened; the thumb-printing had disappeared but there was some evidence of sacculation (Fig. 1B). She had no recurrence of symptoms, and a third enema eight months after the first showed that the colon had returned to normal (Fig. 1 C).

Comment

The clinical course and radiological features in this patient were typical of ischaemic colitis. She had a sudden onset of left-

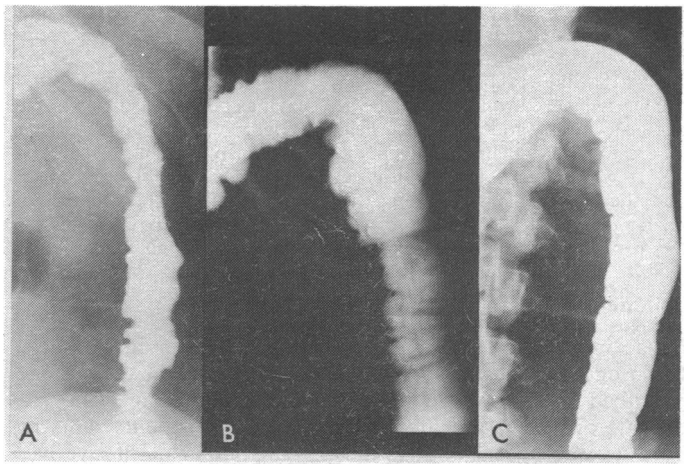

FIG. 1—A, First barium-enema film showing narrowing and thumb-printing of the splenic flexture and descending colon. B, One month later. The segment has widened and sacculation has developed distal to the splenic flexture. C, Eight months later, normal.

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