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CHENODEOXYCHOLIC ACID THERAPY FOR HYPERTRIGLYCERIDAEMIA IN MEN

[1]M.C. BATESON, [2]D. MACLEAN, [2]J.R. EVANS & [1]I.A.D. BOUCHIER

University Departments of Medicine[1] and Biochemical Medicine,[2]
Ninewells Hospital and Medical School, Dundee

1 Ten consecutive patients with hypertriglyceridaemia who adhered to a low carbohydrate diet without complete control of serum triglycerides were started on chenodeoxycholic acid 750 mg daily and followed monthly for 6 months. Nine of these patients were then followed for a further month on placebo capsules and thereafter monthly for a further 6 months on clofibrate 2 g daily.

2 The mean serum triglyceride level fell by 36% after dietary treatment alone ($P < 0.05$) and by 47% from initial values on diet plus chenodeoxycholic acid ($P < 0.01$). In the nine patients who proceeded to clofibrate therapy there was a rise in triglyceride levels on placebo capsules to the level achieved by diet alone, and a further fall on diet plus clofibrate of 47% of initial values ($P < 0.05$).

3 Chenodeoxycholic acid therapy is effective in the management of hypertriglyceridaemia not completely cured by dietary measures, and may be as efficacious as clofibrate.

Introduction

Serum cholesterol and triglyceride levels are each powerful predictors of arterial disease (Kannel, Castelli, Gordon & McNamara, 1971; Carlson & Bottinger, 1972; Westlund & Nicolaysen, 1972; Goldstein, Hazzard, Schrott, Bierman & Motulsky, 1973). The common types of hypertriglyceridaemia (Lorimer, Cox, Greaves, Jubb, Hawthorne, Morgan & Lawrie, 1974) are the endogenous carbohydrate-related pattern (Type IV) (Fredrickson & Lees, 1965) and the mixed pattern associated with significantly raised cholesterol levels (Type IIb) (Beaumont, Carlson, Cooper, Fejfar, Fredrickson & Strasser, 1970). Both forms of hypertriglyceridaemia may respond to dietary carbohydrate restriction alone (Tabaqchali, Chait, Harrison & Lewis, 1974), but it may sometimes be necessary to add drugs such as clofibrate before the abnormal triglyceride levels are controlled. Clofibrate is relatively non-toxic (Oliver, 1967), but unfortunately enhances the cholesterol concentration in bile (Grundy, Ahrens, Salen, Schreibman & Nestel, 1972; Pertsemlidis, Penveliwalla & Kimbal, 1973) thereby enhancing the tendency to form cholesterol gallstones (Coronary Drug Project, 1975).

The primary bile acid chenodeoxycholic acid (CDCA) has been introduced as an agent capable of dissolving gallstones. Observations on patients under treatment for gallstones suggested that CDCA is also capable of lowering serum triglycerides (Bell, Lewis, Petrie & Dowling, 1973; Hoffman, Hoffmann & Thistle, 1974). The lowest effective dose in cholelithiasis so far demonstrated is about 500–750 mg daily. The present study was designed to ascertain whether or not chenodeoxylcholic acid therapy in moderate dose has a useful role in the management of hypertriglyceridaemia not completely responsive to diet.

Methods

Patients referred to the Dundee lipid clinic were seen by a dietitian, advised of their ideal weight and counselled individually about restriction of energy intake and classes of food to avoid. They were subsequently seen frequently by a dietitian.

Ten consecutive patients referred to the Dundee lipid clinic were found to have endogenous hypertriglyceridaemia (> 2.48 mmol/l) which was not completely corrected by dietary advice. Since mild to marked hypertriglyceridaemia had persisted despite dieting to constant mean weight, patients were invited to participate in a trial of chenodeoxycholic acid. Details of patients are given in Table 1. The nature of the drug and purpose of the trial were explained, and informed consent obtained. None of these patients had overt diabetes mellitus, alcoholism, myxoedema or overt liver disease. Two had asymptomatic gallstones discovered at cholecystography. No patients had fasting chylomicronaemia. All had elevated very low

Table 1 Patient characteristics and weight changes in men on diet and drugs for hypertriglyceridaemia

Patient	*Age (years)*	*Diet*	*Energy intake (mJ)*	*Duration (months)*	*Initial weight (kg)*	*Weight after diet (kg)*	*Weight after CDCA (kg)*	*Weight after clofibrate (kg)*
1	57	LAF+ LCHO	4.2	6	67.0	67.5*	66.0	69.0
2	71	LCHO	3.4	2	83.1	74.5	69.2	72.0
3	54	LCHO	7.0	4	61.5	61.0*	60.4	63.0
4	62	LCHO	7.0	6	67.2	64.5*	65.6	69.6
5	54	LCHO	4.2	12	68.5	70.0	67.4	67.7
6	35	LCHO	2.5	3	92.7	89.0	89.8	89.1
7	56	LCHO	3.4	3	87.6	83.3	85.7	—
8	41	LCHO	4.2	7	71.5	65.5*	68.0	69.4
9	42	LAF+ LCHO	4.2	6	80.0	74.5	76.0	85.1
10	50	LAF+ LCHO	4.2	6	86.4	71.5*	72.2	74.5
Mean ± s.d.	52.2 ± 10.6				76.5 ± 10.6	72.1 ± 8.6 $P<0.05$ versus inital weight	72.0 ± 9.2 $P<0.01$ versus inital weight	73.2 ± 8.5 NS versus initial or post-diet weight

LCHO = low carbohydrate diet; LAF = low animal fat diet; * = ideal weight after diet by Metropolitan Life Insurance data.

density lipoprotein, some also had elevated low density lipoprotein.

The following estimations were carried out on fasting blood samples: alkaline phosphatase, aspartate aminotransferase, γ-glutamyl transpeptidase; total protein and albumin; full blood count, and platelet count; serum sodium, potassium, calcium, chloride, phosphate and creatinine; and the blood glucose and urea. Serum cholesterol and triglycerides were estimated by the Technicon Autoanalyser method. Cellulose acetate electrophoresis was performed.

All patients were given chenodeoxycholic acid 250 mg thrice daily. One patient was not able to tolerate this dose, and after the first month continued on 250 mg twice daily. All patients were reviewed monthly, weighed, questioned about symptoms, and the blood tests repeated. After 6 months' therapy, a single-blind crossover to placebo capsules for 1 month was possible in nine patients, who were then continued on clofibrate 1 g twice daily for a further 6 months.

Differences in weight and serum triglycerides were analysed by Wilcoxon's Rank Sum test for paired samples and analysis of variance. Comparisons with initial serum triglyceride results were made after logarithmic transformation. Differences in other blood tests were analysed by Student paired *t*-test. Ranges shown as s.d.

Results

Ten patients completed the trial of CDCA. Mean weight fell from 76.5 ± 10.6 kg initially to 72.1 ± 8.6 kg after diet ($P < 0.05$), and 72.0 ± 9.2 kg

Table 2 Serum triglycerides after diet and drug therapy

	Serum triglycerides (mM)				
Patient	*Initial*	*Diet alone*	*Diet + CDCA*	*Diet + placebo*	*Diet + clofibrate*
1	2.77	2.85	2.44	3.96	2.79
2	3.12	3.26	2.71	1.92	1.60
3	3.31	2.91	2.34	2.56	2.21
4	3.53	3.06	2.86	2.77	3.15
5	3.72	4.03	2.64	3.05	4.20
6	5.65	3.36	3.55	5.54	2.70
7	5.77	3.80	2.62	—	—
8	6.26	3.17	3.10	2.57	3.82
9	6.36	3.72	2.67	3.26	2.20
10	10.20	2.56	2.40	2.90	1.38
Mean ± s.d.	5.06 ± 2.28	3.27 ± 0.45 (64% initial levels, ($P < 0.05$)	2.73 ± 0.36 (53% initial levels, ($P < 0.01$ versus diet-treated)	3.17 ± 1.04 $P < 0.01$ versus levels at 6 months on CDCA) ($P < 0.05$ versus initial levels) (NS versus diet-treated mean = 3.21 mM	2.67 ± 0.94 (53% initial levels, $P < 0.05$) (NS versus placebo + NS versus diet alone)

Table 3 Liver function tests on CDCA and clofibrate therapy (mean ± s.d.)

	On diet	*CDCA*	*Placebo*	*Clofibrate*
Aspartate aminotransferase (IU)	21.54 ± 7.78	24.27 ± 6.78	20.09 ± 3.59	24.81 ± 5.74
γ-Glutamyl transpeptidase (IU at 37°C)	30.72 ± 22.62	26.81 ± 12.81	24.9 ± 11.98	17.72 ± 3.76
Alkaline phosphatase (KAU)	9.81 ± 4.29	10.63 ± 5.32	9.45 ± 4.37	6.90 ± 5.13
Bilirubin (mmol/l)	10.97 ± 4.05	9.78 ± 4.34	10.56 ± 4.02	8.65 ± 2.75

Values on drug therapy are means for months 1–6. No changes achieved statistical significance except the fall in γ-GTP on clofibrate in months 3 and 4 ($P < 0.05$, paired *t*-test).

after 6 months CDCA ($P < 0.01$ versus initial weight). It was 73.2 kg after 6 months clofibrate (NS). Serum triglyceride results are shown in Table 2. Overall changes were also significant by analysis of variance on CDCA ($P < 0.001$) and on clofibrate ($P < 0.05$).

Serum cholesterol levels in the patients completing the crossover trials were also lower than initial values (Table 4). Two of the patients with initially raised blood cholesterol had normal values while on diet alone and these remained satisfactory throughout. One had persistent elevation corrected by clofibrate but not by CDCA. Elevated VLDL and LDL levels tended to fall with both clofibrate and CDCA.

Symptoms while on CDCA therapy

Change in bowel habit was usual with stools becoming looser and more frequent. Since this was specifically sought on questioning, it is not easy to interpret patient reaction except in the one patient who complained spontaneously of such diarrhoea that the dose had to be reduced to 500 mg daily after 1 month (Patient 4).

One patient developed biliary colic for the first time. He was demonstrated to have gallbladder stones prior to therapy, which were unchanged at 6 months. Four attacks occurred in months 4–6 of therapy, did not return after 3 months of placebo capsules, and were abolished by cholecystectomy. No symptoms referable to drug therapy developed while on clofibrate.

The only important alterations in the other blood tests involved are detailed in Table 3. The trend to decline in γ-GTP levels may reflect on effect on synthesis in parallel with the depression of triglyceride synthesis. There is no evidence of serious hepatotoxicity.

Discussion

Our results show that CDCA will lower elevated serum triglyceride levels, probably by inhibition of hepatic synthesis since the agent is largely confined to the enterohepatic circulation.

After an initial fall of 36% in hypertriglyceridaemia in response to dietary restriction alone, the addition of CDCA occasioned a further fall of 11%, compared with initial levels so that values on diet + CDCA fell 47%.

Hoffman *et al.* (1974) and Bell *et al.* (1973) reported a mean fall in normal serum triglyceride levels in gallstone patients on CDCA therapy. When CDCA was first used, the initial doses used were larger, up to the maximum tolerated one (4.5 g daily). Other reports using sustained lower-dose treatment (500–750 mg/day) did not report a fall in normal serum triglycerides (Van Waes, de Weert, Shurgers, Beeckman, Barbier & Demeulenaere, 1975; Barbara, Roda, Roda, Sama, Festi, Mazzella & Aldini, 1976), and this has also been our experience while using CDCA for gallstone dissolution.

Miller & Nestel (1974) studied a heterogenous group of eleven patients with severe hyperlipidaemia, some of rare Types III + V. Diet was not altered prior to therapy, and a dose of 1 g CDCA was given for

Table 4 Serum cholesterol after diet and drug therapy

	Serum cholesterol (mM)				
Patient	*Initial*	*Diet alone*	*Diet + CDCA*	*Diet + placebo*	*Diet + clofibrate*
1	7.48	7.15	7.56	8.19	6.15
2	5.59	6.29	7.35	5.48	5.64
3	6.11	5.90	5.61	5.27	5.69
4	7.22	5.48	6.31	6.44	6.44
5	10.36	8.78	9.01	10.06	6.49
6	8.63	5.27	6.00	6.11	5.90
7	8.45	8.50	8.44	—	—
8	7.48	4.88	5.88	5.46	6.36
9	5.85	5.66	4.80	5.90	5.88
10	9.28	6.63	6.87	6.63	6.51
Mean ± s.d.	7.65 ± 1.55	6.45 ± 1.33 ($P < 0.02$ versus initial)	6.78 ± 1.32 ($P < 0.05$ versus initial) (NS versus diet alone)	6.62 ± 1.56	6.12 ± 0.35 ($P < 0.01$ versus initial) (NS versus diet alone, diet + placebo or diet + CDCA)

4–5 weeks to ten patients, while one received 750 mg. A fall in the mean serum triglyceride level of 41% was recorded, and the mean cholesterol level also fell 10%. These results might be taken to indicate that CDCA alone is as effective in hypertriglyceridaemia as diet + CDCA. This is probably not justifiable in view of the short duration of this trial and unusual patient material. The routine management of patients must be based on diet (Bell *et al.*, 1973; Levy, Morganroth & Rifkind, 1974), and most patients seen have moderate abnormalities of the Fredrickson IIb or IV patterns.

The attraction of using CDCA for the management of dietary-non-responsive hypertriglyceridaemia was the possibility of achieving a triglyceride lowering effect (Bell *et al.*, 1973; Hoffman *et al.*, 1974; Miller & Nestel, 1974) without the increased lithogenicity of bile associated with clofibrate (Pertsemlidis *et al.*, 1973; Coronary Drug Project, 1975). Clofibrate is relatively free from side effects although diarrhoea and raised serum AST levels have occurred (Hartman & Forster, 1969). Patients on CDCA experience a change in bowel habit and this occasionally may be an obstacle to patient compliance. Of more importance are the hepatic effects of chenodeoxycholic acid which usually occur on less than the maximal tolerated dose. Since its toxicity is probably dose related, lower doses are preferable (Bell, Mok, Thwe, Murphy, Henry & Dowling, 1974). This study demonstrated more change in 'liver function' tests on clofibrate than CDCA.

Serious doubt has been cast on the benefit of any drug therapy for hyperlipidaemia (Coronary Drug Project, 1975; Whyte, 1975), at least after arterial disease has become manifest. Attempts to introduce lipid-lowering regimes have been recorded variously as beneficial (Newcastle and Scottish Society of Physicians, 1971) or not (Coronary Drug Project, 1975).

Analysis of the serum lipids of patients on the American Heart Association fat-controlled diet showed that restriction of animals fats elevated serum triglyceride levels in some (Wilson, Hulley, Burrows & Nichaman, 1971). Since both serum cholesterol and triglyceride are predictors of arterial disease this is likely to be self-defeating. Cholestyramine therapy for hypercholesterolaemia has produced a similar 'see-saw-effect' (Jones & Dobrilovich, 1969), converting IIa to IIb abnormalities, without necessarily even lowering the cholesterol level. It is obviously mandatory to monitor both serum lipids if the object is to produce a return to metabolic normality.

The present evidence justifies the use of CDCA alone as primary therapy of hypertriglyceridaemia. No important effect on raised cholesterol levels is likely. CDCA may have a place in the treatment of patients resistant to diet plus clofibrate. It also offers the possibility of combatting an increase in bile lithogenicity caused by low animal fat regimes (Sturdevant, Pearse & Dayton, 1973) or clofibrate (Coronary Drug Project, 1975). CDCA may well prove a valuable alternative to clofibrate in hypertriglyceridaemia. A randomized crossover trial is warranted to investigate this further.

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