PAPERS AND ORIGINALS

Low-cholesterol diet: enhancement of effect of CDCA in patients with gall stones

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British Medical Journal, 1978, 2, 851-853

Summary and conclusions

Fifteen patients with gall stones who were taking chenodeoxycholic acid (CDCA) 15 mg/kg at bedtime participated in two separate experiments to investigate the effects of altering sterol intake on the cholesterol saturation index (SI) of fasting gall-bladder bile. In experiment I the 15 patients on an unrestricted diet had a SI of 0.87 ± 0.04 (mean $\pm$ SE of mean), which fell to 0.75 ± 0.04 after one week in hospital on a diet of 100 mg cholesterol daily. In experiment II seven of the patients were given four different dietary regimens lasting one month each in random order as outpatients. On a diet of 600 mg of cholesterol daily the mean SI was 0.72 ± 0.05 , which fell to 0.67 ± 0.05 when the patients were put on a 100 mg cholesterol diet. The addition of plant sterols (3 g daily) to both diets raised the mean SIs to 0.80 ± 0.05 and 0.77 ± 0.05 respectively. The percentage CDCA in bile was unaffected by alterations in the cholesterol and plant sterol intakes.

We conclude that a low-cholesterol diet but not a high intake of plant sterols enhances the effect of CDCA in patients with gall stones.

Introduction

Chenodeoxycholic acid (CDCA) given by mouth renders fasting gall-bladder bile unsaturated with cholesterol and induces dissolution of cholesterol gall stones.¹⁻³ Some patients, however,

are resistant to treatment at the recommended dose of 15 mg/kg/day.⁴ In patients who do respond complete dissolution is slow, taking six to twelve months for small stones and considerably longer for large gall stones.⁵ It is therefore important to find a method of enhancing the effect of CDCA treatment.

CDCA reduces biliary secretion of cholesterol^{6, 7} by inhibiting its endogenous synthesis in the liver.⁸ We speculate that residual cholesterol secreted during treatment with CDCA is mainly exogenous. Reducing the exogenous intake with a low-cholesterol diet should therefore further reduce biliary cholesterol secretion. Alternatively, inhibition of intestinal absorption of cholesterol by plant sterols⁹ might have the same effect. We studied the effects of a low-cholesterol diet and added plant sterols in patients with gall stones who were taking CDCA. We measured the cholesterol saturation index (SI) of fasting gall-bladder bile because the rate of dissolution of gall stones is related to the cholesterol solubilising capacity of the bile.¹⁰

Patients and methods

PATIENTS

We studied 15 patients (six men and nine women) aged 28-78 years. Oral cholecystography showed gall stones in a well-opacified gall bladder in all cases. Written, informed consent was obtained from each patient. CDCA (15 mg/kg/day⁵) was given in 125 mg gelatine capsules as a single bedtime dose.¹¹ Plant sterols were given as Cytellin (β -sitosterol 65%, campesterol 30%, and stigmasterol 5%) in a dose of 1 g three times daily with meals.

DESIGN OF EXPERIMENTS

Experiment I—All 15 patients participated in this. In order to obtain the full effect of the CDCA while on an unrestricted diet the patients were given it for four weeks at home.¹² They were then admitted to hospital for one week, during which they were given a low-cholesterol (100 mg) diet in addition to the CDCA. Fasting gall-bladder bile samples were collected at 0, 4, and 5 weeks.

Experiment II—Seven of the 15 patients (one man and six women, aged 34-56 years) were given as outpatients four different dietary regimens lasting one month each in random order according to a Latin square design. The regimens were (a) normal-cholesterol diet (600 mg/day); (b) normal-cholesterol diet with plant sterols (3 g/day);

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(c) low-cholesterol diet (100 mg/day); and (d) low-cholesterol diet with plant sterols. During the fifth month CDCA was withdrawn and a 100 mg cholesterol diet given alone. Bile samples were taken at the end of each regimen. The table shows the contents of the normal- and low-cholesterol diets. The difference in cholesterol intake between the two diets was due to the difference in the daily allowance taken in addition to the main meals. In the normal-cholesterol diet two eggs were given each day and whole milk was substituted for skimmed milk. The amounts of dietary fibre and polyunsaturated fat in the two diets were kept constant since these affect the cholesterol saturation of bile.^{13 14} Total energy was also kept constant. There were differences in saturated fatty acid, protein, and carbohydrate contents, which are not known to affect biliary cholesterol saturation.

Composition of low- and normal-cholesterol diets

	Low-cholesterol diet	Normal-cholesterol diet
Breakfast		
Cornflakes, bread, and marmalade	110 g	110 g
Lunch		
Chicken (breast)*	60 g	60 g
Bread	60 g	60 g
Fruit and vegetables	260 g	260 g
Dinner		
Beef (lean)*	50 g	50 g
Bread	75 g	75 g
Fruit and vegetables	340 g	340 g
Daily allowance		
Milk*	300 ml (skimmed)	300 ml (whole)
Margarine (Flora)	30 g	30 g
Sugar (white)	45 g	30 g
Eggs*		2
Lucozade	120 ml	
Caloreen	30 g	
Total intake		
Cholesterol	101 mg	597 mg
Protein	61 g	73 g
Fats	41 g	65 g
Carbohydrate	307 g	240 g
Energy (MJ)	7.59	7.64

*Contains cholesterol

Conversion: SI to traditional units—Energy: 1 MJ $\approx$ 239 kcal.

ANALYSES

Bile sampling—Gall-bladder bile samples were obtained by aspirating bile-rich duodenal fluid via a tube passed after an overnight fast. Gall-bladder contraction was stimulated by intravenous infusion of 75 Ivy dog units of cholecystokinin (Karolinska Institute, Stockholm) dissolved in 150 ml of physiological saline. An aliquot of the most concentrated bile was saved for lipid analysis.

Bile lipid analysis—Total cholesterol was measured by the cholesterol oxidase method of Roda *et al*¹⁵ and phospholipid by the method of Bartlett.¹⁶ Total bile-acid concentration was measured by the 3α -hydroxysteroid dehydrogenase enzyme assay.¹⁷ The proportion of bile acids present as CDCA was determined by a combination of thin-layer chromatography and enzymatic assay using 3α -hydroxysteroid¹⁸ and 7α -hydroxysteroid dehydrogenase.¹⁹ The SI was calculated using the polynomial equation developed by Thomas and Hofmann²⁰ based on the limits of cholesterol solubility defined by Hegardt and Dam²¹ and Holzbach *et al*.²²

Statistical analysis was carried out using Student's *t* test for paired samples.

Results

Experiment I—After four weeks' treatment with CDCA there was a significant reduction in SI from 1.23 ± 0.05 (mean $\pm$ SE of mean) to 0.87 ± 0.04 ($P < 0.001$). Mean cholesterol intake during this period was 652.3 ± 61.5 mg/day, according to dietary history. The SI was further reduced to 0.75 ± 0.04 ($P < 0.01$) after one week in hospital on the 100 mg cholesterol diet.

Experiment II (see figure)—while patients were on the 600 mg cholesterol diet the mean SI was 0.72 ± 0.05 , whereas on the 100 mg cholesterol diet it was only 0.67 ± 0.05 ($P < 0.01$). The addition of plant sterols to both diets raised the mean SIs to 0.80 ± 0.05 ($P < 0.05$)

Effect of altering cholesterol and plant sterol intakes on saturation index of fasting gall-bladder bile in seven patients (experiment II).

and 0.77 ± 0.05 ($P < 0.05$) respectively. Before treatment CDCA constituted $25.1 \pm 2.4\%$ of the total bile acids. There was a significant increase in percentage CDCA during treatment with CDCA and both 600 mg cholesterol ($87.6 \pm 2.6\%$) and 100 mg ($84.6 \pm 2.4\%$) cholesterol diets ($P < 0.001$ in both cases). With the 600 mg cholesterol diet and added plant sterols the percentage CDCA was $87.8 \pm 3.0\%$. There was no significant difference in the percentage CDCA associated with each of these three diets. Percentage CDCA was not measured during the fourth diet. In the absence of CDCA treatment the mean SI in the seven patients on an unrestricted diet (cholesterol intake 704.9 ± 76.3 mg/day) was 1.27 ± 0.06 . There was no significant change when the cholesterol intake was reduced to 100 mg/day (SI 1.15 ± 0.08).

Discussion

We have shown that in patients with gall stones the effect of CDCA treatment on the SI of fasting gall-bladder bile is enhanced by a low-cholesterol diet. The effect of CDCA on the SI correlates with the proportion of biliary bile acids present as CDCA.¹² The enhanced effect that occurred with a low-cholesterol diet was not due to an alteration in percentage CDCA. We have confirmed that a reduction in dietary cholesterol intake has no significant effect on SI in the absence of CDCA treatment.²³ There was a significant rise in SI when plant sterols were added to both low- and normal-cholesterol diets during CDCA treatment. This was unexpected and difficult to explain. It was not due to a reduction in percentage CDCA in the bile.

Bell *et al*,¹⁰ in studies using bile from the rhesus monkey, showed that the rate of dissolution of gall stones is related to the capacity of the bile to dissolve cholesterol. This suggests that a low-cholesterol diet may speed the rate of dissolution in patients with gall stones who are taking CDCA. Long-term clinical trials are necessary to confirm this.

We are grateful to Weddel Pharmaceuticals and the medical research committee, St George's Hospital, for financial support; and to Eli Lilly Company Ltd for providing the Cytellin.

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(Accepted 19 July 1978)

Mortality and morbidity of reusing dialysers

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A report by the registration committee of the European Dialysis and Transplant Association

British Medical Journal, 1978, **2**, 853-855

Summary and conclusions

The practice of reusing dialysers in renal units in the UK was surveyed by examining the patient questionnaires returned to the EDTA registration committee for 1976 and by a special questionnaire sent to all UK renal units. Altogether 65.6% of the 1785 patients treated with non-disposable dialysers and 49.6% of the 1109 treated with disposable dialysers reused their equipment. Reuse of dialysers caused some morbidity but no mortality.

Most centres where disposable dialysers were used accepted that their reuse was necessary because of financial constraints and was ethically defensible.

Introduction

Although effective in preventing death due to end-stage renal disease,¹ regular haemodialysis is expensive. The cost of treat-

ment in the United Kingdom was recently estimated to be £10 000 per year per patient for hospital haemodialysis and £6000 per year for home haemodialysis.² Most doctors therefore accept that they should make all possible economies in materials and staff. Economic measures may reduce safety and additional risks must be acceptable both medically and legally.

Disposable dialysers are gradually displacing non-disposable ones in the UK because they have several advantages over the non-disposable (Kiil) type. They are easier to store and use and patients can use them at home without the structural alterations that may be necessary to accommodate a Kiil dialyser.

Disposable dialysers do not, however, provide dialysis as cheaply as non-disposable parallel-flow dialysers. A modern Meltec Multipoint dialyser with trolley costs £560, and yearly costs for membranes, blood ports, and regasketing are about £100. The dialyser boards and trolley will probably serve an individual patient for at least two and possibly three or four years. The average annual cost for this equipment is thus £240 to £380. Disposable dialysers cost from £10 to £25 each, depending on the type and on bulk purchasing agreements. They therefore cost six to 14 times as much per year as non-disposable equipment. The cost can be reduced if the haemodialysers are not discarded after use but rinsed and reesterilised for reuse. If they are reused three times disposable dialysers are only about twice as expensive as non-disposable equipment, and after seven reuses they are beginning to be cheaper. (These cost comparisons are based on material costs alone. The building, testing, and sterilising of the Kiil type of dialyser takes about one man-hour and unless the patient carries this out himself a skilled kidney builder must be paid to do it.)

We surveyed the practice of reuse in renal units in the United Kingdom and investigated its mortality and morbidity. We also inquired about the views held in renal units about the necessity and ethics of reusing "disposable" dialysers.

Methods

The registration committee of the European Dialysis and Transplant Association collects yearly returns from all UK centres as part of a survey covering 27 countries.³ Information is returned on individual patient questionnaires, which record (among other data) the type of dialyser used most often for the patient and the average number of reuses of the dialyser. Returns for 1976 were received from 54 out of 56 UK units.

Mortality in patients who reused disposable dialysers was compared with mortality in patients who did not reuse. To remove bias due to

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