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Effect of enterocoated cholestyramine on bowel habit after ileal resection: a double blind crossover study

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Abstract

Ileal resection causes malabsorption of bile acid; the increased load of bile acids in the colon induces increased secretion of salt and water and hence diarrhoea. A study was carried out to test the effect of an enterocoated cholestyramine tablet designed to disintegrate in the colon and sequester the bile acids there, thereby minimising diarrhoea induced by bile acids while having no effect on malabsorption of bile acid and jejunal fat absorption.

The study comprised 14 patients who had undergone ileal resection of 40-150 cm for Crohn's disease. A double blind crossover trial was performed with placebo and cholestyramine enterocoated with cellulose acetate phthalate. During treatment with cholestyramine the daily faecal output decreased, the number of defecations each week decreased, and the intestinal transit time increased. Acceptability of the tablets was high, in contrast with general clinical experience with cholestyramine powder. No change was observed in the total faecal output of bile acids or fat.

Cholestyramine tablets caused a reduction in diarrhoea without noticeably interfering with the metabolism of fat or bile acid.

Introduction

Some bile acids are absorbed passively in the proximal small intestine, but there is also an important active transport mechanism in the terminal ileum.^{1,2} Patients with an ileal resection of 30 cm or more may develop malabsorption of bile acid, resulting in an increased passage of bile acids into the colon, where dihydroxy bile acid induces the secretion of salt and water and hence diarrhoea.³ Hitherto, conventional cholestyramine powder has been used with some success to sequester bile acid,^{1,2} but such treatment has two physiological disadvantages. Firstly, the jejunal concentration of non-sequestered bile acids is below the optimum for sufficient solubilisation of the lipolytic products after meals and thus the result is malabsorption of fat, steatorrhoea, and diarrhoea induced by fatty acids. Secondly, malabsorption of bile acid is increased because sequestered bile acids are not available for small intestinal absorption. It might therefore be an advantage to ingest cholestyramine in a tablet that releases the active substance in the colon, thereby not influencing malabsorption of bile acid and fat. In vivo studies of patients who had not had operations and healthy volunteers suggested that cellulose acetate phthalate might be an ideal coating for cholestyramine tablets as the coating, and hence the tablet, disintegrated in the most distal part of the ileum, caecum, or ascending colon.⁴

The aim of our study was to investigate the effect of cholestyramine tablets coated with cellulose acetate phthalate in patients with diarrhoea and malabsorption of bile acid caused by ileal resection.

Patients and methods

Eleven women and three men aged 27-66 (median 42) consented, in accordance with the Helsinki II declaration, to participate in the study, which was accepted by the local human studies committee. The patients had undergone ileal resection of 40-150 cm (median 65 cm) because of Crohn's disease, but at least half of the colon had been preserved. The table gives clinical and laboratory data. The chronic inflammatory bowel disease was mild in all patients and did not change during the study. Five patients received sulphasalazine 3 g daily and two prednisone 2.5-7.5 mg daily.

The study lasted three weeks: one week of treatment with cholestyramine tablets coated with cellulose acetate phthalate; one week of equilibrium (washout period); and one week of treatment with placebo tablets containing barium sulphate coated with cellulose acetate

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phthalate. A randomised double blind crossover design was used, allowing each patient to serve as his own control. Four tablets were ingested three times daily with meals, and two tablets were taken if snacks were eaten between meals. Patients were asked to record their consumption of tablets, attacks of pain, and an overall assessment of wellbeing. For the last three days of each week of treatment patients were admitted for collection of stools. All patients took a standardised diet that supplied 70 g fat/day.

EXAMINATIONS AND ANALYSES

The placebo tablets contained barium sulphate with the same coating as the cholestyramine tablets. On the last day of both treatments the positions and sites of disintegration of the tablets were examined fluoroscopically every 30 minutes from 8 am to 4 pm as described

FIG 1—Effect of enterocoated cholestyramine on number of defecations, stool mass, and faecal output of fat and bile acids ($n=14$).

previously.⁶ Placebo tablets were seen easily and the position of disintegration determined without difficulty. Disintegration of the coatings was assumed to take the same length of time whether the tablets contained the radiolucent cholestyramine or the radio-opaque barium sulphate. Patients were not allowed to see the screen, and the fluoroscopist did not take part in the trial because of his knowledge of the coding of the patients. Fluoroscopy was performed identically during both periods of treatment so that patients remained blinded, but during treatment with cholestyramine minimum radiation was used. The total exposure was less than two minutes—that is, less than 9 mGy (0.9 rads) on a 15.2 cm abdominal field.

Intestinal transit time was determined by oral administration of 20 small radio-opaque plastic markers that were detected in stools on three consecutive days.⁷ The transit time was expressed as the amount of marker recovered as a percentage of the amount ingested. Stool mass was expressed as the mean output on three consecutive days (reference value < 200 g/day). Faecal fat was determined by a standard method (reference value < 25 mmol/day).⁸ Total faecal bile acids were determined enzymatically by the 3α -steroid dehydrogenase method (reference range 0–975 μ mol/day).⁹ This technique, however, excludes bile acids that are bound to cholestyramine. Analyses of calcium and magnesium in stools were carried out by atomic absorption spectrophotometry (Varian Techtron, model AA-6).¹⁰ Faecal sodium and potassium were measured by flame photometry. Haemoglobin con-

centrations, B lymphocytes, and plasma concentrations of albumin, creatinine, cholesterol, and triglycerides were determined by standard methods used at our university.

The active tablets contained compressed granules of cholestyramine (Cuemid 0.5 g; Merck, Sharp and Dohme, United States of America) with an enterosoluble coating made of cellulose acetate phthalate,¹¹ castor oil,¹² and acetone.¹³ The coating was sprayed over the cores of the tablets in a kettle to provide an *in vitro* disintegration time of 10 minutes at pH 7.2 when measured by standard methods.¹⁴ This disintegration time was chosen after a preliminary study of 15 patients showed that coated tablets disintegrated in the jejunum, caecum, and left colon at five, 10, and 15 minutes, respectively.

The rank sum test for paired differences was used for statistical analysis.

Results

DISINTEGRATION OF THE TABLETS

The tablets disintegrated in the most distal part of the remaining ileum or caecum or, in patients who had had a partial colon resection, at the anastomosis between the ileum and ascending or transverse colon. In three patients disintegration did not occur within eight hours

FIG 2—Effect of enterocoated cholestyramine on faecal output of sodium, potassium, magnesium, and calcium ($n=14$).

Conversion: SI to traditional units—Sodium: 1 mmol/24 h = 1 mEq/24 h. Potassium: 1 mmol/24 h = 1 mEq/24 h. Magnesium: 1 mmol/24 h = 24.31 mg/24 h. Calcium: 1 mmol/24 h = 40 mg/24 h.

after ingestion; for practical reasons fluoroscopy was not performed after this time. The tablets in these patients were last seen in the duodenum or jejunum. Disintegration took place in the sigmoid colon in one patient and in the jejunum in another. No problems were observed if the tablets disintegrated somewhere other than in the colon. Thus in five of the 14 patients the tablets did not disintegrate in the desired place. It cannot be excluded, therefore, that the mechanism of action of cholestyramine is independent of the theoretical model of absorption of bile acid.

STOOL VARIABLES

Of the 14 patients, 13 recorded a decrease in the number of defecations. The median number of bowel movements decreased from 23 to 15 per week—that is, by 35% ($p < 0.05$) (fig 1). In one patient

who had an increased number of evacuations the stool volume decreased from 380 to 323 g/24 h. Cholestyramine reduced the median stool mass from 566 g to 313 g/24 h ($p < 0.05$)—that is, by 45% (fig 1). All patients with a normal stool frequency had an abnormal stool mass, and all showed a decrease in stool mass during treatment. In one patient, in whom the tablets were undissolved in the duodenum after eight hours, stool mass increased from 252 to 279 g/24 h. In another, in whom the tablets disintegrated in the sigmoid colon, stool mass increased from 195 to 277 g/24 h. In all patients faecal output of fat and bile acids showed no significant change (fig 1).

During treatment with cholestyramine compared with placebo faecal excretion of electrolytes decreased: median sodium values were 30 and 11 mmol(mEq)/24 h ($p < 0.05$); potassium 30 and 19 mmol

Discussion

Our results show that cholestyramine coated with cellulose acetate phthalate was effective in reducing faecal mass and the number of defecations in patients with moderate ileal resection and mild steatorrhoea without changing faecal excretion of bile acid and fat. These results agree largely with those of a study of cholestyramine powder, in which faecal mass and faecal excretion of sodium and potassium were reduced. The advantage of the tablets is that the usual increase in faecal excretion of bile acid and fat is avoided. In the two patients in our study with an ileal resection of more than 100 cm faecal mass was decreased by

Clinical and laboratory data on patients studied

Case No	Age (years)	Sex	Length of ileal resection (cm)	Colon resection		Analysis of stools			
				Caecum	Ascending colon	Mass (g/24 h)	No/week	Fat content (mmol/24 h)	Bile acid content (μ mol/24 h)
1	32	M	150	+	+	805	28	86	8146
2	37	F	100	+	+	742	25	17	5087
3	39	F	105	+		784	26	49	6055
4	27	F	45	+		159	17	1	1114
5	34	F	60	+		487	23	59	5404
6	61	F	50			719	26	34	6587
7	62	M	70	+		700	17	37	8757
8	66	F	50	+	+	195	18	14	814
9	35	F	55	+	+	518	51	34	4519
10	46	M	90			549	14	89	3680
11	62	F	50	+		583	22	58	5763
12	57	F	90	+	+	380	15	157	2347
13	39	F	75	+	+	252	10	33	1467
14	57	F	40	+	+	1183	37	34	6544

(mEq)/24 h ($p < 0.05$); magnesium 11.3 and 9.5 mmol/24 h (275 and 231 mg/24 h) ($p < 0.05$); and calcium 42 and 33 mmol/24 h (1683 and 1323 mg/24 h) ($p < 0.05$) (fig 2). All blood values, including serum lipid concentrations, were unchanged.

The median transit time was increased by 7% ($p < 0.05$) during treatment with cholestyramine compared with placebo (fig 3). In two patients measurement of transit time failed because the markers were not ingested. The order of treatment did not affect the changes in any of the variables studied.

FIG 3—Effect of enterocoated cholestyramine on intestinal transit time ($n = 12$).

In seven patients the ascending colon had been preserved, and in another seven it had been resected (table). No significant difference was seen between these two groups of patients with respect to the reduction in faecal mass or pattern of faecal excretion of bile acid, fat, sodium, potassium, or calcium during treatment with cholestyramine, but faecal excretion of magnesium was significantly lower in patients in whom the ascending colon had been preserved.

26% and 32%; this contrasts with previous reports showing no effect of cholestyramine powder on faecal mass in such patients.⁵

We found a significant decrease in faecal excretion of calcium, which suggests that enterocoated cholestyramine might reduce the malabsorption of calcium seen in patients with resection of the small bowel.¹⁵ Previous reports have shown excretion of calcium to be unchanged during treatment with cholestyramine powder.⁵

The ascending colon is considered to be the major site of absorption of salt and water in the colon, and in a previous study all patients who responded to cholestyramine had some ascending colon remaining.¹⁶ In our study, however, no significant differences in faecal variables were seen between the patients with and without preserved ascending colon. This indicates that the presence of the ascending colon is not essential for enterocoated cholestyramine to have a beneficial effect. This agrees with a report of treatment with cholestyramine in a patient with an ileal resection of 75 cm and an ileotransversostomy.¹⁷

Compliance of patients with treatment with cholestyramine given as a powder is low because of the drug's bad taste, but in our study compliance and acceptability were high. The daily dose of cholestyramine was 6 g daily (12 tablets). The tablets were palatable and the enterocoating smooth. None of the patients recorded side effects or difficulties in taking the tablets. We therefore suggest that such tablets should be available in the treatment of patients with diarrhoea due to ileal resection. Negotiations are taking place with a drug company that may be willing to produce these tablets on a non-profit basis.

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SHORT REPORTS

Hyperphosphataemic rickets in an Asian infant

We have recently shown that hyperphosphataemic rickets is associated with hyporesponsiveness of renal tubules to parathyroid hormone. Patients with this disorder have extremely low basal excretions of phosphate in their urine; urinary phosphate and cyclic adenosine monophosphate increase only marginally after challenge with parathyroid hormone.¹ After treatment with vitamin D plasma phosphate concentration becomes normal and urinary phosphate excretion increases.² This hyperphosphataemic variant of rickets has hitherto not been described in an infant. We describe one such infant with severe deficiency of vitamin D. So far as we know this is the first reported case of hyperphosphataemic rickets in an infant.

Case history

A baby boy was born to healthy unrelated Asian parents after a full term, non-eventful pregnancy. Both parents were vegetarian and the mother had received only folic acid and iron supplements during her pregnancy. The infant was breast fed. At 13 days of age he developed projectile vomiting and shortly after admission to hospital he had a twitching episode lasting four minutes. Results of investigations were: plasma calcium concentration 1.26 mmol/l (5.0 mg/100 ml); phosphate concentration 2.8 mmol/l (8.7 mg/100 ml); alkaline phosphatase activity 361 IU/l; magnesium concentration 0.57 mmol/l (1.4 mg/100 ml); glucose concentration 3.0 mmol/l (54 mg/100 ml). 25-Hydroxyvitamin D was undetectable in serum samples from the baby and the mother. He recovered after intravenous and oral calcium supplements and intramuscular magnesium sulphate and was discharged from hospital six days later taking multivitamin drops (Abidec) 0.6 ml twice daily (800 IU daily).

The patient was readmitted six days later (age 28 days) with a recurrence of twitching. Plasma calcium concentration was 1.56 mmol/l (6.2 mg/100 ml) and phosphate concentration 2.9 mmol/l (9.0 mg/100 ml). Oral calcium supplements and alfacalcidol 1.25 μ g twice daily were begun. Three generalised grand mal convulsions then necessitated a further admission (age 40 days). Plasma calcium concentration was 1.76 mmol/l (7.0 mg/100 ml) and alkaline phosphatase activity 268 IU/l. He was treated with oral calcium supplements and phenobarbitone. Electroencephalography, radiography of skull, cranial ultrasound examination, and metabolic and infection screens all gave negative results. The parathyroid hormone concentration on day 52 was raised at 86 pmol/l (8.6 pg/ml). He was discharged from hospital (age 57 days) taking alfacalcidol 1 μ g twice daily and multivitamin drops 1.2 ml daily. Plasma calcium concentration rose to 2.05 mmol/l (8.2 mg/100 ml), phosphate was 2.84 mmol/l (8.8 mg/100 ml), and alkaline phosphatase activity was 343 IU/l. Alfacalcidol was discontinued at 108 days of age. At 6 months he was thriving and taking no medication. Calcium concentration was 2.4 mmol/l (9.6 mg/100 ml), phosphate 2.2 mmol/l (6.8 mg/100 ml), alkaline phosphatase activity 360 IU/l, and parathyroid hormone concentration 36 pmol/l (3.6 pg/ml). A chest radiograph on day 40 was reported as normal but on retrospective examination showed severe splaying and rarefaction of the anterior ends of the ribs.

Comment

This infant's biochemical abnormalities were accounted for by severe vitamin D deficiency: the features were low calcium concentration; raised alkaline phosphatase activity; non-detectable 25-hydroxyvitamin D in both the infant and the mother; raised

Chest x ray appearances on day 40 showing splaying and rarefaction of anterior ends of ribs.

parathyroid hormone concentration; and, finally, response to an antirachitic dose of vitamin D in multivitamin drops, which increased his calcium concentration from 1.26 to 1.76 mmol/l (5.0 to 7.0 mg/100 ml) before the introduction of alfacalcidol. Such a dose of vitamin D is unable to raise the plasma calcium value in patients with hypoparathyroidism and pseudohyperparathyroidism. The only unusual biochemical feature in this patient was the greatly increased plasma phosphate concentration, which initially led to considerable confusion about the diagnosis. It was only in retrospect that we arrived at the diagnosis of "hyperphosphataemic rickets." Review of the chest radiograph at that time showed severe splaying and rarefaction of the anterior ends of the ribs. These changes could have heralded the formation of a rachitic rosary. Hyperphosphataemia in association with rickets has recently been shown by us to be due to severe vitamin D deficiency and a severely diminished end organ (especially renal tubular) response to parathyroid hormone.¹ These patients require large doses of vitamin D, at least initially, since their vitamin D reserves are totally depleted.

These data emphasise that hypovitaminosis D is the commonest cause of hypocalcaemia in Asian neonates.^{2,3} Thus even in the presence of the unusual feature of a raised plasma phosphate concentration, vitamin D deficiency must be considered as the primary cause of hypocalcaemia.