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# Double-blind trial of cholestyramine in post-vagotomy diarrhoea

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SUMMARY The effect of cholestyramine in post-vagotomy diarrhoea has been assessed under double-blind conditions. Cholestyramine produced a significant improvement in frequency, urgency, and consistency of stool as well as episodic diarrhoea. Faecal bile acid excretion was significantly higher in the post-vagotomy group when compared with normal controls. These findings confirm the effectiveness of cholestyramine and support the concept of a bile acid mediated aetiology in post-vagotomy diarrhoea.

A truncal vagotomy and drainage procedure is the most common operation performed for duodenal ulceration today. Diarrhoea is a common complication of this procedure, occurring in 25% or more of cases (Burge *et al.*, 1961; Cox and Bond, 1964). Severe diarrhoea is less common but when it occurs it is frequently intractable and unpredictable and thus socially disabling.

The cause of post-vagotomy diarrhoea is unknown. None of the many suggested aetiologies has been confirmed and treatment along conventional lines is frequently unsuccessful (Collins, 1966). However, in 1972 Ayulo reported that 11 of 13 patients with post-vagotomy diarrhoea responded to cholestyramine. He postulated that the diarrhoea was mediated by bile acids.

This present study was undertaken to assess the effect of cholestyramine under double-blind conditions. Bile acid output was investigated in six patients by faecal bile acid estimation, and 12 patients had serum immunoglobulins measured.

## Methods

Twenty patients took part in the trial. All had truncal vagotomies and the drainage procedure was a pyloroplasty in nine cases and gastroenterostomy in 11. Nineteen of the patients were male and one female, and the operation had been performed between one and 15 years earlier.

In all cases, the diarrhoea, consisting of the persistent passage of three or more loose bowel actions per day, began within two weeks of surgery. In six cases the diarrhoea was severe, with the persistent passage of six or more bowel actions daily.

All antacids and medications used for the treatment of diarrhoea were discontinued. The patients were then given one of two code-marked tins containing powder and instructed to take 4 g (one scoop) in water four times daily, with meals. Cholestyramine was given in the form of Questran[1], and the placebo powder used had a taste and appearance similar to Questran.

The patients were reviewed at one week and again at four weeks and any alteration in bowel habit was recorded and side-effects were noted.

When the trial ended, and the code had been broken, patients who had been taking placebo were started on cholestyramine.

Faecal bile acids were measured in six patients and four age- and sex-matched controls by gas liquid chromatography by the method of Campbell and McIvor (1975).

Serum immunoglobulins A, G, and M were measured in 12 patients by the radial immunodiffusion technique. Three of these patients had severe diarrhoea with the persistent passage of six or more bowel actions daily.

## Results

The effect of cholestyramine on urgency, frequency,

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[1]Questran and placebo powder (Mead Johnson Company).

and consistency of stools as well as episodic diarrhoea is shown in Table 1. All 10 patients had urgency and this was alleviated in seven of the 10 patients after cholestyramine. Frequency was diminished in eight patients to one or two bowel actions per day. Stools became more formed in eight of 10 patients and episodic diarrhoea persisted in only three patients after cholestyramine. In these three patients episodic diarrhoea was reduced in severity and frequency in one and remained unchanged in the other two. After a response was obtained, it was possible gradually to reduce the dose of cholestyramine in all cases.

The effect of placebo after four weeks is shown in Table 2. In contrast, only two patients experienced relief of urgency, and only two had a significant drop in frequency. Stools became more formed in two of the patients on placebo. Two patients were free of episodic diarrhoea at the start of the trial and of the remaining eight patients this persisted in all but two.

At the completion of the trial, the 10 patients on placebo were given cholestyramine and seven responded with an improvement in symptoms.

Defining a response as an improvement in at least three of the four features of post-vagotomy diarrhoea outlined, eight out of 10 patients on cholestyramine responded, compared with two out of 10 of those on placebo. This difference is significant, $P < 0.01$ (Chi square with Yates' correction).

Six out of 10 patients taking cholestyramine complained of nausea. This was usually mild and transient, though two cases required a reduction in dosage of the drug. Five patients developed mild abdominal pain which was colicky in three cases and resembled dyspepsia in two cases. Two patients noted flatulence. In the placebo group one patient developed nausea, one abdominal pain, and four flatulence.

The mean faecal bile acid excretion in patients with post-vagotomy diarrhoea was 1024 mg/day with a range of 745 mg/day to 1168 mg/day (Fig. 1). This was significantly greater than the control group, with a mean excretion of 473 per day and a range of 204 mg/day to 620 mg/day ($P < 0.0025$) (Student's $t$ test).

Serum immunoglobulin levels measured in 12 patients with post-vagotomy diarrhoea were within normal limits (Fig. 2).

## Discussion

This double-blind trial demonstrates the effectiveness of cholestyramine in post-vagotomy diarrhoea, in that eight out of 10 patients improved compared with two out of 10 patients on placebo. This confirms under double-blind conditions the finding of other workers (Ayulo, 1972; Condon *et al.*, 1974, 1975).

The demonstration of increased faecal bile acid excretion is in agreement with Allan *et al.* (1973), and

Table 1 *Post-vagotomy diarrhoea: effect of cholestyramine*

| | *Urgency* | | *Frequency* | | *Consistency* | *Episodic diarrhoea* | |
|---|---|---|---|---|---|---|---|
| | *Before* | *After* | *Before* | *After* | *After* | *Before* | *After* |
| 1 | + | − | 3-8 | 1 | More formed | + | − |
| 2 | + | − | 3-6 | 1-2 | More formed | + | + |
| 3 | + | + | 3-8 | 3-8 | Unchanged | + | + |
| 4 | + | + | 3-5 | 1 | More formed | + | − |
| 5 | + | − | 6-10 | 2 | More formed | + | − |
| 6 | + | + | 8-10 | 8-9 | Unchanged | + | + |
| 7 | + | − | 8-20 | 1-2 | More formed | + | − |
| 8 | + | − | 3-4 | 2 | More formed | + | − |
| 9 | + | − | 4-10 | 1 | More formed | + | − |
| 10 | + | − | 6-8 | 2 | More formed | + | − |

Table 2 *Post-vagotomy diarrhoea: effect of placebo*

| | *Urgency* | | *Frequency* | | *Consistency* | *Episodic diarrhoea* | |
|---|---|---|---|---|---|---|---|
| | *Before* | *After* | *Before* | *After* | *After* | *Before* | *After* |
| 1 | + | − | 6-8 | 2 | More formed | + | − |
| 2 | + | + | 5-10 | 5-10 | Unchanged | + | + |
| 3 | + | + | 3-4 | 3-4 | Unchanged | + | + |
| 4 | + | − | 4-5 | 1 | More formed | + | − |
| 5 | + | + | 3-5 | 2-4 | Unchanged | + | + |
| 6 | + | + | 3-5 | 3-4 | Unchanged | − | − |
| 7 | + | + | 3 | 2 | Unchanged | − | − |
| 8 | + | + | 3-8 | 3-8 | Unchanged | + | + |
| 9 | + | + | 6 | 6 | Unchanged | + | + |
| 10 | + | + | 3-5 | 3-5 | Unchanged | + | + |

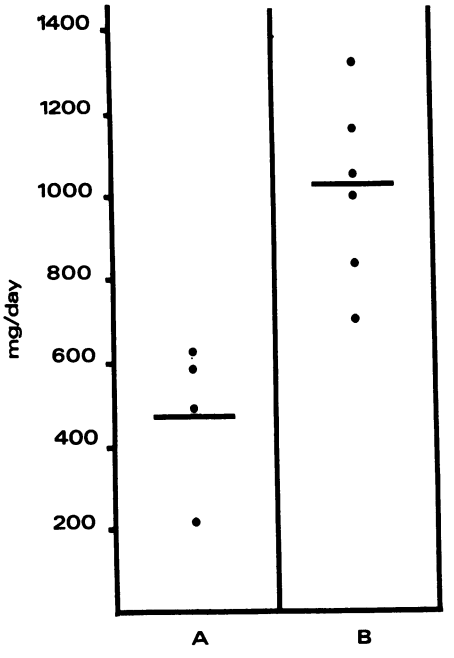


Fig. 1 *Faecal bile acid excretion in control subjects (A) and post-vagotomy diarrhoea patients (B).*

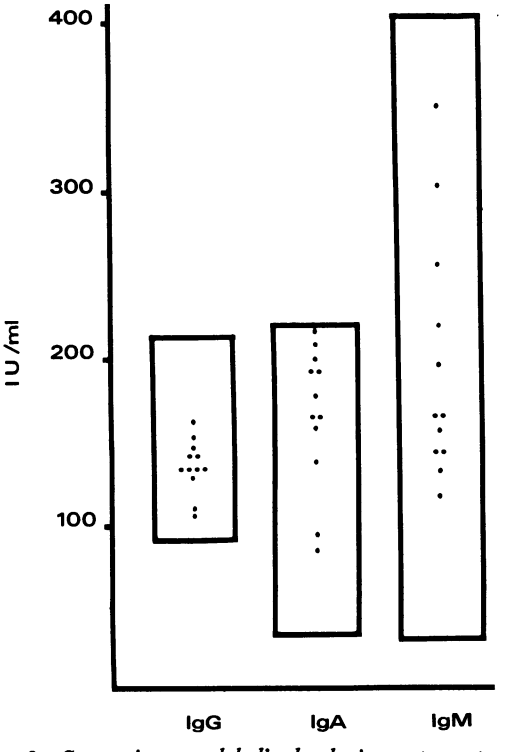


Fig. 2 *Serum immunoglobulin levels in post-vagotomy diarrhoea (normal values within squares).*

Gerskowitch *et al.* (1973), and further supports the concept of a bile acid mediated diarrhoea.

Bile acids cause diarrhoea by inhibition of colonic absorption of potassium, sodium, and water (Mekhjian and Phillips 1970; Mekhjian *et al.*, 1971). The cause of increased faecal bile acid excretion after vagotomy is unknown. However, the close association between post-vagotomy diarrhoea and division of the hepatic branches of the vagus nerve was shown when Burge *et al.* (1964) demonstrated that careful preservation of these fibres reduced the incidence of diarrhoea from 30% to 2%. This finding has been confirmed by a similar dramatic decrease in the incidence of post-vagotomy diarrhoea after highly selective vagotomy (Johnston *et al.*, 1972; Kennedy *et al.*, 1975; Kronborg and Madsen, 1975). Furthermore, this low incidence of diarrhoea is maintained even when the posterior trunk of the vagus is completely divided (Smith and Farris, 1963, Burge *et al.*, 1964). This suggests that denervation of the small intestine and pancreas does not play a major role in post-vagotomy diarrhoea.

The effect on the biliary system of division of these hepatic vagal branches, however, remains controversial. Both reduced bile flow and/or reduced bile salt concentration in the intestine after truncal vagotomy has been demonstrated in the dog (Fritz and Brooks, 1963; Fletcher and Clark, 1969) and in man (Fields and Duthie, 1965). Baldwin *et al.* (1966) demonstrated a reduction in insulin stimulated bile flow in man after atropine.

However, Saburov (1961) showed that vagotomy in dogs increased bile secretion four to five hours after a meal, and Smith *et al.* (1973) demonstrated a significant increase in bile salt concentration in the intestine one year after vagotomy in man.

Althought these studies are contradictory, faecal bile acid excretion is consistently raised after vagotomy (Allan *et al.*, 1973; Gerskowitch *et al.*, 1973), confirming that excess amounts of bile acids are passing through the colon.

Dilatation of the gallbladder after vagotomy has been reported by several groups (Johnson and Boyden, 1952; Rudick and Hutchison, 1964). Condon *et al.* (1975) proposed that a dilated gallbladder may play an aetiological role in post-vagotomy diarrhoea by storing excessive volumes of bile salts which swamp the reabsorptive capacity of the small intestine on contraction during a meal. They further suggested that cholecystectomy may alleviate the symptoms. However, two patients in this present series had a cholecystectomy performed, one before and one after vagotomy. Furthermore, the patient who had cholecystectomy after vagotomy noticed a worsening of his diarrhoea after removal of his gallbladder. The authors are aware of another patient (Burfitt-

Williams, 1975), who had normal bowel habit after partial gastrectomy until a cholecystectomy six years later, when he developed severe diarrhoea which responded to cholestyramine. These cases do not support the concept that the gallbladder is important in the aetiology of post-vagotomy diarrhoea.

Other workers have shown that cholestyramine usually results in only a mild increase in faecal fat excretion (Hofmann and Poley, 1969; Condon *et al.*, 1975; West and Lloyd, 1975). However, long-term cholestyramine therapy may result in folate deficiency, low prothrombin time, acidosis, constipation, intestinal obstruction, and osteomalacia (Heaton *et al.*, 1972; West and Lloyd, 1975). In view of these complications, patients on long-term cholestyramine therapy should be given supplements of both fat soluble vitamins and folate, and should be maintained on the lowest effective dose. It is of interest that it was possible to reduce the dose of cholestyramine in all cases, and in three cases to suspend it completely, without the diarrhoea recurring over a follow-up period of more than five months. This remains an unexplained finding.

Another clinical situation in which diarrhoea is reported to respond to cholestyramine is diabetic diarrhoea (Condon *et al.*, 1973, 1975), and a vagal neuropathy has been postulated. Recently, a further group of patients has been described with a severe diarrhoea who excrete faecal bile salts without any evidence of vagal damage. These patients respond to cholestyramine and the condition has been termed functional cholerrhoeic enteropathy (Thaysen and Pedersen, 1975). In contrast, when diarrhoea is present without excess faecal bile acids, as in ulcerative colitis, there is no response to cholestyramine (Miettinen, 1971). Similarly, in tropical diarrhoea cholestyramine and placebo are equally ineffective (McCloy and Hofmann, 1971).

McLoughlin *et al.* (1976) reported 14 patients with severe post-vagotomy diarrhoea and noted that six of these patients had severe IgA deficiency. These findings have not been confirmed in this study, where immunoglobulin levels in all 12 patients studied were normal. However, only three of these patients had severe diarrhoea as defined by those authors and there may be regional variations in the prevalence of IgA deficiency in the community. Patients with IgA deficiency frequently have an enteropathy, and it may be that a bile salt load will precipitate diarrhoea in these patients. Thus, patients who fail to respond to cholestyramine should be investigated for other causes of diarrhoea such as coeliac disease, blind loop syndrome, and parasite infestation, particularly with *Giardia lamblia*.

This double-blind trial confirms the effectiveness of cholestyramine in post-vagotomy diarrhoea. Although many aspects remain unexplained, cholestyramine represents an advance in the understanding and management of post-vagotomy diarrhoea.

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