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# Effect of Cholestyramine on Gastrointestinal Transit in Patients with Idiopathic Bile Acid Diarrhea: A Prospective, Open-Label Study

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**Abstract** *Background.* Patients with idiopathic bile acid diarrhea (IBAD) have accelerated transit in the small bowel and in the colon. This study evaluated the effect of cholestyramine, a bile acid binder, on transit in the small bowel and in the colon. *Methods.* Thirteen subjects with IBAD (4 male, 9 female; aged 23-67 years) were included. Gastrointestinal transit was investigated in all subjects before and during treatment with cholestyramine. *Results.* Stool frequency was reduced ($P < .05$), and stool consistency was harder ($P < .01$) during treatment. A tendency to prolonged small bowel transit time was shown ($P = .05$). Transit in the transverse colon was prolonged by treatment ($P < .02$). *Conclusions.* A bile acid binder is an effective treatment in IBAD, probably by reducing transit in both the small bowel and in the colon. The results also indicate that the small bowel as well as the colon has a pathophysiological role in IBAD.

**Keywords** bile acids; diarrhea; gastrointestinal transit; small bowel

## 1. Introduction

Idiopathic bile acid diarrhea (IBAD) was first described by Thaysen in 1975 [22], and is now recognized as a common cause of chronic diarrhea [11,27]. However, the pathophysiology of this disorder is still not clear. Initially, defective uptake of bile acids was thought to be the main cause [5], but this seems to be rare [2,10,12,23]. Later, it was shown active bile acid uptake was upregulated and increased the bile acid pool [23,24]. The mechanism causing diarrhea in IBAD is mainly thought to be secretion of sodium and water into the colon [9], and increased colonic permeability [8]. Other mechanisms are accelerated colonic transit [15], increased secretion of mucus, and stimulation of defecation [13]. The recommended treatment is bile acid sequestrants, which by binding to the bile acids prevent secretion from the colonic mucosa. However, the transit time in the small bowel has also been shown to be accelerated in IBAD [15]. An increased secretion in the colon and thus an increased volume load may result in an accelerated transit in the colon but not in the small bowel. The aim of this study was to evaluate whether bile acid binders affected motility in the small bowel as well as in the colon.

## 2. Materials and methods

### 2.1. Subjects

Thirteen newly diagnosed, untreated subjects with IBAD from our outpatient clinic (4 male, 9 female; age range 23–67 years, mean age 49 years) were included. The diagnosis was based on $^{75}$SeHCAT ($^{75}$Se-labeled homocholic acid taurine) measurement, showing a mean 2.2% (range 0.5–5.7%) retained activity on day 7. All subjects had undergone clinical investigation with at least an upper endoscopy and a colonoscopy with biopsies from the duodenum and the colon to rule out other causes of diarrhea. Subjects with other causes of bile acid diarrhea, including previous cholecystectomy, were excluded. Gastric emptying, small bowel transit time and colonic transit time as well as recording of frequency of bowel movements and bowel consistency were determined prior to treatment and during treatment after titration to a stable daily dose of cholestyramine, the standard treatment for bile acid diarrhea. The dose of cholestyramine was adjusted to give the patient good effect with acceptable side effects. No other drugs affecting motility in the gastrointestinal tract or laxatives were allowed within two weeks before the measurements. The measurement during treatment was performed after treatment with cholestyramine for at least one month. During the second measurement, the patients had their ordinary dosing of cholestyramine. Cholestyramine was not given on the morning, the measurement day.

A 3-grade scale was used for stool consistency; solid ($= 1$), loose ($= 2$), or watery ($= 3$). Stool consistency was calculated as the number of loose or watery stools registered during the measurement period before and during treatment.

### 2.2. $^{75}$SeHCAT

The $^{75}$SeHCAT test was carried out according to the method described by Thaysen [21]. After an overnight fast, a capsule containing 0.3 MBq $^{75}$SeHCAT was swallowed with a glass

of water. Measurements were performed in patients in a supine position with an uncollimated camera positioned at a distance of 60 cm. A measurement over the abdomen 3 h after ingestion of the capsule gave the baseline value (100%). A repeated measurement was performed after 7 days. The cut-off value for bile acid malabsorption was 10% retention on day 7 [27].

### 2.3. Gastrointestinal transit measurements

Gastrointestinal transit measurements were performed using radiopaque markers. For study flow chart, see Table 1. For colonic transit, the subjects ingested 10 radiopaque markers daily for 5 days. On day 6, the dose was divided, 5 rings in the morning and 5 rings at 20:00 h, in order to improve the precision of the measurement of rapid colonic transit [14]. All measurements were made on day 7. After an overnight fast, the remaining rings were counted using fluoroscopy. Colonic transit was calculated by dividing the remaining rings by 10, i.e., the daily dose [1]. The subjects then had a 400-kcal breakfast of oatmeal porridge and a cheese sandwich. Twenty spherical radiopaque markers, 4 mm in diameter, with a density of 1.27 g/mL, were added to the meal. It has been demonstrated that these markers can exit the stomach without occurrence of an antral phase III and are thus suitable for determination of gastric emptying [20]. The markers were counted by fluoroscopy every 30 min until at least 10 markers had reached the cecum or for a maximum of 8 h. By plotting the number of spheres in the stomach, the small bowel and the colon against time we obtained profiles for gastric emptying and small bowel transit. Details about the reproducibility, counting procedure and location of the markers are described elsewhere [14, 15].

Maximum exposure to radiation was about 2 mS, corresponding to 200 mRem. The organ dose exposure has been published in a previous work [17].

### 2.4. Segmental colonic transit

The colon was divided into four segments: (1) the cecum and the ascending colon; (2) the transverse colon; (3) the descending colon; and (4) the sigmoid colon and the rectum. By counting the remaining radiopaque rings in each part on day 7 and dividing by 10, we obtained an estimate of the segmental transit time in days.

### 2.5. Gastric emptying

Gastric emptying in hours = area under the curve/number of markers emptied from the stomach during the observation time.

### 2.6. Small bowel transit

To calculate small bowel transit time (SBTT), we considered only the markers reaching the colon during the observation time. The rational for this is the assumption that the markers first reaching the colon are those first emptied from the

**Table 1:** Measurement flow diagram.

| | |
|---|---|
| **Day 1–5** | Ingestion of 10 radiopaque rings daily. Questionnaire. |
| ↓ | |
| **Day 6** | Ingestion of 5 rings in the morning and 5 rings at 20:00. Questionnaire. |
| ↓ | |
| **Day 7** | Counting of remaining rings in the colon using fluoroscopy. |
| ↓ | |
| **Day 7** | Test meal with 20 spherical markers. |
| ↓ | |
| **Day 7** | Counting of markers by fluoroscopy every 30 min until at least 10 markers had reached the cecum or for a maximum of 8 h. |

stomach. The locations of the markers were facilitated by several factors: the colon and the cecum were outlined by the previously ingested rings, the postprandial accumulation of markers made the stomach easy to identify, and different fluoroscopy projections were used [15].

To calculate SBTT, the following formula was used: SBTT = Area under the small bowel transit profile/number of markers reaching the colon. The small bowel transit time (SBTT) was calculated as the mean of the markers reaching the colon during the observation time.

### 2.7. Statistical analysis

Results are given as the median and 10th and 90th percentiles. The Wilcoxon signed rank test was used to investigate differences before and after treatment, with significance at $P < .05$.

### 2.8. Medical ethics

The study was approved by the ethical committee and the radiation protection committee of Göteborg University. Informed consent was obtained from all participants.

## 3. Results

The median duration of treatment with cholestyramine before the second measurement was 34.5 months, and the median daily dose of cholestyramine was 8 g, Stool frequency decreased significantly, from 3.6 defecations/day (2.3–7.9) at baseline to 2.5 defecations/day (1.6–3.8) during treatment ($P < .05$) (Figure 1). Stool consistency was significantly harder during treatment; number of loose stools during the registration period before treatment were 18 (6 and 46) (median and percentile 10 and 90) vs 5 (1 and 12) during treatment ($P < .01$).

SBTT was not significantly prolonged by treatment, from 2.5 h (1.3–5.5) at baseline to 4.1 h (1.9–16.6) ($P = .05$ with the Wilcoxon signed rank test; Figure 2). Two of the three subjects with the largest prolonging of small bowel transit also had the largest decrease in frequency of bowel movements.
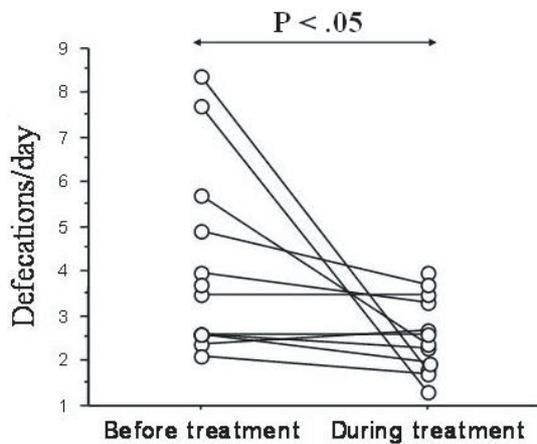
**Figure 1:** Stool frequency before treatment and during treatment with cholestyramine.
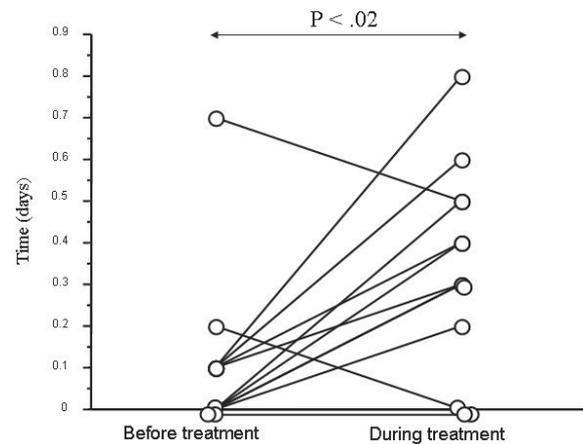


**Figure 2:** Small bowel transit time before treatment and during treatment with cholestyramine.



**Figure 3:** Segmental transit in the transverse colon before treatment and during treatment with cholestyramine.
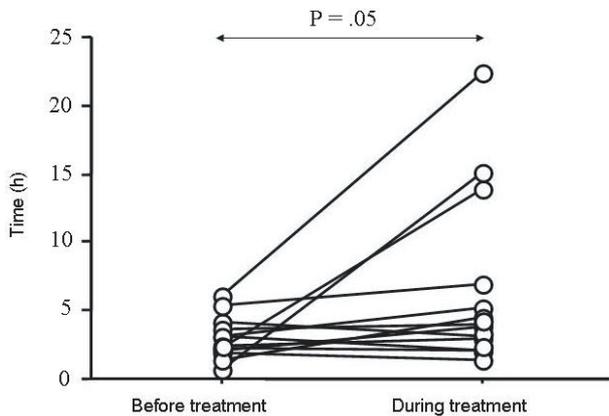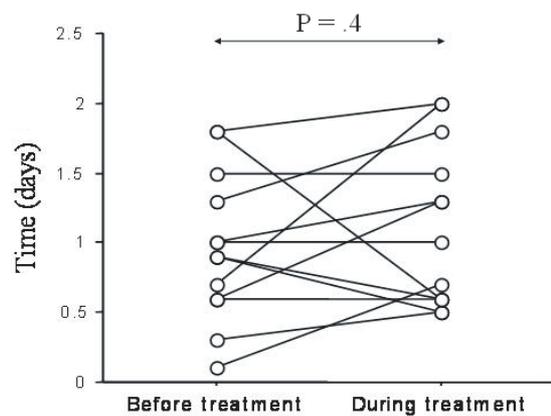


**Figure 4:** Colonic transit before treatment and during treatment with cholestyramine.

Transit in the transverse colon was significantly prolonged by treatment, from 0.0 days (0–0.3) to 0.3 days (0–0.6) ($P < .02$ with the Wilcoxon signed rank test, Figure 3). Total colonic transit was not affected, 1.0 days (0.5–2.0) vs. 0.9 days (0.3–1.8) at baseline ($P = .4$; Figure 4). Gastric emptying and segmental transit in the right and left colon were not significantly different before and after treatment.

## 4. Discussion

In this prospective, open-label study, we have shown that treatment with bile acid binders in IBAD significantly prolongs transit in the transverse part of the colon. There was also a trend to prolonged transit time in the small bowel. Total colonic transit was not affected. Our findings support the idea that bile acid binders may exert their effect not only in the colon but also in the small bowel. We have previously shown that patients with IBAD have accelerated transit both in the small bowel and the colon compared with healthy controls [15]. IBAD is also associated with increased jejunal

hypersecretion of chloride during phase III of the enteric migrating motor complex (MMC) cycle [3]. In a previous study, we found that chloride secretion, hence the magnitude of fluid secretion, was negatively correlated with the outcome of the [75]SeHCAT test; i.e., a larger secretory index was seen in the proximal small bowel in patients with lower [75]SeHCAT retention. Together with possible direct stimulation of colonic secretion or motility, increased neurogenic fluid secretion from the small intestine may contribute to the pathophysiology of the IBAD syndrome [3]. This supports the view that an increased production of bile acids is the key to development of IBAD. An overload of bile acids already in the small bowel may explain both the changes in small intestinal secretion and motility, and the possibility that colestyramine exerts an effect in the small bowel. This fits well with the new finding of reduced negative feedback in IBAD [6, 26]. An effect on the small bowel might be a primary motor effect, an effect arising from changes in volume load, or both. Most likely, an effect is a combination,

since distension of the small bowel is known to induce propagating motor patterns leading to accelerated transit [19].

It has been shown previously that patients with IBAD have an enlarged bile acid pool [4, 25, 26]. Theoretically, treatment with bile acid binders may decrease this enlarged pool to normal levels, which in turn decreases the bile acid load to the small intestine. This could lead to less chloride and fluid secretion, and also to less propulsive activity, resulting in normalization of the transit time. This present study showed a normalization of the transit time and also a parallel improvement in diarrhea symptoms and in the consistency of the feces.

There are several limitations in the present study. First, the number of patients was small. However, the fact that the patients with the greatest increase in transit time also were those who derived the most benefit from treatment in terms of reduced bowel frequency support the findings. Another possible explanation for the variability in the results is the fact that the treatment was made in a clinical setting; i.e., the dosing of colestyramine was determined by the balance between effect and side-effects. Some patients may prefer a smaller reduction of symptoms in favor of fewer side effects.

Previous studies on gastrointestinal transit in IBAD [15, 18] have shown conflicting results. One major study, which found no correlation between small intestinal transit and IBAD, used the lactulose breath test for measurement of transit (25); and most authors agree that this test is an imprecise method with many pitfalls. The study from Sadik et al. [15] showed the test with radiopaque markers to be a more reliable method for measurement of gastrointestinal transit; hence, the results of this study are more likely to be valid.

The gold standard for measuring small bowel transit is scintigraphy, and one could discuss if the use of the method with radiopaque markers could have affected the results. The main concern with radiopaque markers is the ability to accurately locate the markers in the small intestine. Several precautions have been taken to ensure this [14], and the usefulness of the marker method has been shown in several studies on a large number of patients [7, 14, 15, 16, 17].

It is somewhat unexpected that total colonic transit was not prolonged by treatment, with only segmental transit in the transverse colon prolonged. One explanation could be that different parts of the colon are affected differently by treatment. However, a small increase in colonic transit could be missed in a limited number of patients; thus, a larger study is warranted.

## 5. Conclusions

In conclusion, a bile acid binding agent is an effective treatment in IBAD and acts probably in both the small bowel and in the colon. This also indicates that the small bowel as well as the colon has a pathophysiological role in IBAD.

## Abbreviations

IBAD          Idiopathic bile acid diarrhea.
SBTT          Small bowel transit time.
$^{75}$SeHCAT    $^{75}$Se-homocholic acid taurine.

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