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## Drug-induced hypochlorhydria causes high duodenal bacterial counts in the elderly

S. P. PEREIRA, N. GAINSBOROUGH\* & R. H. DOWLING

Gastroenterology Unit, Guy's Hospital Campus, Division of Medicine, UMDS, London, UK; and \*Department of Health Care of the Elderly, Guy's Hospital, London, UK

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### SUMMARY

**Background:** Small bowel bacterial overgrowth secondary to drug-induced hypochlorhydria may be of particular importance in the elderly, in whom anti-ulcer drugs are commonly prescribed and the consequences of malabsorption may be severe.

**Methods:** Duodenal aspirates were obtained from elderly individuals before ( $n = 24$ ) and during a 2-month treatment course with either omeprazole (20 mg daily;  $n = 8$ ) or ranitidine (300 mg b.d.;  $n = 6$ ), and from six patients with small bowel bacterial overgrowth who had diarrhoea and malabsorption.

**Results:** Before treatment, duodenal bacterial counts were normal ( $< 10^4$  colony forming units/mL) in 23 elderly subjects (96%). However, six of 14 patients (43%) treated with omeprazole (5 of 8) or ranitidine (1 of 6) developed bacterial counts  $> 10^5$  cfu/mL. All remained asymptomatic and had normal lactulose breath  $H_2$  profiles during treatment.

**Conclusion:** Drug-induced hypochlorhydria causes high duodenal bacterial counts in the elderly but, in the short term, this bacterial overgrowth is not associated with malabsorption.

### INTRODUCTION

Small bowel bacterial overgrowth (SBBO) is a syndrome characterized, in its florid form, by weight loss, diarrhoea, malabsorption of nutrients and some vitamins, and altered bile acid metabolism. It is due to proliferation, in the small intestine, of an abnormal bacterial flora that is predominantly anaerobic and which closely resembles the colonic flora, with bacterial counts in the upper intestinal lumen above  $10^5$  colony forming units (cfu) per mL of aspirate.<sup>1–3</sup>

Small bowel bacterial overgrowth appears to be common in the elderly,<sup>4–8</sup> and may be the most frequent cause of occult malabsorption in this age group.<sup>9–12</sup> Although the reasons for high duodenal bacterial counts in elderly subjects are multifactorial,

any disorder that results in hypochlorhydria—for example, chronic atrophic gastritis, pernicious anaemia, or the use of drugs which reduce gastric acid secretion—may predispose to SBBO. In normal individuals, treatment with standard doses of  $H_2$ -antagonists only reduces intragastric acidity by 1–2 pH units.<sup>13–15</sup> Therefore, SBBO as a consequence of treatment with standard doses of cimetidine<sup>16, 17</sup> or ranitidine<sup>18</sup> has been reported only infrequently.

There are few data on the effects of more profound gastric acid inhibition on the small intestinal flora, such as that achieved with high-dose  $H_2$ -antagonists (for example, ranitidine 300 mg b.d.), or during omeprazole therapy. The potential for drug-induced hypochlorhydria to predispose to SBBO may be of particular importance in the elderly, in whom anti-ulcer drugs are commonly prescribed for long periods, and the consequences of malabsorption may be severe. The aims of the present study were: (i) to compare duodenal bacterial

Correspondence to: Prof. R. H. Dowling, Gastroenterology Unit, 18th Floor, Guy's Tower, Guy's Hospital, London Bridge SE1 9RT, UK.

flora in patients over the age of 65 years with and without SBBO, and (ii) to determine the effects, in this age group, of a 2-month treatment course with either omeprazole or ranitidine, on duodenal bacterial counts and morphology, as well as on indirect tests of SBBO.

## METHODOLOGY

### *Patients*

Two groups of patients were studied. Group 1 consisted of 24 elderly (arbitrarily > 65 years) patients (16 women, eight men; mean age 76 years, range 65–86 years) who were referred to Guy's Hospital for upper gastrointestinal endoscopy. None of the patients had: (i) known chronic atrophic gastritis or small bowel disease, (ii) a history of gastric or small bowel surgery, or (iii) been treated within the preceding 4 weeks with antibiotics or drugs which reduce acid secretion.

Group 2 consisted of six patients (three women, three men; mean age 74 years, range 60–84 years) with symptomatic SBBO (positive controls). Based on the results of previous investigations, two of the patients had pernicious anaemia, two had jejunal diverticulosis but in the remaining two, no predisposing factor for their high duodenal bacterial counts, fat and carbohydrate malabsorption, and chronic diarrhoea, had been identified.

### *Duodenal aspirate and culture*

In both groups, luminal contents were aspirated from the duodenum at the time of endoscopy, via a sterilized polyethylene tube passed through the suction channel of the endoscope.<sup>19</sup> The aspirates were obtained ≈15–30 cm distal to the pylorus, corresponding to the third part of the duodenum. Both aerobic and anaerobic cultures were performed, using standard techniques.<sup>19–21</sup> Aerobic bacterial counts of < 10<sup>4</sup> cfu/mL of duodenal juice were considered normal, while counts of 10<sup>4</sup>–10<sup>5</sup> cfu/mL were regarded as equivocal. Small bowel bacterial overgrowth was defined as the presence of any anaerobes in the duodenal aspirate, or aerobic counts of ≥ 10<sup>5</sup> cfu/mL.<sup>3</sup>

### *Gastric acidity and duodenal morphology*

Following aspiration of duodenal contents, the polyethylene tube was flushed with 1 mL saline then repositi-

oned in the stomach for aspiration of gastric juice. The pH of the fasting gastric and duodenal aspirates were determined by pH strips (Merck, Darmstadt, Germany). Pinch biopsies of the duodenal mucosa were also taken endoscopically, placed in formal saline, mounted in paraffin blocks, sectioned (5 µm slices) and stained with H&E for histological assessment.

### *Effect of drug-induced hypochlorhydria*

A second aim of the study was to determine the effect of drug-induced hypochlorhydria on small bowel bacterial counts. To do this, 14 patients in Group 1 in whom: (i) the first endoscopy was abnormal, (ii) anti-ulcer therapy was indicated, and (iii) a repeat endoscopy was desirable (moderate to severe oesophagitis in nine, gastric ulcer in three, complicated duodenal ulcer in two), were randomized, in an open-labelled fashion, to an 8-week course of either omeprazole (20 mg daily; *n* = 8) or ranitidine (300 mg b.d.; *n* = 6). These 14 patients underwent repeat endoscopy and aspiration of duodenal contents during the second month (median 6 weeks) of treatment.

### *Lactulose breath H<sub>2</sub> tests*

In those patients who had high duodenal bacterial counts during treatment (*n* = 6), lactulose breath H<sub>2</sub> tests were performed within the next 2 weeks during continued anti-ulcer therapy. Following an overnight fast, breath samples were collected from patients before, and then at 15-min intervals for a total of 3 h after, ingestion of 10 g lactulose in 100 mL water. SBBO was defined as a transient breath H<sub>2</sub> peak of > 10 p.p.m. above baseline, distinguishable from the later colonic peak.<sup>22</sup>

### *Ethical considerations*

Before entry into the study, all patients were informed of the aims and diagnostic procedures involved, and written consent was obtained. The study was approved by the Lewisham and North Southwark Committee on Ethical Practice.

### *Statistics*

Statistical comparisons of the data were carried out using Student's *t*-test or Wilcoxon's signed rank test as

appropriate. The  $\chi^2$  or Fisher's exact test was used for binary outcome variables. Duodenal bacterial concentrations were compared using  $\log_{10}$  transformed data. A probability level of  $P < 0.05$  was regarded as statistically significant.

**RESULTS**

Before acid suppression treatment, duodenal bacterial counts were normal ( $< 10^4$  cfu/mL) in 23 of the 24 patients (96%) in Group I. The remaining patient had an equivocal overgrowth of  $8 \times 10^4$  cfu (*Pseudomonas* species) per mL of duodenal juice. None of the patients had positive anaerobic cultures.

In contrast, duodenal bacterial counts were abnormal in all six patients from Group II with diarrhoea and malabsorption. Five of the six had aerobic coliform counts of  $\geq 10^5$  cfu/mL, while in two of the six, anaerobic Gram-negative bacilli were also present, at concentrations of  $4 \times 10^3$  cfu/mL and  $1.2 \times 10^4$  cfu/mL, respectively (Table 1).

*Effect of drug-induced hypochlorhydria*

In the 14 patients from Group 1 in whom gastric acid suppression and repeat endoscopy were indicated clinically, duodenal aspirates taken during the second endoscopy showed that four patients (29%) had coliform counts of  $\geq 10^5$  cfu/mL—two of whom also had high ( $\geq 10^5$  cfu/mL) anaerobic counts. In two further patients, anaerobes alone were isolated, at concentra-

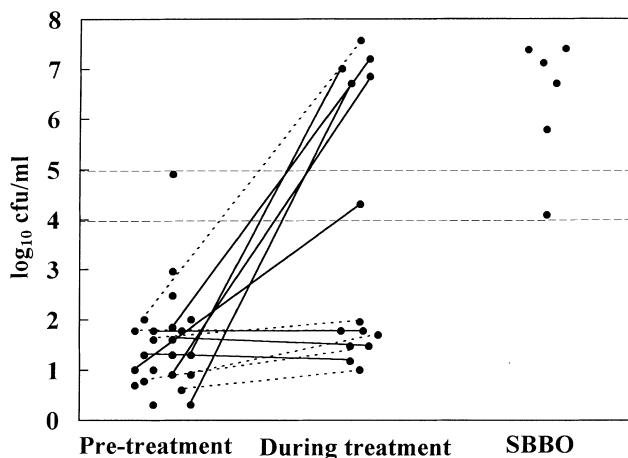


Figure 1. Duodenal bacterial counts (cfu/mL of aspirate) in: (a) elderly patients before ( $n = 24$ ) and during ( $n = 14$ ) treatment with either omeprazole (●—●) or ranitidine (●—●), and (b) six patients with malabsorption and diarrhoea due to small bowel bacterial overgrowth (SBBO). Counts of  $10^4$ – $10^5$  cfu/mL, as indicated by the horizontal lines, were regarded as equivocal.

tions of  $1 \times 10^7$  and  $2 \times 10^4$  cfu/mL, respectively. This 43% ( $n = 6$ ) prevalence of abnormal duodenal flora in the 14 treated patients represented a significant ( $P < 0.002$ ) rise over the low bacterial counts in the pre-treatment group ( $n = 24$ ). In the omeprazole-treated patients, the prevalence of duodenal colonization (five of the eight patients treated with omeprazole developed high duodenal bacterial counts) was higher than in those given ranitidine (one of six patients had a count  $\geq 10^5$  cfu/mL), although this difference was not statistically significant (Figure 1). Overall, there was no

Table 1. Small bowel bacterial counts (cfu/mL of duodenal juice) in six of 14 patients during short-term treatment with omeprazole or ranitidine (Group 1), and in six patients with symptomatic small bowel bacterial overgrowth (Group 2)

Patient	Sex	Age	Treatment	Aerobes	Anaerobes
<i>Group 1</i>					
1	F	84	Omeprazole	$7 \times 10^6$	$1 \times 10^5$
2	F	72	Omeprazole	$1.6 \times 10^7$	$1.1 \times 10^5$
3	F	84	Omeprazole	$< 100$	$1 \times 10^7$
4	F	86	Omeprazole	$< 100$	$2 \times 10^4$
5	F	76	Omeprazole	$5 \times 10^6$	$< 100$
6	F	77	Ranitidine	$3.7 \times 10^7$	$< 100$
<i>Group 2</i>					
1	M	69		$2.4 \times 10^7$	$< 100$
2	M	60		$1.8 \times 10^2$	$1.2 \times 10^4$
3	F	71		$2 \times 10^3$	$4 \times 10^3$
4	M	80		$2.5 \times 10^7$	$< 100$
5	F	77		$1.3 \times 10^8$	$< 100$
6	F	84		$5 \times 10^6$	Not done

significant difference in either the concentrations or the species of duodenal bacteria from the six patients with acquired colonization during treatment with omeprazole or ranitidine, and those from the six with known SBBO (Table 1).

*Gastric and duodenal pH.* In the 14 patients from Group 1 who underwent repeat endoscopies, the median gastric pH before treatment (2.0; range 2.0–4.5) rose significantly ( $P < 0.01$ ) during treatment (to 4.5; range 2.0–7.0). This increase in gastric pH was due, predominantly, to the omeprazole (median gastric pH of 5.0 during treatment), rather than to the ranitidine (median pH 3.8) treatment. The corresponding median duodenal pHs before and during treatment in the 14 patients were 6.3 (range 5–7.5) and 7.0 (range 6.0–8.0), respectively ( $P < 0.02$ ).

*Small bowel absorption and morphology.* None of the 24 patients in Group I, including the six who had high duodenal bacterial counts, developed symptoms during treatment. Lactulose breath  $H_2$  tests were performed during continued anti-ulcer therapy in five of the six patients who developed high duodenal bacterial counts—none of the five had evidence of an early breath  $H_2$  peak suggestive of SBBO. Furthermore, duodenal biopsies taken before and during treatment were within normal limits histologically in all cases.

## DISCUSSION

Bacterial colonization of the upper small bowel has been reported in 38% of healthy, elderly individuals<sup>7</sup> and in 52–71% of elderly patients with clinical evidence of malabsorption and/or undernutrition.<sup>6, 7, 9, 23, 24</sup> In this age group, the most common predisposing factor to high small bowel bacterial counts is atrophic gastritis, which is present in 20–30% of healthy, elderly subjects.<sup>25, 26</sup> Anatomical disorders of the small intestine, particularly jejunal diverticulosis, are also a relatively common predisposing factor.<sup>6, 9, 23</sup> The role of age-related changes in intestinal motility, in the absence of other predisposing factors to SBBO, remains unproven.<sup>27–29</sup> In elderly patients with diarrhoea and high duodenal bacterial counts, the role of antibiotic therapy in the correcting of malabsorptive defects of SBBO, and improving nutrition, is well-established.<sup>6</sup> However, whether or not duodenal colonization in otherwise

healthy elderly individuals is of any clinical significance, remains controversial.

The present study has shown that, in 24 well-nourished elderly patients without known atrophic gastritis, none had evidence of duodenal bacterial counts  $\geq 10^5$  cfu/mL before treatment with omeprazole or ranitidine. However, during the second month of an 8-week treatment course, 43% of patients developed bacterial colonization of the upper small intestine. In four patients, duodenal counts of coliforms and/or anaerobic Gram-negative bacilli at concentrations of  $> 10^6$  cfu/mL were detected, while in two others, anaerobes alone were present. There were no apparent differences in the concentrations or species of the duodenal flora between these six patients and the six who had clinical and biochemical evidence of malabsorption secondary to SBBO.

Although there are few data on the effects of drug-induced hypochlorhydria on the small intestinal flora in elderly subjects,<sup>30</sup> the present findings are in accord with other studies in younger adults. Fried *et al.*<sup>31</sup> reported high ( $\geq 10^5$  cfu/mL) duodenal counts in 14 of 25 (56%) patients (mean age 53 years) during a 6-week course of omeprazole 20–40 mg daily. In contrast, none of 15 control subjects had duodenal colonization—findings similar to those of the present study. Similarly, in a recent study of 47 patients with peptic disease by Thorens *et al.*<sup>17</sup>, 53% of those receiving omeprazole, but only 17% of those receiving cimetidine, had high duodenal bacterial counts. No patient developed signs of malabsorption or an increase in gastric *N*-nitroso compounds during treatment.

The clinical significance of high duodenal bacterial counts in hypochlorhydric elderly patients is controversial, with previous reports reaching opposite conclusions.<sup>6, 8</sup> In a recent study of 17 healthy elderly subjects (mean age 70 years) with high duodenal bacterial counts associated with atrophic gastritis or omeprazole treatment (40 mg/day), there was no evidence of fat malabsorption (72-h faecal fat excretion) or clinically significant carbohydrate malabsorption (as determined by faecal pH and the 25 g D-xylose breath test).<sup>30</sup> Our results are in accord with these findings. None of the patients in the present study developed diarrhoea, or abnormal breath hydrogen profiles suggestive of malabsorption, during treatment. Moreover, duodenal morphology remained normal in all patients. Although major changes in small bowel histology due to bacterial colonization are rare,<sup>1–3</sup> villous atrophy and an increase in intra-epithelial lymphocytes—which resolve during

antibiotic therapy—have been reported in elderly patients with SBBO.<sup>5</sup>

The present results, taken together with those of other recent studies,<sup>17, 30, 32</sup> suggest that short-term gastric acid inhibition with proton pump inhibitors such as omeprazole is not associated with clinically significant small bowel malabsorption. In the elderly, there are few data on the effects of long-term acid suppression on small bowel absorption. In a study of 40 patients aged 23–79 years given omeprazole 20 mg daily,<sup>33</sup> [<sup>14</sup>C]-glycocholate breath tests were normal both before and during 26 weeks of treatment, while in a very recent series of 44 elderly people,<sup>34</sup> glucose breath hydrogen tests were positive in 45% of those taking omeprazole compared with 59% of age-matched controls. However, breath tests appear to be poorly predictive of SBBO in this age group,<sup>30, 35</sup> and further studies of the effects of long-term drug-induced hypochlorhydria on the small bowel bacterial flora and tests of absorption, seem warranted.

#### ACKNOWLEDGEMENTS

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