Gastric Bacterial Overgrowth Accompanies Profound Acid Suppression

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Abstract

Background: Suppression of gastric acid may lead to gastric colonization by aerobic and anaerobic bacteria, and consequent clinical manifestations. The risk is likely to be higher with poor environmental hygiene.

Aims: To study the effect of short-term acid suppression with omeprazole on gastric bacterial flora.

Methods: Twenty-five ambulatory patients with acid-peptic diseases underwent clinical assessment and gastric juice collection (for pH and culture) prior to start of therapy with 20 mg omeprazole daily, on days 7 and 14 of therapy, and 7 days after omission of therapy (day 21).

Results: Eighteen patients completed the study. The median gastric pH was 1.8, 7.5, 7.5 and 3.4 on days 0, 7, 14 and 21 respectively. Positive gastric cultures were obtained in 13 of 25, 17 of 21, 18 of 18 and 14 of 18 patients on respective study days, with median colony counts of $1.5 \times 10^4$, $7.5 \times 10^5$, $8.7 \times 10^7$ and $7.3 \times 10^6$ cfu/mL respectively. Three patients developed self-limiting diarrhea during therapy and two more immediately after discontinuing therapy.

Conclusions: Gastric colonization is common with short-term profound acid-suppression, and may cause diarrhea. Acid suppressive therapy should be used with caution especially in patients with poor environmental hygiene.

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Introduction

Gastric acid has many important functions. Apart from facilitating peptic digestion of dietary proteins and the intestinal absorption of iron and probably calcium, it destroys ingested microorganisms and thereby has an important protective function. Omeprazole, a parietal cell H⁺/K⁺ ATPase (proton) pump inhibitor, inhibits gastric acid secretion and leads to virtual gastric anacidity after prolonged administration. Such profound acid suppression may impair the protective action of gastric acid against ingested microorganisms. This could lead to respiratory infections and small bowel bacterial overgrowth and may increase susceptibility to enteric infections. Such a situation is more likely in immunocompromised subjects and in those exposed to unhygienic surroundings; this may explain why reports from the West are conflicting.

The present study was undertaken to evaluate the effect of short-term omeprazole therapy on gastric flora in patients with acid-peptic diseases from a tropical country.

Methods

Twenty-five ambulatory patients (14 men, 11 women; median age 29 years, range 20-58) with duodenal ulcer (15 cases), prepyloric ulcer (2), duodenal and prepyloric ulcers (2), gastric ulcer (1), or gastrooesophageal reflux disease (5) were included in the study. Most patients belonged to the lower or middle socio-economic strata, with suboptimal hygiene at home. Informed consent was obtained from each subject and the study was approved by our institution's ethics committee.

The exclusion criteria were: use of acid-suppressive drugs or antimicrobials in the preceding four weeks, need for any concomitant drug therapy including antacids, associated local or systemic complications or illnesses including the Zollinger-Ellison syndrome, immunocompromised individuals and pregnant women.

Omeprazole was administered as a 20 mg dose around 8:00 a.m. daily for two weeks, starting about 48 hours after the diagnostic endoscopy. Patients were followed up weekly.

Gastric fluid collection and analysis

Gastric fluid collection was done on day 0 (just before starting therapy), on days 7 and 14 (while on therapy), and on day 21 (seven days after discontinuing therapy), using sterile nasogastric intubation after an overnight fast (24 hours after the previous dose of omeprazole on days 7 and 14). We used an open-ended tube since earlier reports and our experience (unpublished observation) showed that this gave results similar to those with the use of sealed tubes.
Table: Gastric aspirate culture results

<table>
<thead>
<tr>
<th>Test</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>21</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Positive culture (%)</td>
<td>13</td>
<td>17**</td>
<td>18**</td>
<td>14</td>
</tr>
<tr>
<td>CFU &gt; 10^5/mL (n)</td>
<td>3</td>
<td>12</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Coliforms grown (n)</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

p < 0.05, ** < 0.001 as compared to day 0 (chi-square test)

The overnight secretion was discarded, and aspirate was collected over the next 15 minutes by slow suction. If the aspirate showed presence of blood or was mucoid or bilious, it was discarded and a fresh sample was obtained. An aliquot of gastric aspirate was also collected in a separate vial for estimation of pH, using a double-electrode pH meter (Elko, Bombay; pH range 0-14, sensitivity 0.01) with built-in correction for temperature variation.

Enriched brain-heart agar, tomato juice agar (for lactobacillus) and Sabouraud's agar (for yeast) (all from Hi-Media, Bombay) were used for culture studies. The organisms were identified on the basis of colonial morphology on selective media, Gram stain and biochemical tests. Anaerobic studies were not carried out.

Statistical analysis
Pre and post treatment data were compared using the Mann-Whitney test an \( \chi^2 \) test, as applicable. No separate control group was studied.

Results
Of the 25 patients recruited, only 21 reported for follow-up on day 7, and 18 each on days 14 and 21.

The median gastric pH was 1.8 prior to treatment with omeprazole. This increased to 7.3 on days 7 and 14 of therapy and dropped to 3.4 one week after discontinuation of therapy (day 21).

Gastric culture (Table)
The median colony count on day 0 was 1.5 x 10^6 CFU/mL (range 0 to 2.0 x 10^7). The predominant organisms cultured were staphylococci and yeasts.

On day 7, the median colony count rose to 7.5 x 10^5 (range 1.5 x 10^5 to 4.9 x 10^5) CFU/mL \( (p = 0.03) \). Staphylococci and yeasts were again the predominant organisms. Coliforms (Escherichia coli, proteus and klebsiella) were isolated in four patients.

On day 14, median colony count of 8.7 x 10^7 (range 9.0 x 10^7 to 1.2 x 10^8) CFU/mL was statistically similar to the count on day 7. Staphylococci and yeasts were the predominant isolates; coliforms were isolated in five patients.

On day 21 (one week after discontinuing therapy), the median colony count of 7.3 x 10^6 (range 5.4 x 10^5 - 5.7 x 10^6) CFU/mL was significantly lower \( (p = 0.046) \) as compared to the count on day 14, and was similar to the count on day 0. In addition to staphylococci and yeasts, coliforms could be cultured in two patients.

Morbidity
On day 7, one patient complained of small-volume diarrhea without blood or mucus; omeprazole was continued. By day 14, two other patients had developed similar symptoms; all three had spontaneous recovery before reporting on day 14. Two other patients had diarrhea for 2 days after discontinuation of therapy, which improved spontaneously. No additional medication was given to any patient.

All the patients who developed diarrhea had coliforms in their gastric aspirate. There was no other difference in the type of organisms between those with and without diarrhea.

Discussion
Omeprazole is a potent suppressor of H^+ ion secretion. In one study, after 7 days of treatment with 10, 20 and 30 mg omeprazole daily, 24-hour H^+ activity had decreased by 37%, 90% and 97% respectively. We studied the effect of the standard 20 mg daily dose. At the end of one week, median gastric pH had increased significantly to 7.5. This was accompanied by an increase in the number of patients with positive gastric cultures and a significant rise in total colony count to 7.5 x 10^5/mL.

A colony count of more than 10^5 organisms/mL of gastric aspirate is considered pathological.

In addition, there was a qualitative change in gastric flora. Coliforms were isolated from the gastric aspirates of four patients; staphylococci, streptococci, lactobacilli and yeast were the other organisms isolated. Organisms that are normal commensals in the oral cavity travel down during swallowing, for example, and survive in the stomach when the gastric pH is between 4 and 5; at pH above 5, active proliferation occurs.

In the second week on omeprazole, the pattern of increase in colony counts with increase in pH was maintained. One week after discontinuing omeprazole, the gastric pH and colony count were decreasing but were still high as compared to pre-treatment levels; coliforms were isolated from two samples.

Studies from the West have evaluated the effect of short-term profound acid suppression with omeprazole on gastric flora. Sharma et al. used omeprazole in a dose of 30 mg daily for 2 weeks in 10 healthy volunteers and found a significant rise in the number of bacteria in the gastric juice. However, the organisms isolated were all...
present prior to initiating omeprazole; no new organism was isolated. More recently, Verdu et al11 found proliferation of bacteria, including nitrate-reducing bacteria, but no increase in N-nitroso compound concentration, with two weeks' therapy with omeprazole. Emphasis in these studies has been on the long-term implications of bacterial overgrowth, including the possibility of carcinogenesis.

The two studies from India (including the present one) throw light on a more immediate problem: the presence of coliforms in the upper gastrointestinal aspirates in patients receiving omeprazole. The first report from Calcutta, a city with environmental problems similar to ours, showed bacterial overgrowth (including coliforms) in antral biopsy and jejunal aspirate samples among ten patients on omeprazole 20 mg daily for four weeks.12 The origin of these coliforms may be contaminated food and water which these patients are exposed to.

Five of our patients study developed diarrhea. Three of ten patients in the other Indian study developed diarrhea on therapy.12 It is not possible with present evidence to establish a direct link between the coliforms and diarrhea, but the possibility needs to be studied. Bardhan et al12 also reported diarrhea in 5 of 63 patients receiving omeprazole.

Short-term profound lowering of intragastric acidity is thus associated with bacterial overgrowth in the stomach. The danger arising from such a finding in the underdeveloped world is not just in its long-term implications but the more immediate risk of pathogenic infections. Colonization by coliforms is possible in environments with poor hygiene. Diarrhea is a frequent association. These facts must be borne in mind when considering acid-inhibitory therapy especially in patients exposed to such environments; indiscriminatory or unsupervised use of these drugs in such situations should be discouraged.

References