Omeprazole-associated changes in the gastric mucosa of children

R Drut, E Altamirano, E Cueto Rúa

ABSTRACT

Aims: To describe histological findings in gastric mucosa biopsy specimens of children treated with proton-pump inhibitors (PPIs) for different periods of time.

Methods: Biopsy specimens from 12 children (aged 8 months to 15 years) treated with PPIs and 8 controls were processed for paraffin embedding and stained with H&E as well as immunohistochemically for sialyl-Tn antigen.

Results: The main changes were related to parietal cells which showed brisk cytoplasmic eosinophilia, apical cytoplasmic protrusions to dilated glands, cytoplasmic and nuclear hypertrophy, dilated intracytoplasmic canaliculi, binucleation and multinucleation. The intracellular canaliculi surface showed strong immunohistochemical reaction for sialyl-Tn antigen, apparently a marker for this structure. Some of the patients were biopsied after a short period of oral or intravenously administered omeprazole; the changes may therefore occur rapidly.

Conclusions: PPIs induce the same changes in the gastric mucosa of children as in adults, but the number of nuclei is increased. These effects have not been reported previously in this age group. It is suggested that the changes result from a combination of effects of PPIs and gastrin release.

MATERIAL AND METHODS

Table 1 presents the clinical data of the patients. Case 1 is the same as case 5 and is included twice as there were two temporally apart biopsies. In the first there was a mild active gastritis, with a few bacteria consistent with Helicobacter pylori, as well as omeprazole-related changes; the second specimen was devoid of the inflammatory process. In both episodes the girl received intravenous omeprazole due to vomiting, which was clinically related to mild pancreatitis.

A control group consisted of 8 patients (7 boys, 1 girl; mean age 7.7 years, range 1–15) who underwent to endoscopic biopsies but had not received PPIs.

Biopsy samples were processed routinely for paraffin-embedding and H&E staining. Sialyl-Tn antigen immunostaining was performed manually following the usual immunoperoxidase procedure.

HISTOPATHOLOGY FINDINGS

Table 2 summarises histopathological findings. In brief, all the cases presented parietal cell hypertrophy with enlarged nuclei, and PCP extending to dilated glandular lumina. Binucleated parietal cells were present in all cases; there were multinucleated (more than two nuclei) cells in five biopsy specimens. The parietal cell hypertrophy was associated with a peculiar bright eosinophilia of the cytoplasm in which dilated cytoplasmic canaliculi were easily seen (figs 1 and 2). Apoptosis of parietal cells was seen in the two patients who had undergone liver transplantation (cases 2 and 3). Glandular cysts were not found. None of these changes were evident in the control cases.

The sialyl-Tn antigen immunohistochemistry was intensely positive in the cytoplasmic canalicul profiles of the parietal cells (figs 3 and 4) in a pattern remarkably different from that found in the controls (fig 5) with respect to extension and intensity of the staining. The biopsy specimens of treated patients showed numerous parietal cells with strong reactivity in the numerous cytoplasmic canaliculi versus the lighter and sparse staining in the control group biopsy specimens.

DISCUSSION

Omeprazole, a type of substituted benzimidazole, is a proton-pump inhibitor that suppresses gastric acid secretion by specific inhibition of H⁺/K⁺-ATPase in the gastric parietal cell. By acting specifically on the proton-pump, omeprazole blocks the final step in acid production, thus reducing gastric acidity.¹

The histopathological effects of omeprazole have largely been determined from experimental reports and clinical studies with prolonged administration...
of the drug in adults. The paper which reported gastric polyps in children under prolonged omeprazole therapy is difficult to interpret since the two reported examples were found in patients having gastrostomy tubes.\(^7\) Our present report extends the known changes in the gastric mucosa, mainly in the parietal cells (fundic gland cysts and fundic gland polyps were not found), to the paediatric group of patients.

Remarkably, some of the patients had received omeprazole for a very short period of time before the biopsy was performed. It seems therefore that the acute pharmacological effect is also associated with microscopic recognisable changes in the parietal cells, at least in children. The findings favour the interpretation that blocking the proton-pump in the parietal cells acutely triggers a mechanism for compensating this effect, most

Table 1  Omeprazole-associated changes in gastric mucosa in children; clinical data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, sex*</th>
<th>Main disease</th>
<th>Omeprazole†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 y, F</td>
<td>Helicobacter pylori gastritis; mild pancreatitis, 2 m previously</td>
<td>IV, 48 hours</td>
</tr>
<tr>
<td>2</td>
<td>12 y, F</td>
<td>Liver transplant; portal hypertension</td>
<td>40 days</td>
</tr>
<tr>
<td>3</td>
<td>14 y, F</td>
<td>Liver transplant; portal hypertension</td>
<td>IV, 72 hours</td>
</tr>
<tr>
<td>4</td>
<td>11 m, F</td>
<td>Down syndrome; malabsorption syndrome; tTG--; gastro-oesophageal reflux</td>
<td>Several days</td>
</tr>
<tr>
<td>5</td>
<td>8 y, F</td>
<td>Same patient as case 1, 9 months later</td>
<td>IV, 48 hours</td>
</tr>
<tr>
<td>6</td>
<td>10 y, M</td>
<td>Portal hypertension‡</td>
<td>10 months; IV, 2 doses (1 day and 3 days)</td>
</tr>
<tr>
<td>7</td>
<td>12 y, M</td>
<td>Duodenal peptic ulcer</td>
<td>2 months</td>
</tr>
<tr>
<td>8</td>
<td>14 y, M</td>
<td>Chronic gastro-oesophageal reflux</td>
<td>Several months</td>
</tr>
<tr>
<td>9</td>
<td>15 y, F</td>
<td>Chronic gastro-oesophageal reflux; oesophagitis; Nissen’s funduplication 1 y previously</td>
<td>1 year</td>
</tr>
<tr>
<td>10</td>
<td>10 y, M</td>
<td>Nephrotic syndrome; vomiting; urea breath test +</td>
<td>Several months</td>
</tr>
<tr>
<td>11</td>
<td>5 y, F</td>
<td>Malabsorption syndrome; vomiting; low weight and height; urea breath test +</td>
<td>Several cycles</td>
</tr>
<tr>
<td>12</td>
<td>8 m, F</td>
<td>Gastro-oesophageal reflux; vomiting</td>
<td>4 days</td>
</tr>
</tbody>
</table>

* y, years; m, months; F, female; M, male. † Oral administration (2–3 mg/kg/day), except as specified. Intravenous (IV) doses: 1 mg/kg/day. ‡ Portal hypertension secondary to portal vein thrombosis due to umbilical vein catheterisation at neonatal period.

Table 2  Omeprazole-associated changes in gastric mucosa in children; histopathology findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Mucosa type</th>
<th>PCP</th>
<th>Bi/multiN PC</th>
<th>PC N/C hypertrophy</th>
<th>Dilated glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermediate</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Fundic</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Fundic</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fundic</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Fundic</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Intermediate</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Fundic few</td>
<td>+/-</td>
<td>Mild</td>
<td>Focally</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Fundic</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
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<td>9</td>
<td>Fundic</td>
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<tr>
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<td>Intermediate</td>
<td>+</td>
<td>+/-</td>
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<td></td>
</tr>
</tbody>
</table>

Multinucleated: more than 2 nuclei.

In cases 1 to 4 the intracellular canaliculi of parietal cells were easily seen. Cases 1 and 5 showed apoptosis of a few parietal cells.

PCP, parietal cell protrusions; bi/multiN, binucleated/multinucleated; N, nucleus; C, cytoplasm.

Figure 1  Low power view of fundic mucosa type sample showing dilated glands, parietal cell protrusions, parietal cell cytoplasm and nuclear hypertrophy, and dilated intracellular canaliculi.

Figure 2  Areas of different biopsy specimens including dilated glands, parietal cell protrusions, parietal cell cytoplasm and nuclear hypertrophy, binucleated and multinucleated parietal cells, and dilated canaliculi as clear spaces near or around the nuclei.
probably gastrin release, resulting in DNA synthesis, RNA synthesis and the ensuing nuclear and cytoplasmic changes through its well known trophic action. This trophic effect might also account for the presence of more than one nucleus. In children these cellular modifications develop very rapidly.

Although we do not have a direct explanation, we speculated that this might be related to the combined effect of omeprazole, the multiple immunosuppressive drugs given to these patients, and a kind of subclinical graft-versus-host disease. Parietal cell apoptosis was evident only in the patients who had had liver transplantation.

Sialyl-Tn antigen (CD175s) is a carbohydrate associated with apomucins MUC1 and MUC2, which is produced in the initial steps of the mucin biosynthetic pathway. In accordance with this observation the immunostaining was intensely positive in this zone in all cases, in a pattern different from that of normal mucosa. This observation adds to the parietal cell alterations but is not required for diagnosing them.

In brief, the gastric mucosa of children shows the main omeprazole-induced changes as reported in adults (but fundic gland cysts and fundic gland polyps), but with an additional, unique observation, namely binucleated and multinucleated parietal cells. These findings may prove useful as a histopathology contribution for studies as suggested by Gibbons and Gold.

Competing interests: None declared.

REFERENCES

Take-home messages
- When given to children, even for short periods, proton-pump inhibitors induce almost the same cellular and histological changes in the gastric mucosa as seen in adults, but they occur faster.
- An increase in the number of nuclei in the parietal cell seems to be a unique finding for children.
- Changes may result from the combined effect of the medication and the trophic effect of gastrin.
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