Leading article

Are antacids cytoprotective?

Ever since the discovery of hydrochloric acid in the human stomach, a major premise of ulcer therapy has been that neutralisation of acid leads to ulcer healing. Research into antacid pharmacology centred on acid neutralising capacity. The aim of dosage and schedule of administration of antacids was to keep the intragastric pH as neutral as possible.¹ Research which showed the effectiveness of low dose antacids (with a neutralising capacity of 100–200 mmol/day)^{2,3} was pretty much ignored, even though complete acid neutralisation could not have played a major role in the treatment.

With the introduction of the H₂ receptor antagonists the demise of antacids appeared imminent. Why use large volumes of a distasteful liquid preparation when a single H₂ antagonist tablet could stop the parietal cells from secreting acid? Why neutralise acid when acid secretion could be stopped at the source? Antacids appeared to have no future in the treatment of ulcer disease.

Pronouncements of the demise of antacids in management of ulcer bring to mind the statement by Mark Twain: 'reports of my death are greatly exaggerated'. Phoenix like, antacids appear to be taking on a new life in ulcer therapy, as new findings show mechanisms of action other than acid neutralisation, which could account for their therapeutic effectiveness.

Several studies have shown that antacids are as effective as H₂ receptor antagonists in healing of ulcer and symptomatic relief.^{4–6} Antacids have also been found to be more effective than H₂-antagonists in preventing stress-induced ulceration and bleeding.^{7–8} Furthermore, much to everyone's surprise, acid neutralisation alone does not explain the clinical efficacy of antacids in ulcer healing and in the prevention of stress induced bleeding.⁹

Recent information has shown that antacids stimulate the protective and reparative properties of the gastric mucosa in experimental animals^{10–14} and man.^{9,15} Aluminium containing antacids have been found to prevent injury by alcohol^{12,14,16} and to stimulate mucosal restitution and secretion of prostaglandin by the normal stomach.^{12,16} Antacids' ability to prevent alcohol injury is an important finding, because this form of injury is independent of gastric acid and cannot be prevented by H₂ blockers.¹⁴ Moreover, when antacids are acidified with hydrochloric acid, they still protect against alcohol injury (Tarnawski and Hollander, unpublished data).

How do antacids protect the gastric mucosa against injury if acid neutralising capacity is unimportant, eliminated, or minimised? The answers to these important questions are just beginning to appear. Aluminium, as it is present in antacids (as Al(OH)₃), or in sucralfate (as aluminium sulfate), appears to stimulate gastric mucosal protection.^{12,17,18} Apparently specific forms of aluminium protect the stomach against injury by prostaglandin dependent and prostaglandin independent mechanisms.^{12,19}

The paper by Prelik *et al* in this issue of *Gut* clearly shows that

aluminium-containing antacids stimulate the synthesis of prostaglandins by specimens of human gastric mucosa. One mechanism which may thus account for the protective and healing effects of antacids is their ability to stimulate endogenous secretion of prostaglandins by the gastric mucosa. Endogenous prostaglandins are important in gastric mucosal defence and their stimulation should enhance mucosal defence and render the mucosa more resistant to injury.

The story became even more interesting recently with the finding that bismuth containing compounds also confer protection and stimulate prostaglandin release by the human stomach.²⁰ Apparently aluminium and bismuth stimulate the protective and reparative properties of the gastric mucosa by increased synthesis and/or release of mucosal prostaglandins. Whether both metal ions act through a common pathway, remains unknown.

The role of both metal ions needs clarification. Do compounds containing aluminium or bismuth activate phospholipase A2 and thereby provide arachidonic acid for prostanoid synthesis by the gastric mucosa? Recent studies have shown that the macrophages of the gastric mucosa take up sucralfate and colloidal bismuth.^{17,20} This finding raises the possibility that aluminium and bismuth interact directly with specific cells in the gastric mucosa, such as macrophages, to generate prostaglandins or other protective compounds.

Chronic ingestion of antacids has a profound effect on the gastric endocrine cells which consists of a significant increase in the gastrin to somatostatin cell ratio and a three-fold increase in serum gastrin in rats.²¹ Even a single dose of antacid has been shown to cause morphological changes and secretory stimulation in the gastric mucosa.¹⁶ These observations are exciting, because they open new avenues in the search for the complex series of events that allow the gastric mucosa to promote the healing of mucosal ulceration, or to protect itself against injury.²² More work is needed to clarify the role of antacids in the area of cytoprotection. Clearly, recent observations which account for the effectiveness of antacids by mechanisms of action other than acid neutralisation have given new life to antacids in the treatment of ulcer disease.

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