Summary of an international and a regional symposium: Acid-related diseases – improving the treatment options

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AN INTERNATIONAL WORKSHOP, 'Appropriate acid suppression for, the healing of acid-related diseases', (Hertfordshire, United Kingdom, November 15 to 18, 1991) and an international symposium, 'Acid-related diseases – improving the treatment options', (Vienna, Austria, November 22, 1991) provided important new information on the treatment of acid peptic disorders. A western Canadian meeting, 'The clinical management of duodenal ulcer and esophageal reflux disease', (Vancouver, British Columbia, January 11, 1992) provided the results of a national study of the symptomatic treatment of dyspepsia due to esophagitis and duodenal ulcer disease using a pump blocker or an H2-receptor blocker. The clinical impact of the new findings reported at these meetings will be examined.

ACID SECRETION

The sight, smell and thought of food stimulates the hypothalamus which, in turn, stimulates the vagus nerve via...
preganglionic cholinergic M1-receptors; these stimulate the parietal cells in the gastric mucosa. The muscarinic receptors on parietal cells are M1-receptors and these, together with H2- and gastrin-receptors, stimulate gastric acid secretion. Gastric enterochromaffin-like cells also have gastrin-receptors and (at least in the rat) contain granules possessing peptides including histamine. Stimulation of the enterochromaffin-like cells leads to histamine release, which stimulates the H2-receptors on the basolateral membrane of the parietal cell.

Anticholinergic drugs such as pirenzepine act on vagal M1-receptors, making their effect on the parietal cell M3-receptors nonspecific and their acid-inhibiting effect modest. The most important receptor on the parietal cell related to acid secretion is the histamine H2-receptor which can be blocked effectively by drugs such as cimetidine, ranitidine, famotidine and nizatidine.

The H+/K+-ATPase is located on the secretory canalicular membrane of the parietal cell. Irrespective of the stimulus to acid secretion, this proton pump represents the final common pathway in acid secretion and may be blocked by drugs such as omeprazole. Omeprazole, a highly specific inhibitor of the proton pump not affecting H+/K+-ATPase at other locations, is a prodrug which must be absorbed, metabolized in the parietal cell and bound to the actively secreting canaliculi. Omeprazole is a potent, specific and non-reversible inhibitor of the acid pump, inhibiting acid secretion in both the basal and stimulated state including, importantly, the food-stimulated state.

Therapeutic options for omeprazole include treatment of gastroesophageal reflux disease (GERD) with esophagitis, duodenal and benign gastric ulcer disease, and ulceration associated with hypersecretery state such as the Zollinger-Ellison syndrome. There are possible new roles for omeprazole in the treatment of nonsteroidal anti-inflammatory drugs (NSAID)-associated gastritis, Helicobacter pylori chronic active gastritis-associated peptic disease and gastrointestinal bleeding.

**NSAID-ASSOCIATED MUCOSAL DAMAGE**

Acid present in the gastric lumen may aid the absorption of aminosalicylic acid (ASA) and play a permissive role in the development of nonacidic NSAID damage to the gastric mucosa. Following the acute onset of superficial injury to the gastric mucosa, some healing takes place, leaving deeper focal lesions which may persist for weeks (1). Acid plays at least a permissive role in acute damage, suggested by several observations: the reduction in acid secretion by administration of ranitidine will reduce ASA-associated blood loss (2); cimetidine will diminish ASA-associated mucosal damage (shown by the decreased endoscopic score of mucosal damage) (3); cimetidine 800 mg at bedtime will reduce duodenal damage induced by oral indomethacin 150 mg; 1000 mg ASA-induced endoscopic damage to the gastric mucosa is reduced by omeprazole (4); and omeprazole 40 mg bid reduces gastric blood loss occurring in association with ASA (5).

Most agents used to treat active gastric or duodenal ulcer disease will heal NSAID-associated lesions as long as the NSAIDs are discontinued; however, many patients for whom NSAIDs are prescribed develop disabling joint discomfort when the NSAIDs are stopped. The real issue is to identify an agent which will heal these lesions even when NSAIDs are continued.

Meta-analyses have suggested that approximately 20% of NSAID-associated gastric ulcers will heal in eight weeks while the patient is treated with placebo compared with 70% ulcer healing in eight weeks with active agents. In a subset analysis of patients with gastric ulcers treated with ranitidine while NSAIDs were continued, the approximate four- and eight-week healing rates, respectively, were 30 and 53% for ranitidine, 60 and 80% for omeprazole 20 mg daily and 80 and 95% with omeprazole 40 mg daily (6).

There are large, well-controlled control studies suggesting that ranitidine will prevent NSAID-associated duodenal but not gastric ulcers, whereas both types may be prevented with misoprostol (7). It is unknown whether any of these agents are useful in treating congestive gastropathy occurring in portal hypertension. The role of omeprazole in the prevention of NSAID-associated gastric or duodenal ulcers is as yet unknown, but clinical trials are in progress.

**HELCOBACTER PYLORI AND PEPTIC DISEASES**

Acid normally destroys H pylori, so why does it survive in the gastric lumen? H pylori produces ammonium from endogenous urea by way of H pylori urease, which likely neutralizes sufficient gastric acid around this bacteria to prevent gastric acid's bactericidal effect. While the food-stimulated gastrin response is higher in H pylori-positive than-negative persons, acid secretion is unaltered. The physiological role of this hypergastrinemia needs to be questioned. Bombesin-stimulated gastrin release is greater in H pylori-positive than-negative individuals, but again the pathophysiological importance of this hypergastrinemia needs to be established. Both ranitidine and omeprazole reduce H pylori in the short term, but the mechanism of this bacteriostatic effect is unknown. The H pylori often will recur in the gastric antrum, and duodenal ulcer recurrence is common in the presence of H pylori.

The minimal inhibitory concentrations of antibiotics such as amoxicillin, erythromycin and ciprofloxacin in vitro decrease by an order of magnitude when the intergastric acidity falls and the pH increases from 3.5 to 5.5. When omeprazole is given alone, only 4% of H pylori-positive patients become negative; however, when omeprazole is combined with amoxicillin for two weeks, H pylori is eradicated in 54% of patients and six months later, 84% of these patients have remained free from symptoms of H pylori (8). A German study demonstrated an H pylori eradication rate of 80% with no relapses over nine months (9).

While the in vitro activity of metronidazole is not affected by changes in intergastric pH, treating duodenal ulcer patients for 10 days with metronidazole followed by a two-week course of...
amoxicillin plus omeprazole has been reported to result in 60% eradication (10). The combination of omeprazole, erythromycin and a bismuth compound may also be successful to eradicate H pylori. Thus, omeprazole would appear to improve the effect of some antibiotics to eradicate H pylori, and to heal acute duodenal ulcer and prevent its recurrence. However, the optimal therapeutic approach for treating H pylori has not yet been established.

GASTROINTESTINAL BLEEDING AND STRESS ULCERATION

Blood clotting and thromocyte aggregation may be impaired at a low pH; this may provide the rational basis for using an antisecretory agent to stem the flow of bleeding from a peptic ulcer. In an intensive care unit patient bleeding from a peptic lesion, ranitidine 400 mg given over 24 h by bolus injection was less effective than omeprazole 80 mg given for 24 h by perfusion (11). It is recommended that intravenous omeprazole be given first as a bolus of 80 mg, followed by 8 mg/h for 12 h with 4 mg/h thereafter. Occasionally, reversible water retention will be noted in women receiving high doses of intravenous omeprazole. The mechanism of this fluid retention is unknown.

Ongoing studies will establish whether intravenous omeprazole is associated with an increased risk of nosocomial infections, whether the outcome is superior with coagulation therapy plus acid inhibition and whether the underlying ulcer will heal more rapidly when the patient subsequently is switched to an oral preparation.

GASTROESOPHAGEAL REFLUX DISEASE

How common is GERD? Approximately 40% of the American population will experience heartburn at least once each month and approximately 10% will experience heartburn daily. If one bases the diagnosis of GERD on the presence of an abnormal upper gastrointestinal x-ray, the prevalence is roughly 86 cases per 10,000 per year, whereas the incidence falls to 4.5 if endoscopy is used as the end-point (12). Thus, it generally is agreed that the prevalence of GERD depends upon its definition. From the patient's perspective, GERD needs to be treated to reduce the frequency and severity of symptoms; from the physician's perspective it also is important to treat complicated GERD to reduce the complications. Complications: It has been suggested that approximately 20% of patients with esophagitis will have complications including ulceration (5%), stenosis (5%), hemorrhage (2%, although possibly occult bleeding is more common) and perforation (less than 0.2%). Barrett's epithelium occurs in as many as 10% of patients with GERD, but it is difficult to be certain of the exact prevalence because insensitivity of the esophagus has been reported in patients with GERD, reducing their pain perception which may hinder detection until development of a stricture, an adenocarcinoma or a post mortem examination. Unfortunately, there are no data to suggest that Barrett's epithelium can be prevented on a regular and predictable basis by either medical or surgical therapy.

Fortunately, the mortality rate from GERD is low (approximately one death per 10^5 per year). Even when GERD is treated appropriately, there is a high rate of recurrence, but this can be prevented with maintenance therapy with an acid-inhibiting drug. Thus, the aim of therapy is to reduce symptoms to a level that does not impair the patient's quality of life and that prevents complications. The recurrence of GERD symptoms and esophagitis is higher in patients treated with standard doses of H2-receptor antagonists than in those treated with omeprazole.

While it generally is accepted that NSAIDs may be associated with gastric (and less commonly duodenal or small intestinal) lesions, it has only recently been recognized that a higher proportion of patients with peptic stricture of the esophagus have used NSAIDs than did a control population with a relative risk of approximately 3:1 (13,14). Patients with GERD without peptic stricture may also have recently used ASA with a relative risk of approximately 2.5:1 (15).

Daytime reflux is important for most patients with GERD, but nighttime exposure also is important for those with severe disease. H2-blockers have a modest effect on food-stimulated acid secretion and a more marked effect on nighttime acid secretion. Several studies have reported the superiority of omeprazole — compared with standard doses of H2-receptor antagonists — for the symptomatic improvement and healing of GERD (16).

It is important when considering these reports, however, that the endpoint is understood; of patients presenting with heartburn and regurgitation, only 61% will have an abnormal endoscopy, 73% will have reduced lower esophageal sphincter pressure, 88% abnormal Bernstein test and 94% of patients will have abnormal histology (17). Thus, therapy for GERD may be useful for symptoms, but objective endpoints, such as endoscopic healing, need to be considered. The criteria for endoscopic healing also need to be better standardized. Finally, since it is apparent that patients with GERD generally require greater acid inhibition to achieve healing than do patients with duodenal ulcer, results of high dose H2-receptor antagonist therapy will be awaited with interest.

Over a 12-month interval, 75% of GERD patients treated with ranitidine 150 mg bid will recur compared with 68% treated with omeprazole 20 mg on weekends (Friday, Saturday and Sunday) and only 11% treated with omeprazole 20 mg daily. In 98 patients with esophagitis resistant to three months of treatment with ranitidine, many were kept in remission with omeprazole 20 mg daily over one year (18). Omeprazole 10 mg/day is more effective in this regard than 20 mg on weekends when given to patients who initially healed their esophagitis on omeprazole (79 versus 46%) (19).

In patients with grade II or III esophagitis, healing occurred in 60% of patients at four weeks, 80% at eight weeks and 100% at six weeks when treated with omeprazole 40 mg/day (20). In a five-year follow-up of 91 patients, 75% remained in remission on maintenance therapy with 20 mg daily, but some patients required 40, 60 or 80
mg/day for maintenance therapy. Few patients with GERD will have acid hypersecretion (21), but duration of acid exposure to the esophagus will also relate to the degree of impairment of the lower esophageal sphincter pressure (or possibly variabilities in the absorption, metabolism and excretion of omeprazole). For example, 15 of 19 GERD patients who relapsed had a lower esophageal sphincter pressure less than 6 mmHg and 18 of 19 had a pressure less than 10 mmHg.

What is the rational basis for the use of antisecretory agents to reduce intragastric acidity and thereby achieve healing of GERD? There is an inverse linear relationship between number of hours per day that the intragastric pH is less than 4 and number of hours per day that the intragastric pH is less than 4 (Figure 1). There is also a linear relationship between the number of hours per day that the intragastric pH is over 4 and the eight-week healing rate of esophagitis (22). For example, there is almost 100% healing of esophagitis achieved with omeprazole 60 mg taken each morning, which achieves approximately 22 h/day of intragastric pH over 4. Symptom severity also is related to acid exposure; the more severe the patient's symptoms or the endoscopic grade of esophagitis, the longer the esophageal pH is less than 4.

The superior healing rate of omeprazole compared with standard doses of an H2-blocker may be due to differences in intragastric, and therefore intrasophageal, pH. For example, the percentage of time that the intrasophageal pH is less than 4 is 2.5% with omeprazole 20 mg versus 6.3% with ranitidine 150 mg tid, with 20 versus 49 reflux episodes with omeprazole compared with ranitidine and only an average of 1.5 (compared with four) of these reflux episodes longer than 5 min. However, ranitidine 300 mg gid may be comparable with omeprazole 20 mg/day. Of even greater importance is the establishment of a consensus as to whether patients with GERD should be treated in a graded fashion (initially with lifestyle changes and antacids, then with standard doses of H2-blockers and/or promotility agents, and then using pump blockers only for patients with resistant symptoms), or initially be placed on potent acid inhibition.

**PEPTIC ULCER DISEASE**

Most patients with duodenal ulcer disease will have antral gastritis; in approximately 80%, the gastritis is caused by *H pylori*, in 5% it may be autoimmune in origin and in 5% it is of unknown etiology. Chronic active gastritis may progress to atrophy and will be associated with reduced secretion of gastric acid and pepsin, and loss of the integrity of the mucosa. Acid output will fall with increasing atrophy and with increasing age of the patient. *H pylori*-associated antral gastritis often is associated with duodenal ulcer; atrophy of the gastric body is not associated with duodenal ulcer but may be associated with gastric ulcer. Severe atrophy of the gastric body is associated with an increased risk of the development of gastric cancer (23).

Chronic atrophic gastritis (type A/B) is associated with gastric enterochromaffin-like cell hyperplasia in patients with peptic ulcer disease, usually of the micronodular or linear type. Atrophic gastritis also is associated with hypergastrinemia which, in turn, may have some role to play in enterochromaffin-like hyperplasia. It should be noted, however, that the hypergastrinemia of Zollinger-Ellison syndrome and pernicious anemia causes a different (diffuse) form of enterochromaffin-like hyperplasia. In young and middle-aged men with gastritis, the cumulative risk of developing a peptic ulcer within the following 10-year period is 30% (compared with an almost negligible risk in those with a normal stomach) (24). Thus, the increase in endocrine cell volume density may be related to the severity of the associated gastritis rather than to the effect of associated drug therapy.

Examination of gastric biopsies performed on patients using omeprazole for compassionate reasons for one to four years revealed that none showed neoplastic or dysplastic changes, 14.1% showed linear and/or diffuse hyperplasia without micronodular hyperplasia and 28.3% showed some form of enterochromaffin-like hyperplasia; all types of argyrophil cell hyperplasia, however, were present in pretreatment biopsies. In patients treated with omeprazole there was an increase in micronodular hyperplasia from 2.5 to 10.4% and the number of patients with chronic active gastritis increased from 1 to 13%, particularly in patients over 49 years old. In patients with a history of gastric ulcer without drug treatment, the presence of chronic atrophic gastritis of the gastric body increased from 7% at the time of ulcer diagnosis.
to 67% two years later (25); at that point 23% of all biopsies showed micro-
odu lar hyperplasia (26). It would seem, therefore, that over time chronic
atrophic gastritis progresses and that this progression to chronic atrophic
 gastritis – rather than the use of an
antisecretory agent – is responsible for
the development in micronodular hy-
perplasia observed during long term
treatment with omeprazole.

From the patient's perspective, im-
provement in dyspeptic symptoms is
important. Symptom relief is achieved
with H2-receptor antagonists as well as
with pump blockers. In a large
Canadian study performed with the
assistance of family physicians, general
practitioners and gastroenterologists,
patients with endoscopically proven
esophagitis of different grades and
patients with endoscopically or radi-
ologically demonstrated duodenal ulcer
were randomized to receive either ran-
tidine 150 g bid or omeprazole 20 g
daily (27). Treatment was double-blind
and patient symptoms were reassessed
(healing of the underlying GERD/ duo-
den al ulcer was not re-evaluated).
A greater percentage of patients treated
with omeprazole experienced symptom-
atic improvement compared with
those treated with ranitidine.

There are criticisms of the study,
such as the mixed group of patients, use
of radiology instead of endoscopy in
some duodenal ulcer patients, lack of
follow-up endoscopy to correlate heal-
ing with symptom improvement and
potential subjectivity of the assessment
dyspepsia improvement. Nonetheless,
from the patient perspective of pain
improvement and relief, the pump block-
er was superior to the receptor blocker.

SAFETY EXPERIENCE WITH
PUMP BLOCKERS

Hypergastrinemia develops in many
patients treated with antisecretory
therapy. Acidification of the antrum
normally 'brakes' the release of gastrin
from G cells, allowing antisecretory
drugs to remove partially this normal
inhibition. Food stimulates gastrin
release and causes hypergastrinemia.
H2-receptor antagonists only have a
modest effect on food-stimulated acid
secretion, whereas omeprazole blocks
both stimulated and unstimulated acid
secretion. In a study of 1208 patients,
55% had a two- to fourfold increase
in gastrin when treated with omeprazole,
but the hypergastrinemia peaked
within two to four months and quickly
returned to normal when the pump
blocker was discontinued. It is impor-
tant to stress, however, that there is
enormous variation in plasma gastrin
measurements between individuals
when they are given omeprazole.

It is even possible that gastrin, by
way of its trophic effect on the gastric
mucosa, may be useful for ulcer healing
or may stimulate ulcer healing by
releasing transforming growth factor-
alpha and epidermal growth factor. (Of
course this is speculative, but is an
interesting hypothesis.)

The actual risk of developing gastric
cancer following gastric surgery is
reduced from the time of surgery until
14 years later; between 15 and 20 years
there is no difference in cancer rate and
after 20 years the relative risk is only
1.7 (unpublished data). It is incorrect
to equate clinically reduced gastric
acid, mild hypergastrinemia and de-
velopment of gastric cancer. It should be
noted that gastrin levels are decreased
after Billroth resection, and the poten-
tial risk of stump carcinoma may be
related more to bile reflux than to hy-
pergastrinemia. Hypergastrinemia oc-
curs in some patients following gastric
surgery, while vagotomy is associated
with the same gastrin profile as in
patients treated with omeprazole 20 mg
daily.

Gastric irradiation performed to
reduce gastric acid secretion is not asso-
ciated with an increased risk of gastric
tumours. In patients with pernicious
anemia, approximately one patient in
1000 will develop a tumour but serum
gastrin is fourfold higher in pernicious
anemia patients than in patients
-treated with omeprazole.

Hypergastrinemia has been sug-
gested in two studies – but refuted in
others – to be associated with an
increased risk of colonic polyps or can-
cer. Three gastrin measurements would
need to be performed over 12 months
to detect three patients out of 100 with
hypergastrinemia greater than 400 pg/
ml (28), and it clearly is unnecessary to
monitor serum gastrin levels in patients
on either an H2- or a pump blocker.

Omeprazole has no effect on vita-
min B12 metabolism. It has been ques-
tioned whether there is an association
between gynecomastia and omeprazole,
but patient prolactin levels were not
reported and there is no known effect of
omeprazole on the prolactin system.
Cytochrome P450 activity is affected
by cimetidine and, to a lesser extent,
by ranitidine and omeprazole. Therapeu-
tic doses of omeprazole do not alter the
metabolism of ophyl ine or caffeine but
may have an effect on warfarin or pheno-
tyoin. Ranitidine, cimetidine and niz-
tidine (but not famotidine or omepra-
 zole) increase the systemic availability
of alcohol by way of their inhibition of
the gastric alcohol dehydrogenase
activity. The significance of these modest
changes is unknown.

SUMMARY

Chronic atrophic gastritis (type
A/B) and gastric enterochromaffin-like
cell hyperplasia may occur in the ab-
sence of hypergastrinemia; the enter-
ochromaffin-like cell hyperplasia
associated with hypergastrinemia likely
is due to the associated chronic active-
gastitis. The slight increase in the
volume and density of gastric entero-
chromaffin-like cells which occurs in
some patients on long term omeprazole
may be linked to the age-related
progression of chronic active gastritis,
rather than to the associated hyper-
 gastrinemia or use of a pump blocker.

Healing of esophagitis can be pre-
picted from the inhibitory effect of an
antisecretory or intragastric agent and,
therefore, from intraesophageal acidity.

Potent acid inhibition may enhance
the effect of antibiotics on H pylori-as-
associated chronic antral gastritis, lead-
ing to higher rates of its eradication.

Pump blockers may accelerate the
healing of peptic lesions occurring in
association with continued use of
NSAIDs and may be superior to H2-
receptor blockers in the relief of
dyspeptic symptoms arising from GERD
or duodenal ulcer occurring in patients
reporting to community physicians.
REFERENCES


