Pharmacotherapy of peptic ulcer disease

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F MOLINA, MM VOHRA, CN WILLIAMS. Pharmacotherapy of peptic ulcer disease. Can J Gastroenterol 1991;5(1):21-33. The etiology of peptic ulcer is multifactorial; except for omeprazole, all drugs used for the treatment of peptic ulcer result in healing with no statistical difference at four weeks. The healing rate increases with time for active medication and placebo, and is lower among smokers than nonsmokers for all drugs but misoprostol. Mucosal protectives (or 'cytoprotectives') as a group seem to have a lower relapse rate than the H_2 receptor antagonists at one year. Combination therapy has not yet proved to be better than single drug therapy; however, the number of studies is still small, and more clinical trials are necessary. Resistant ulcers have demonstrated that acid is one of several etiological factors and that more research is needed to elucidate the reason(s) for refractoriness. The choice of therapeutic agent is generally made according to patient compliance, medication cost, side effects, effectiveness, relapse rate and physician experience with the drug. Long term maintenance therapy is effective in the prevention of ulcer relapse and is especially recommended for selected patient groups, including patients with recurrent or bleeding ulcer, patients with concomitant nonsteroidal anti-inflammatory drug use, and elderly women. Omeprazole is the treatment of choice for moderate to severe esophagitis and should be reserved for large and resistant ulcers.

Key Words: *Drug therapy, Duodenal ulcer, Peptic ulcer*

Pharmacothérapie de l'ulcère gastro-duodénal

RESUME: Les causes de l'ulcère gastro-duodénal sont multifactorielles; à l'exception de l'oméprazole, tous les médicaments utilisés dans le traitement de cette affection provoquent la guérison sans aucune différence statistique à quatre semaines. Le taux de guérison augmente avec le temps sous traitement actif et traitement placebo, et il est plus bas pour les fumeurs que pour les non-fumeurs dans le cas de tous les médicaments sauf le misoprostol. Le groupe des cytoprotecteurs semble donner un taux de récidive inférieur à celui des anti-H_2 à un an. Le

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THE ETIOLOGY OF PEPTIC ULCER DISease is multifactorial (1,2), and factors such as environment, ethnicity, pre-existing disease condition (3), cigarette consumption (4-7) and nonsteroidal anti-inflammatory drugs (3,8) have been implicated. The pathophysiological mechanisms suggest an imbalance between aggressive factors (acid, pepsin and *Helicobacter pylori*) and defensive factors (mucus, bicarbonate, bloodflow, epithelial cell regeneration, gastric emptying and pyloric function).

The importance of acid in the development of peptic ulcers is supported by the fact that 80% will heal after four to six weeks of treatment with an acid-reducing agent (9). However, maximal acid output in patients with duodenal ulcer overlaps that in normals (3), and basal acid output is not generally increased (3). In contrast, meal-stimulated acid and nocturnal acid secretion are increased in peptic ulcer patients (3,10). The pivotal role of acid in peptic ulcers is further indicated by the fact that these ulcers heal when nocturnal acid secretion is inhibited (10).

Duodenal ulcer patients release more gastrin in response to food than people without ulcers, with less feedback inhibition by luminal acid, and greater parietal cell sensitivity to the secretory effect of gastrin (11).

traitement par une association médicamenteuse n'a pas encore prouvé sa supériorité par rapport à la monothérapie; cependant, le nombre d'essais est encore bas et il est nécessaire de multiplier les études cliniques. Les ulcères rebelles ont démontré que la sécrétion acide est l'un des nombreux facteurs étiologiques et qu'il faut poursuivre la recherche pour découvrir les raisons de la résistance au traitement. Le choix de l'agent thérapeutique est généralement déterminé en fonction de l'adhésion du patient, du coût du médicament, des effets secondaires, de l'efficacité, du taux de récidive et de l'expérience du médecin avec le médicament prescrit. La thérapie de maintien à long terme est efficace dans la prévention des récidives ulcéreuses et elle est surtout recommandée pour les groupes de patients sélectionnés – les malades porteurs d'ulcères récidivants ou hémorragiques, ceux qui suivent un traitement concomitant d'anti-inflammatoires non stéroïdiens, et les femmes âgées. L'oméprazole est le traitement de choix dans les oesophagites modérées à sévères et il devrait être réservé aux ulcères de grandes dimensions et rebelles.

Without acid, pepsin (to which glycoproteins in gastric mucus, collagen and elastin in the gastric and duodenal mucosa are susceptible) is unable to damage the mucosa, but in combination with acid it produces more severe damage than acid alone (12,13).

The mucus secreted by the surface epithelium of the stomach forms an adherent layer (14) that delays back diffusion of hydrogen ions into the epithelium (15,16), and pepsin diffuses poorly through the mucus (17). However, the amount of mucus secreted is not likely to be enough by itself to maintain a neutral pH near the epithelial surface when the luminal pH is 2.0 (18). Stimulated by luminal acid, surface epithelial cells also secrete bicarbonate (19). Although the amount secreted basally is no more than 10 to 15% of basal acid production (18), and thus is not sufficient to protect the mucosa alone, mucus and bicarbonate together form a barrier that produces a pH gradient (neutral pH near the mucosa and an acid pH in the lumen) (20,21) which prevents mucosal damage from the acid. Another element of defence is a hydrophobic lining of glycolipids over the epithelium, impeding proton diffusion and proteolysis of the mucosa (22).

Mucosal ischemia is the most important factor in acute gastric ulceration (23), because bloodflow is critical in the maintenance of normal mucosal energy stores, aerobic metabolism, buffering and disposal of acid that enters the tissue (24). Hence, gastric blood supply plays an important role in the defence system.

Gastric emptying increases in patients with duodenal ulcer, and the normal response of decreased emptying with acidification of the duodenum is impaired (25). In addition, retrograde duodenal movements are less frequent, less pronounced and less effective, leading to a deficiency in the transport of neutralized duodenal contents and bicarbonate from distal to proximal duodenum, thus lowering pH in the duodenal bulb (26). Motility abnormalities found in experimental ulcers include decreased waves and mixing waves in the proximal duodenum and increased waves in the distal duodenum (27). Their interaction causes a diversion of biliary and/or pancreatic secretions, with increased incidence and severity of posterior wall ulcer induced by cysteamine in the rat. Correction of this diversion reverses the effect (28).

Recently *H pylori* has been implicated in the etiology of duodenal ulcer. This microorganism has been found under the gastric mucus layer, adherent to epithelial cells and sometimes concentrated over intracellular junctions (29). *H pylori* produces a large amount of urease, and the release of ammonia by urease may increase gastric pH, protecting *H pylori* from gastric acid (30) and undermining gastric mucosal integrity. *H pylori* was detected in 85% of 232 patients with duodenal ulcers. It was found in the overlying mucosa of duodenum showing gastric metaplasia, as well as in the gastric mucosa (31). Of 39 patients whose duodenal ulcers healed, 59% relapsed at one year. The relapse rate was 27% among patients who were *H pylori* culture-negative but 79% among patients who were *H pylori* culture-positive (32). In another group of patients in whom *H pylori* was eradicated, 66% had a relapse of duodenal ulcer with *H pylori* recurrence, while only 10% with no recurrence of *H pylori* had duodenal ulcer relapse (32).

Antimicrobial agents and bismuth compounds reduce *H pylori* infection, which is accompanied by healing rates comparable to those obtained with acid suppression, with the added advantage that they may also reduce the relapse rate of duodenal ulcer (33,34). Thus, a combination of tinidazole (an antimicrobial similar to metronidazole) with colloidal bismuth subcitrate healed a greater proportion of patients with duodenal ulcer and eradicated *H pylori* better than placebo or drug alone. It is likely that the concept of treating duodenal ulcer disease with an antibiotic will be pursued enthusiastically in the near future. The ideal agent, correct dose, duration of therapy for eradication of the organism and rate of recurrence of both organism and ulcer are unknown at this time.

GOALS AND PRINCIPLES OF DRUG THERAPY FOR PEPTIC ULCER

The goals of therapy are elimination of symptoms, ulcer healing, prevention of recurrence and prevention of complications (35).

The ideal drug for peptic ulcer treatment would: have a 100% healing rate and no side effects; require only one dose every 24 h; provide antisecretory effectiveness for 24 h; enhance mucosal defence; and benefit the natural history of the disease (36). Unfortunately, no presently available drug fulfills all of these requirements. Patients should avoid the following: foods that provoke symptoms, because although diet changes cannot heal ulcers by themselves, they may alleviate symptoms (37); smoking, because it impairs healing (38); and ulcerogenic medications (39).

The following drugs will be dis-

cussed: histamine H_2 receptor antagonists (cimetidine and related drugs), anticholinergic drugs (pirenzepine), proton pump inhibitors (omeprazole), antacids, sucralfate, bismuth compounds and prostaglandins (misoprostol, enprostil). These agents can be classified according to their sites of action: the parietal cell; the gastric and duodenal lumen; the gastric and duodenal mucosa.

DRUGS THAT ACT ON THE PARIETAL CELL

Physiological mechanisms of acid production: Gastric parietal cells produce acid in response to three main stimuli: gastrin from G cells in the antral area; acetylcholine from the vagal endings; and histamine from mast-like cells in the fundus area (40). Each of these substances acts on its own receptor site on the parietal cell: muscarinic M_1 receptors for acetylcholine, histamine H_2 receptors for histamine, and gastrin receptors for gastrin. Their actions parallel and facilitate one another ('permissive effect') (41). Receptor activation produces a second messenger (for example, calcium is increased by gastrin and acetylcholine, and cyclic AMP by histamine) with subsequent activation of other cellular processes, leading finally to the activation of the H^+,K^+ATPase (the proton pump) and acid production (42,43) (Figure 1).

Histamine H_2 receptor antagonists: There are now four of these drugs available on the Canadian market: cimetidine, ranitidine, famotidine and nizatidine. All of them act by competitive binding to the H_2 receptor.

Cimetidine, the first generation of the histamine H_2 receptor antagonists, inhibits acid output in response to all known stimulants of acid secretion, induces prostaglandin synthesis in the gastric mucosa (44), and inhibits the action of gastrin and acetylcholine (45). Reviews of endoscopic studies of the efficacy of cimetidine versus placebo in the healing of duodenal ulcer have found healing rates of 60 to 80% at four weeks and 85 to 95% at eight weeks for cimetidine, compared to 35 to 45% for placebo; this difference was statistically significant (46-48).

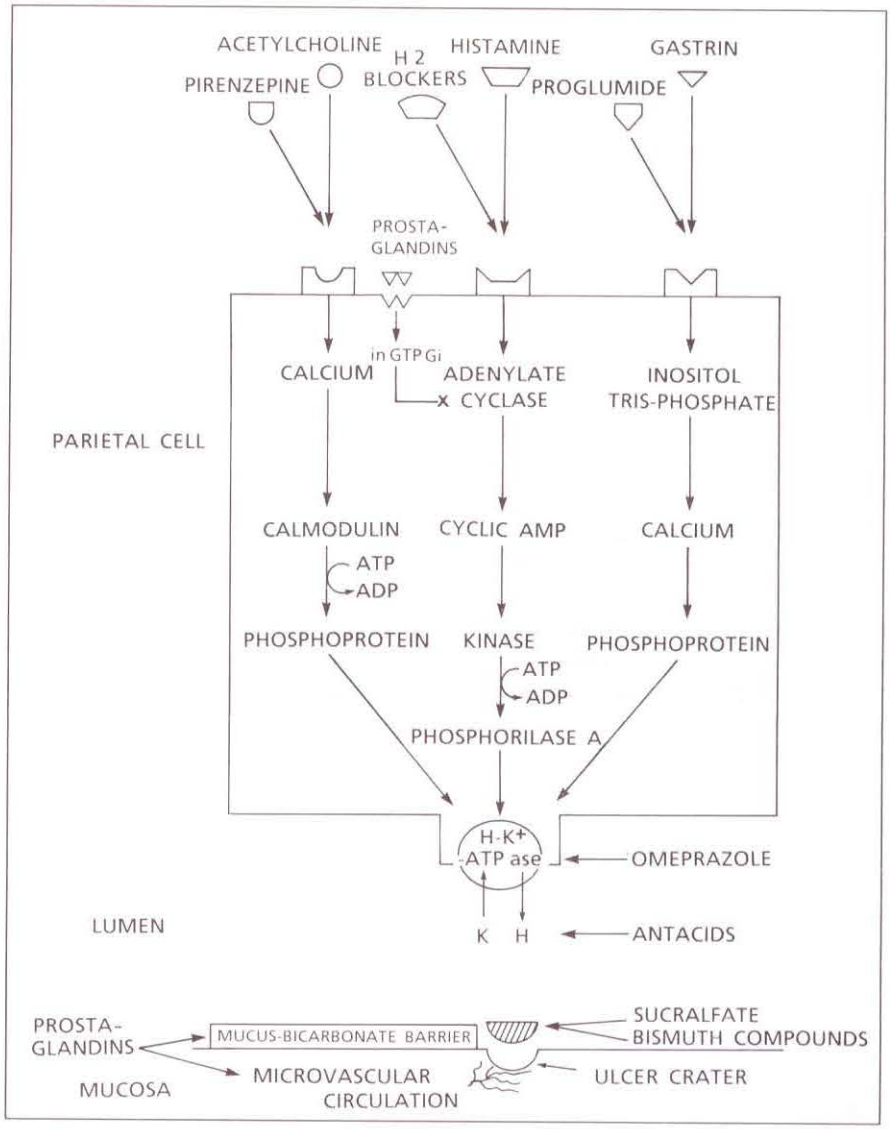

Figure 1) *Mechanism of acid production and mechanism of action of different antiulcer drugs. in GTP Gi Inhibitory GTP binding protein Gi; x Inhibits*

Originally the recommended dose of cimetidine was 300 mg four times a day, but a dose of 600 mg twice a day was later found to be equally effective in the healing of peptic ulcer (49), and 800 mg at night time has lately proven to be as effective in treating duodenal ulcer as 400 mg twice a day (50). Cimetidine's efficacy is lower among smokers than nonsmokers (51,52), and drug requirement is increased after hemodialysis.

After treatment is discontinued, 80% of patients healed with cimetidine will relapse in one year (53); however, the relapse rate in the first year is lower among patients receiving cimetidine 400 mg at night for two years than among patients receiving no treatment (54). Patients who received one year of treatment with cimetidine 200 mg twice a day, 300 mg twice a day or 400 mg at night had a symptomatic recurrence rate of 15% (versus 35% among those receiving placebo), and relapse was more common among smokers than nonsmokers (55).

The main side effects of cimetidine include interaction with the hepatic cytochrome P450 system, thus inhibiting the metabolism and thereby increasing the effect of many drugs, especially theophylline, anticoagulants and anticonvulsants (56). Cimetidine produces hyperprolactinemia (57) and may have antiandrogenic effects with male breast tenderness, gynecomastia

and impotence (58). It may also cause confusion and disorientation in elderly patients and in those with hepatic and renal dysfunction (59). Cholestasis, hepatitis and pancreatitis have also been reported (56).

Most clinically significant adverse effects occur because cimetidine's action is not specific to gastric H_2 receptors (60). Thus, cimetidine crosses the blood-brain barrier and binds to some brain receptors (61,62). These side effects occur in a very small percentage of patients under treatment and are reversed when drug administration is stopped.

Ranitidine is a second generation histamine H_2 receptor antagonist. It has highly effective, specific competitive binding to H_2 receptors in the parietal cell; mole for mole, it is four to five times more potent than cimetidine (63). Although ranitidine has the same pharmacological actions as cimetidine, side effects are much less a problem in patients taking ranitidine (46,56). Ranitidine also interacts with the hepatic cytochrome P450 system, but because it does so with an affinity about 10 times lower than that of cimetidine, the interaction is of no clinical significance (64). Unlike cimetidine, it does not have antiandrogenic effects (65), does not elevate prolactin levels at therapeutic doses (66), and does not cause mental side effects even though it crosses the blood-brain barrier (56). Hepatitis and transient increases in gammaglutamyltransferase and lactate dehydrogenase have been reported (67).

The healing rate of duodenal ulcer for ranitidine 150 mg bid is 60 to 75% at four weeks and 85 to 90% at eight weeks (46,68,69). In other studies, healing rates between 54 and 92% have been reported at four weeks versus 8 to 46% for placebo (56). Ranitidine 150 mg bid is as efficacious as 300 mg at night in healing duodenal ulcer (70). The relapse rate with 150 mg at night is 38% at one year and 48% at two years, versus 86% with placebo (71). Ranitidine's effectiveness in healing ulcers is impaired by smoking (72); comparisons between ranitidine and cimetidine in healing duodenal ulcer in short term treatment have not yielded any statistically significant differences (73). However, ranitidine 150 mg at night was superior to cimetidine 400 mg at night. In long term treatment for prevention of duodenal ulcer relapse, 23% of patients receiving ranitidine and 37% receiving cimetidine relapsed (74). In another study the relapse rate was 15% for ranitidine and 44% for cimetidine (75). Ranitidine 300 mg at night suppressed nocturnal acid secretion by 85% and 150 mg bid by 54% (76), whereas cimetidine 600 mg bid suppressed nocturnal acid secretion by 85% (77).

Famotidine is a thiazole derivative, different from the imidazole ring of cimetidine and the furan ring of ranitidine. On a molecular basis, it is about 20 times more potent than cimetidine and 7.5 times more potent than ranitidine. Its action can last for 7 h or more (78). Nocturnal acid secretion is decreased by 80% with 10 to 20 mg at bedtime. Basal acid and pepsin output are also suppressed (78-81). Famotidine lacks the antiandrogenic activity and drug interactions associated with cimetidine (81,82). Its high potency makes it suitable for treating Zollinger-Ellison syndrome.

Famotidine 20 or 40 mg bid or 40 mg at night produced healing rates at two, four and eight weeks (83, 81 and 75%, respectively, at four weeks) that were not statistically different from one another or from the healing rate with ranitidine 150 mg bid (83). Side effects – diarrhea, anxiety, decreased libido, and mild elevation of bilirubin – were present in a very small percentage of the patients, most frequently in those receiving famotidine 40 mg bid (83). Another study comparing famotidine with ranitidine reported a healing rate of 93% for ranitidine and 90.2% for famotidine 40 mg bid, 90.5% for famotidine 40 mg at night, and 83.3% for famotidine 20 mg bid; again, the differences were not statistically significant (84). Famotidine 20 mg bid was found to have a healing rate comparable to that of cimetidine 200 mg bid (85). In long term treatment to prevent ulcer recurrence, 32% of patients taking famotidine 20 mg at night and 63% of those taking placebo had recurrence at six months of therapy. Constipation was present in 1% of patients in the famotidine group (85). The overall incidence of side effects observed in patients taking famotidine is similar to that observed in patients taking ranitidine; however, more clinical experience is needed to determine famotidine's overall place in the therapy of peptic ulcer disease.

Nizatidine, like ranitidine, contains a furan ring and is a potent, specific and orally well tolerated histamine H_2 receptor antagonist. It reduces gastric acid secretion for up to 8 h and is as potent as ranitidine and three to four times more potent than cimetidine (86). Nizatidine is excreted via the kidney, so renal impairment decreases its elimination.

Basal, nocturnal, and food and chemically stimulated gastric acid secretion is inhibited in a dose-dependent manner (87). Unlike cimetidine, nizatidine does not inhibit the microsomal hepatic cytochrome system, and thus does not inhibit metabolism of agents affected by this system, such as theophylline and diazepam (88). It has no antiandrogenic effect and causes less prolactin release than cimetidine (89). Nocturnal acid secretion is decreased up to 90% with a dose of 300 mg (90).

Nizatidine 150 mg bid and 300 mg at night were equally effective in healing duodenal ulcer at four weeks (67 versus 68%), and were superior to placebo (29% of healing rate, $P<0.02$); nonsmokers' ulcers healed more often than did smokers' ($P<0.002$) (91). In a study comparing nizatidine with ranitidine, the healing rates were 81 versus 80% at four weeks and 92 versus 93% at eight weeks, respectively (92).

As maintenance therapy for duodenal ulcer in remission, nizatidine 150 mg at night was superior at one year to placebo (recurrence rates were 34 and 64%, respectively, $P<0.001$) (93). In the prevention of recurrence at six months, nizatidine was comparable in efficacy (relapse rate 18%) to ranitidine (relapse rate 13%) (94). Side effects reported on these trials were the same and not statistically different from those reported by patients taking placebo.

Currently, the histamine H_2 receptor antagonists are the cornerstone of prescription peptic ulcer therapy. Effective in healing and preventing relapse of duodenal ulcer, this family of drugs has revolutionized the treatment of peptic ulcer disease by decreasing the likelihood of complications and surgical interventions. Compliance with H_2 receptor antagonists is easy: most are available as a once daily dose leading to complete ulcer healing in four to six weeks (although smoking decreases the efficacy of all of them). Because their healing rates and mechanisms of action are similar, the selection of an H_2 receptor antagonist often depends on 'soft' factors such as previous response to therapy, likelihood of compliance and undesirable side effects. Drug interactions, patient age and the presence of other systemic disease are also important considerations in drug selection, as is cost, since the newer H_2 receptor antagonists are much more expensive than cimetidine.

Anticholinergic drugs: Pirenzepine is an anticholinergic drug that has a high affinity for, and inhibits relatively selectively, the muscarinic M_1 receptor sites located in the parietal cell (95). Thus pirenzepine, which is about one-tenth as potent as atropine, inhibits the acid secretion stimulated by the vagus with a minimum of undesirable cardiac, visual or urinary side effects (96,97). It is a tricyclic pyridobenzodiazepine which structurally resembles the tricyclic antidepressants but, being quite hydrophilic, does not cross the blood-brain barrier and has no central effects (46). Pirenzepine 100 mg reduces nocturnal acid secretion by 41% (98). Delayed gastric emptying has not been observed with pirenzepine (99). It has a long half-life (11 h), and most of the drug is excreted unchanged in the urine.

In duodenal ulcer treatment, pirenzepine 100 mg has shown superiority over placebo, with a healing rate of 70 to 80% versus 32 to 57%, respectively, at four weeks (100). Studies comparing pirenzepine with cimetidine (101) and ranitidine (41) showed comparable healing rates. Long term treatment with pirenzepine 100 mg/day to prevent relapse of duodenal ulcer has been shown to be superior to placebo and comparable to cimetidine (102). In a study comparing pirenzepine with placebo, pirenzepine 100 mg/day for one year had a duodenal ulcer relapse rate of 58%, versus 96% with placebo; this difference was statistically significant (103). Pirenzepine produces side effects at a therapeutic dose of 100 mg (including dry mouth, constipation and urinary delay) in 7% of patients (104); however, doses lower than 100 mg/day did not produce as good results as 100 mg in the short term treatment of duodenal ulcers (105). The presence of troublesome side effects when adequate doses are employed indicates a lesser role for this agent, especially when agents without these side effects are now in routine use.

Proton pump inhibitors: Omeprazole, a substituted benzimidazole, is the most powerful inhibitor of gastric acid secretion available. It irreversibly inhibits the H^+,K^+ATPase (the proton pump) located in the secretory membrane of the parietal cell, which is the terminal step in the acid secretion pathway. It thus blocks all forms of stimulated and basal acid secretion, producing achlorhydria independently of the nature of the stimulus (106,107). Omeprazole appears to be activated at acidic pH to a hydrogen ion-activated derivative (a sulphone) which binds irreversibly to the H^+,K^+ATPase. This dependence on an acid pH makes the drug highly selective for actively secreting parietal cells. Also, being a weak base, omeprazole seems to concentrate in the acid environment of the parietal cell (108).

Omeprazole is eliminated rapidly through the liver and kidney, primarily as sulphone, sulphide and hydroxyomeprazole derivatives (mostly the latter). It inhibits reactions mediated by the cytochrome P450 system to the same extent as an equimolar dose of cimetidine; however, as the dose of omeprazole needed for treating duodenal ulcer is 25 to 50 times lower than that of cimetidine, this interaction has little clinical importance, although delays in the elimination of aminopyrine and diazepam have been reported (47). Omeprazole is highly protein bound (95%); its plasma half-life is about 1 h; and its pharmacokinetic profile is not altered in chronic renal failure or by hemodialysis. Omeprazole 20 to 40 mg once a day inhibits gastric acid secretion for up to five days, after which time it reaches a plateau (47). A dose of 40 mg decreases acid production by 99%; after the drug has been discontinued for one week, acid production is still inhibited by 26% (107,109).

Transient side effects include diarrhea, nausea, dry mouth, dizziness, weakness, headache and numbness (77,110). Carcinoid lesions derived from enterochromaffin cell-like have appeared in mature rats after two years on large doses of omeprazole, but this enterochromaffin cell-like hyperplasia seems to be species specific. These tumours are thought to be caused by hypergastrinemia, as high dose ranitidine also causes hypergastrinemia and carcinoid tumours in rats. In addition, prolonged achlorhydria increases gastric bacterial counts, with increased concentrations of nitrates and nitrosamines, which are carcinogenic (108). In another study, these changes were found to return to normal within three days after the drug was stopped (111). Hypergastrinemia also returns to normal after the drug is discontinued (112).

At present omeprazole is only approved for short term treatment in duodenal ulcer disease. Omeprazole 30 mg daily in the treatment of duodenal ulcers had a healing rate of 83% at two weeks and 98% at four weeks (113); in another study, 78% of duodenal ulcers healed at two weeks and 94% at four weeks, with 30 mg producing better results than 10 mg (109). Compared with cimetidine, omeprazole 30 mg healed 73% of ulcers at two weeks and 92% at four weeks; cimetidine 1 g healed 46% at two weeks and 74% at four weeks (114). In a Canadian study, omeprazole 20 mg and cimetidine 600 mg bid were not statistically different in healing rates at two and four weeks: 58 and 84% for omeprazole and 46 and 80% for cimetidine, respectively. There appeared to be a trend in favour of

omeprazole at two weeks, but not at four weeks (77). Recurrence after discontinuation of treatment is the same as with H_2 receptor antagonists (114).

It is likely that omeprazole will be reserved for use in patients with resistant duodenal ulcers and resistant or unusual gastric ulcers (eg, large or multiple ones). Omeprazole is especially useful in Zollinger-Ellison syndrome and will become the drug of choice for moderate to severe cases of peptic esophagitis.

DRUGS THAT ACT IN THE GASTRIC AND DUODENAL LUMEN (ANTACIDS)

Until 1977, when cimetidine was introduced, antacids were the treatment of choice for duodenal ulcer. Their long term use and clinical trials have now proved their efficacy in this condition. Antacids reduce the acidity of gastric contents by neutralizing hydrochloric acid, and this rise in pH reduces pepsin activity (pH higher than 3.5 to 4). In addition, aluminum-containing antacids bind bile. All of these actions decrease damage to the duodenal mucosa and promote healing of the ulcer (104). Antacids can be classified into two groups: those whose reactivity with acid is defined by the anion portion of the molecule (sodium bicarbonate, calcium carbonate) and those in which the cation is more important (magnesium hydroxide, aluminum hydroxide) (115). Dose size and timing should be balanced to promote ulcer healing and avoid side effects. A dose is administered 1 and 3 h after meals and at bedtime, for a total of seven daily doses.

The buffering capacities of the various antacids vary considerably (6 to 105 mEq); it has been suggested that a neutralizing capacity of 200 to 280 mmol is necessary to heal ulcers (46,116). The healing rate using this neutralizing capacity was 85% at four weeks of treatment in patients with duodenal ulcer (117). In three studies, the healing rates among patients taking antacids with neutralizing capacities of 560 to 1064 mmol for their duodenal ulcers were comparable to those in patients taking cimetidine 800 to 1200 mg (104).

Maalox TC (Rorer) three tablets bid (neutralizing capacity 162 mmol) prevented ulcer relapse about as effectively as cimetidine 400 mg at bedtime and better than placebo or Maalox TC at bedtime (118). Antacids in liquid suspension have been considered more effective pharmacologically than antacid tablets; however, when the effect of magnesium-aluminum hydroxide antacid tablets or liquid on food-stimulated gastric acidity was evaluated in vivo in eight patients with duodenal ulcer, the duration of effect of tablets was greater than that of liquid suspension (119). Smoking impairs the healing of duodenal ulcer treated with antacids. The relapse rate after treatment is discontinued is the same as when cimetidine is discontinued (120).

The side effects of antacids will depend on the particular antacid in use. Most antacids on the market are mixtures of aluminum hydroxide and magnesium hydroxide, which balance the constipation and diarrhea that the former and the latter, respectively, can cause. Hypernatremia, hypercalcemia, hypermagnesemia, hyperaluminemia, hypophosphatemia, alkalosis, milk-alkali syndrome, renal impairment, kidney stones, decreased absorption of fluoride, iron and tetracyclines, and increased absorption of weakly basic drugs (eg, guanidine) have all been reported (121,122). Antacids containing calcium are not recommended in the treatment of duodenal ulcer because they stimulate acid secretion and may thus cause acid rebound (123,124).

DRUGS THAT ACT ON THE GASTRIC AND DUODENAL MUCOSA

Sucralfate: Sucralfate is a basic aluminum salt of sucrose substituted with eight sulphate groups (125). It is a highly effective, essentially nonsystemic drug for treating peptic ulcer. In the acidic environment of the stomach, aluminum hydroxide dissociates from the sulphate residues in sucrose octasulphonate, leaving it with a negative charge. This reaction is followed by both intra- and intermolecular bridges, producing a variety of polymers and forming a viscous substance (active form) (126). The latter binds preferentially to partially denatured or degraded proteins (positively charged) in the ulcer base, forming a protective barrier against back diffusion of hydrogen ions (127). Since the optimal pH for binding to the ulcer crater is 2 to 3, sucralfate should be taken when the stomach is empty. Sucralfate also inhibits pepsin activity and adsorbs bile salts (127). It increases prostaglandin synthesis and secretion in the gastric mucosa (128). It is poorly absorbed. Side effects reported are constipation (3 to 4%), diarrhea, nausea, dry mouth and hypophosphatemia; because of potential aluminum toxicity, its long term use in patients with renal failure should be approached cautiously (129,130). Sucralfate does not interfere with physiological functions of the digestive system (acid secretion or motility) (131). Although sucralfate contains aluminum, acid neutralization does not contribute substantially to its therapeutic effect (127).

The healing rate at four weeks in patients with duodenal ulcer treated with sucralfate is 60 to 97%, compared with 24 to 64% with placebo (129). Compared with cimetidine, the healing rate for sucralfate was similar (132). The relapse rate one year after treatment has been discontinued is 70%, similar to that of cimetidine (133). In a study using a 2.5 g daily dose of sucralfate maintenance therapy, the relapse rate at one year was 44% compared with 82% for placebo (134); another study with 2 g sucralfate daily showed a relapse rate at six months for sucralfate of 21.2% and for placebo of 50% (135).

Bismuth compounds: Tripotassium dicitrate bismuthate, or colloidal bismuth subcitrate, is a bismuth salt of citric acid. It heals ulcers by binding to proteins and necrotic debris at the ulcer base to form a barrier to the diffusion of acid (136), adsorbing and reducing the concentration and output of pepsin in the stomach for at least 24 h after the last oral dose (137). In the presence of acid, colloidal bismuth subcitrate yields bismuth oxide and an oxychloride precipitate that forms a tenacious coagulum upon the digestive mucosa. The precipitate acts as a protective layer against erosive chemical attack by acid or pepsin. Also, colloidal bismuth

has a marked ability to fix chloride ions, with the formation of insoluble bismuth oxychloride, which prevents the diffusion of bismuth ions into the circulation and thus minimizes the systemic toxicity of bismuth. It also stimulates mucus secretion, chelates pepsin and binds bile. Its effectiveness is highly dependent on the pH of the gastric juice, being greater at low (1.0 to 3.5) than at high (3.5 to 6.5) pH (41,129,138-140). Bismuth compounds colour the tongue and stool black. The liquid preparation has an unpleasant taste and ammoniacal smell. Bismuth compounds are potentially neurotoxic; however, this side effect has never been reported in clinical trials (129).

Healing rates at four weeks of 50 to 89% (versus 8 to 42% for placebo) have been reported; all studies showed statistical superiority in favour of bismuth compounds (36,129). Against ranitidine, no statistical difference was found at four and eight weeks of treatment (141). The rates of duodenal ulcer relapse at one year after healing with no maintenance treatment were 39% with bismuth, 85% with cimetidine (142, 143), 62% with bismuth and 89% with ranitidine (141). These data are statistically significant in favour of bismuth. The lower relapse rate after treatment with bismuth compounds has been related to eradication of *H pylori* (33,34). The result was not affected by patient smoking habits (141).

Colloidal bismuth subcitrate is not yet available in Canada except for compassionate use, but it is likely that bismuth subsalicylate, which is available in Canada, is as effective. Bismuth subsalicylate is also the drug of choice for eradication of *H pylori*. It is the authors' practice to add oral metronidazole 250 mg qid to bismuth subsalicylate 30 mL qid to increase the likelihood of eradicating *H pylori*, with rechecking after eight to 12 weeks of therapy. This is particularly relevant for recurrent duodenal ulcer disease and the more controversial symptomatic chronic active antral gastritis.

Prostaglandins: Prostaglandins are a family of biologically related unsaturated fatty acids consisting of 20 carbons and derived from arachidonic acid. They are present in the gastrointestinal tract, especially the stomach, and affect smooth muscle activity and gastric and intestinal secretion. Basal gastric acid secretion and secretion stimulated by food, acetylcholine, gastrin, histamine and insulin hypoglycemia are inhibited by prostaglandins (144). High affinity binding sites for E type prostaglandins have been identified in canine parietal cells; I and F prostaglandins bind only weakly to this site, and cimetidine and histamine do not bind to it at all. These findings indicate the existence of a particular receptor in the parietal cell for the E prostaglandins (145). Prostaglandin E_2 inhibits histamine-stimulated acid secretion by inhibiting adenylate cyclase via the inhibitory GTP binding protein Gi, which subsequently decreases cyclic AMP production (146).

Prostaglandins have a trophic action on the gastric mucosa, increasing bicarbonate and mucus production in the stomach and duodenum (147-150) and mucosal bloodflow (151). All of these properties have been called 'cytoprotective' (this term has been challenged and some authorities recommend 'mucosal protection', but for the purpose of this review we shall retain 'cytoprotection'). It has been proposed that a deficiency of prostaglandins exists in duodenal ulcer patients. Ahlquist et al (152) found that prostaglandin synthesis in response to acid and food was blunted in duodenal ulcer patients and was markedly higher in normals.

Misoprostol is a synthetic analogue of prostaglandin E_1 that reduces the volume and concentration of pepsin and acid production in humans (153), decreases gastric acid secretion in response to histamine, pentagastrin and meals in dogs (154) and does not increase gastrin levels (155). Gastrin inhibition by misoprostol is dose-related; its action starts 1 h after administration and is negligible after 4 to 5 h (156). While misoprostol has all of the properties of cytoprotection in addition to its antisecretory action, the contribution of cytoprotective activity to misoprostol's clinical efficacy in healing established ulcers is doubtful, since the drug is not superior to placebo when a low antisecretory dose (less than 100 µg four times a day) has been used (157). Following oral administration, the drug is rapidly absorbed and de-esterified into its free acid form, which is as potent as the parent compound. Peak concentration is reached in 30 to 60 mins. Misoprostol is about 85% serum protein bound; it is metabolized in the liver and excreted via the kidney (158).

In a study comparing misoprostol 50 or 200 µg qid with placebo in the healing of duodenal ulcer, the ulcers of 42.6% of patients taking 50 µg qid, 51% taking placebo, and 76.6% taking 200 µg qid had healed after four weeks of treatment; the higher dose of misoprostol was statistically superior to the lower dose of misoprostol and placebo (159). Another study reported that, after four weeks, the ulcers of 64.9% of patients taking misoprostol 100 µg qid and 47.4% of patients taking placebo had healed, with significant statistical difference in favour of misoprostol (160). Diarrhea has been the side effect most frequently reported with misoprostol; its frequency is dose-dependent: 4% with 50 µg qid, 8.5% with 100 µg qid and 13.1% with 200 µg qid, against placebo (5%). The diarrhea resolves when the drug is discontinued (159,160). Other side effects reported include abdominal cramps, dyspepsia, nausea and headache. Note that misoprostol, like the E prostaglandins, can stimulate uterine contractility and hence is contraindicated during pregnancy or in women at risk of becoming pregnant. Misoprostol 400 µg bid has been reported to be as effective as 200 µg qid in the treatment of duodenal ulcer; 200 µg bid, however, was no better than placebo (161). After four weeks of treatment, cimetidine 300 mg qid, misoprostol 50 µg qid and misoprostol 200 µg qid produced healing rates of 67, 41 and 60%, respectively. There was no statistically significant difference between misoprostol 200 µg and cimetidine; both drugs were superior to misoprostol 50 µg qid (162). Cigarette smoking does not impair the healing action of misoprostol in duodenal ulcers (163). Studies are not yet available concerning the use of

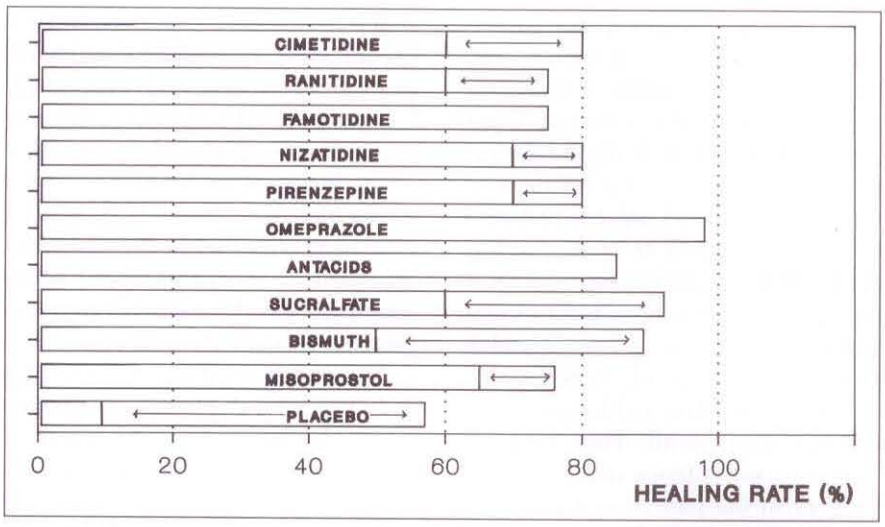

Figure 2) *Healing rates of duodenal ulcer with different antiulcer drugs after four weeks of treatment. Arrows show the ranges among multiple studies*

misoprostol, which is approved in Canada for the treatment of duodenal ulcer, as maintenance therapy for the prevention of recurrence.

Enprostil is a synthetic analogue of prostaglandin E_2 with the same properties as misoprostol. Although not yet approved for the treatment of duodenal ulcer in Canada, enprostil has been shown to be superior to placebo in duodenal ulcer healing, and a dose of 35 µg bid is as effective as cimetidine 400 mg bid (157). However, after four weeks of treatment, ranitidine 150 mg bid produced a healing rate of 93%, versus 46% with enprostil 35 µg bid; ranitidine was statistically superior (164). Side effects and contraindications are the same as with misoprostol (164).

Nicholson et al (165) reviewed 49 trials of treatment of duodenal ulcer with cytoprotective drugs or H_2 receptor antagonists. The relapse rate at one year was lower for cytoprotective drugs. As Figure 2 shows, the healing rates in patients with duodenal ulcer are comparable for all drugs except omeprazole.

COMBINATION THERAPY

Theoretically, using two antiulcer drugs with different mechanisms of action should result in a synergistic effect and a better healing rate than using a single drug. Work reported thus far, however, has not substantiated this hypothesis. One study compared cimetidine 300 mg qid, sucralfate 1 g qid a combination of both and found no statistically significant difference among the three groups at two, four and eight weeks of treatment, although at two weeks there was a trend in favour of the combination (166).

In another study, randomly assigning patients whose ulcers had not healed after eight weeks of treatment with cimetidine 800 to 1000 mg/day or ranitidine 300 mg/day to receive cimetidine 800 mg/day or cimetidine 800 mg plus pirenzepine 100 mg/day for six weeks, produced a healing rate of 70% for both groups (167). Investigations of combined therapy have involved small patient samples, so further studies with larger samples are necessary before any generalizations for or against combined therapy can confidently be made.

REFRACTORY DUODENAL ULCER

Bardhan (168) has defined a refractory duodenal ulcer as one that fails to heal after treatment with cimetidine 1 g daily for three months. He found a 7% failure in healing of duodenal ulcers after continuous treatment for three months. In a study of 66 patients with refractory duodenal ulcers, 42% did not heal after an average of 9.4 months of treatment, despite increment to 2 or 3 g of cimetidine daily. Nine underwent surgery – five of these had poor results. Patients with refractory ulcers were younger than 40 years and had longer histories, frequent episodes of bleeding, a family history of peptic ulcer, previous treatment with cimetidine, ulcers of medium or large size, and moderate or severe duodenitis compared with patients who responded to cimetidine treatment (168).

The cause of refractoriness is unknown. Noncompliance, genuine resistance (168) and excessive vagal drive (169) have been proposed as explanations of the phenomenon. A pathophysiological failure of H_2 blockers to suppress acid secretion, especially at night, has been implicated (170). Measurements of intragastric acidity indicated that acid inhibition was lower from midnight to midday and over 24 h in 10 patients whose ulcers did not heal after three months of treatment with famotidine 40 mg or ranitidine 300 mg at bedtime than in controls (171). In this situation, omeprazole may be the answer. However, the finding by Deakin and Williams (172) that some patients' ulcers did not heal after six weeks of treatment with cimetidine 400 mg twice a day produced overnight achlorhydria, serves to reinforce the multifactorial nature of duodenal ulcer etiology. Thus, when 25 patients whose duodenal ulcers did not heal after four weeks of treatment with a standard dose of cimetidine were randomized to receive colloidal bismuth subcitrate one tablet qid or cimetidine 400 mg qid for four weeks, after which patients whose ulcers did not heal in either treatment were crossed over, the cumulative healing rate was 85% for colloidal bismuth subcitrate and 40% for cimetidine (173). Similarly, after patients whose duodenal ulcers had not healed after 10 weeks of treatment with cimetidine or ranitidine were randomized to receive misoprostol 200 µg qid or placebo for four weeks, 42% of those receiving misoprostol and 17% of those receiving placebo had their ulcers heal (174).

In 1990, very few patients have truly refractory duodenal ulcers, so the need for surgery is minimal in uncomplicated duodenal ulcer disease. With frequent recurrence, however, a maintenance program is required, and in this situation a case can be made for highly selec-

tive vagotomy to reduce the acid load permanently and thus reduce the risk of recurrent duodenal ulceration, particularly if the patient is a young adult who might otherwise face years of drug therapy. Also, the lesson to be learned is: if a patient does not respond to one class of antiulcer drug, increase the dose (in the absence of side effects) or prescribe a drug with a different mechanism of action.

In conclusion, there are many efficacious drugs for the treatment of peptic ulcer disease. The choice of the drug(s) is based on individual preferences and other medical history of the patient, particularly smoking, concomitant medications, age and cost of the medication, which can vary up to three to fourfold for the treatment of duodenal ulcers.

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