REVIEW ARTICLE

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Histamine H_2-Receptor Antagonists in Peptic Ulcer Disease

Efficacy in Healing Peptic Ulcers

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Contents

Summary

Duodenal ulcer healing depends on the degree and length of inhibition of gastric secretion and upon the duration of therapy, while gastric ulcer healing is dependent mainly on the duration of therapy.

Currently marketed doses of the histamine H_2-receptor antagonists heal between 77 and 92% of duodenal ulcers at 4 weeks, and adjuvant treatment to eradicate *Helicobacter pylori* increases this rate. Once-daily administration is as effective as more frequent dosing regimens and may even result in higher healing rates. Gastric ulcers heal more slowly, but 75 to 88% of ulcers heal after 8 weeks of treatment.

While newer more potent acid suppressors such as omeprazole heal ulcers slightly more quickly, the H_2-receptor antagonists have an unparalleled safety record of over 15 years. It is unlikely that the prostaglandin analogues can improve on the efficacy of the H_2-receptor antagonists with as low an incidence of side effects.

The development of H_2-receptor antagonists, introduction of cimetidine to clinical practice in 1976, and subsequent development of ranitidine, famotidine and nizatidine has revolutionised the treatment peptic ulceration. There is no doubting their overall effectiveness. The market is huge and at least 3 other H_2-receptor antagonists, roxatidine, mifentidine and sufotidine are currently undergoing clinical trials.

The most clearly defined indications for the use of H_2-antagonists is in the treatment of duodenal and gastric ulceration and in reflux oesophagitis. This review concentrates on the healing data for duodenal and gastric ulcers when treated with the 4 compounds currently marketed in the UK. The introduction of more powerful gastric acid suppressors such as the substituted benzimidazoles (e.g. omeprazole), prostaglandin analogues (e.g. misoprostol), and the realisation of the importance of *Helicobacter pylori* has caused us to review the efficacy of the H_2-receptor antagonists in the context of these recent developments.

Cimetidine was the third histamine H_2-receptor antagonist developed by James Black and colleagues. The first 2 compounds, burimamide (Black et al. 1972) and metiamide (Black et al. 1973), were unsuccessful. Intravenous administration of burimamide produced marked inhibition of pentagastrin and histamine-stimulated gastric acid secretion in humans (Wyllie et al. 1972), but when taken orally the compound had limited activity. Modification of the side chain of burimamide led to the synthesis of metiamide which was effective when taken orally. Metiamide was actually used to treat active duodenal ulcers in clinical trials, but while initial studies were promising (Pounder et al. 1975), cases of reversible neutropenia were reported in humans and the drug was withdrawn (Forrest et al. 1975). This adverse reaction was thought to have been caused by the thiourea moiety of metiamide which was replaced by a cyanoguanidine group, resulting in cimetidine (fig. 1). Ranitidine was developed subsequently by Glaxo and is similar to cimetidine but has a furan ring as a nucleus instead of an imidazole ring. Famotidine is structurally re-

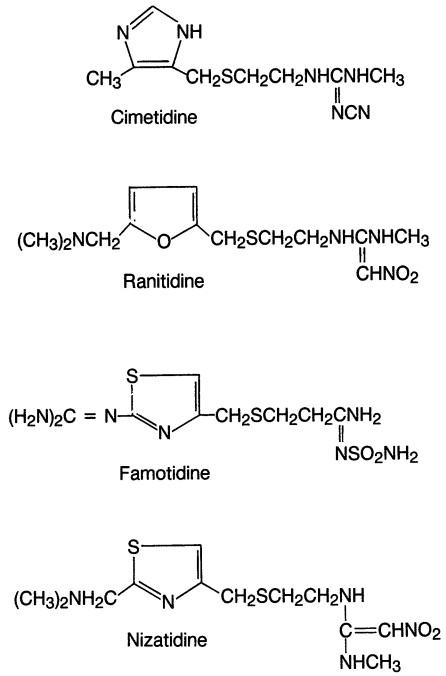

Fig. 1. Structural formulae of cimetidine, ranitidine, famotidine and nizatidine.

of the imidazole ring, while nizatidine combines the thiazole ring of famotidine and the side chains of ranitidine (fig. 1).

1. Duodenal Ulcer Healing

1.1 Development of Dosing Regimens

Cimetidine was introduced for clinical use at a time when other medical therapies for duodenal ulceration were relatively ineffective, although antacids, anticholinergic drugs and bismuth were available. Surgical treatment for ulcer disease was commonplace and often the only effective treatment option. Vagotomy reduced gastric secretion continuously and so the initial concept in H_2-blockade was to achieve pharmacological suppression of gastric secretion throughout the whole 24-hour period. A 4-times-daily dosing regimen was proposed and tested, i.e. cimetidine 200mg 4 times a day. The effect of this dosing regimen on the con-

aspiration of gastric contents using a nasogastric tube, was compared with the higher dose of cimetidine 400mg 4 times daily (Pounder et al. 1975, 1976). The main conclusions from these studies were that cimetidine was better at suppressing basal rather than meal-stimulated gastric acid secretion, and while 400mg was more effective than 200mg at suppressing overnight gastric secretion, the extra effect on meal-stimulated secretion was small (mainly because both doses were relatively ineffective). These studies led to the recommendation of the somewhat complicated dosing regimen for cimetidine, i.e. 200mg 3 times daily with 400mg at night. In a review of the first 8 studies in the world literature in 1978, Winship (1978) reported an average 6-week healing rate of 71% for cimetidine and 37% for placebo.

Ranitidine was introduced clinically in 1981 as a twice daily dosage regimen (i.e. 150mg twice daily). This acted as a stimulus to the study of Kerr (1981), which showed that cimetidine 400mg twice daily was as effective at healing ulcers as the more complicated regimen mentioned above. This simplified regimen did not remain standard for long, however, and treatment with a large single night-time dose (800mg) was proposed in 1983 (Gledhill at al. 1983), based on the fact that a larger night-time dose can completely suppress acid secretion during the night while additional daytime doses add little 'extra' effect.

As a final refinement to once-daily dosing, drug administration earlier rather than later in the evening has certain theoretical advantages. Clinical pharmacolological studies such as those described by Gledhill et al. (1983) showed that although a large night-time dose results in near achlorhydria overnight, the effect is largely abolished by the stimulus of breakfast. Administration of the H_2-receptor antagonist earlier in the evening has the advantage that the antisecretory effect is 'stretched out', to cover the longest single period of unbuffered intragastric acidity – from the evening meal until breakfast. Studies where intragastric acidity has been measured over a 24-hour period have

tent than late evening dosing (Deakin et al. 1985; Merki et al. 1987). One word of caution, however, is that if lower dose regimens are used in the early evening, the drug effect can tail off overnight.

1.2 Comparisons Between Histamine H_2-Receptor Antagonists

The literature on the different dosing regimens of cimetidine and on comparisons between the different H_2-receptor antagonists is now vast. Table I summarises the earlier studies with different doses of cimetidine and placebo. Relief of symptoms can be difficult to reliably assess, but response is generally rapid with all the H_2-receptor antagonists (see reviews by Grant et al. 1989; Langtry et al. 1989). Typical figures are 76% of patients free from night pain at 2 weeks and 88% at 4 weeks (Gitlin et al. 1987).

The rate of duodenal ulcer healing induced by antisecretory compounds depends mainly on 3 variables: (a) the degree of acid inhibition; (b) the length of acid inhibition; and (c) the duration of therapy (Burget et al. 1990; Jones et al. 1987).

The study by Jones et al. (1987) shows particularly elegantly the linear relationship which exists between the degree of suppression of total 24-hour intragastric acidity by different antisecretory regimens and duodenal ulcer healing rate at 4 weeks. As alluded to earlier, suppression of nocturnal intragastric acidity is the single most important factor in explaining healing with the H_2-receptor antagonists and daytime suppression has little 'extra' benefit.

The currently recommended treatment regimens are cimetidine 800mg, ranitidine 300mg, nizatidine 300mg or famotidine 40mg taken once daily at bedtime. These are simpler than earlier regimens and may even lead to higher healing rates because of more effective suppression of night-time secretion or possibly through better patient compliance.

Ranitidine is between 5 and 8 times more potent on a molar basis than cimetidine (Daly et al.

Table I. Median (range) percentage of duodenal ulcers healed in endoscopically controlled studies following 1 to 8 weeks' treatment with placebo or cimetidine (Cim)

Treatment	Week						References
	1	2	3	4	6	8	
Placebo	11.5 (8-15)	21 (11-50)	17[a]	48 (20-79)	38 (19-63)		1,2,3,4,5,6,8,11,14
Cim 200mg qid	15		80[a]	59[a]	86[a]		1,5
Cim 200mg tid and 400mg on		57 (42-83)		78 (61-85)	74 (66-82)	92.5 (90-95)	2,3,4,6,7,8,9, 10,11,12,13,14
Cim 400mg bid				73 (66-81)		94 (88-94)	12,13,16,17,18
Cim 800mg on	16[a]	38[a]		77[a]		94 (92-96)	15,16,17,18

a Data from 1 study only.

Abbreviations: bid = twice daily; on = at night; qid = 4 times daily; tid = 3 times daily.

Data taken from: 1 Bodemar & Walan (1976); 2 Gray et al. (1977); 3 Lambert et al. (1977); 4 Dobrilla et al. (1978); 5 Ippoliti et al. (1978); 6 Villalobos et al. (1978); 7 Galmiche et al. (1979); 8 Bardhan et al. (1979); 9 Fedeli et al. (1979); 10 Gilsanz et al. (1979); 11 Ubilluz (1979); 12 Eckardt (1981); 13 Kerr (1981); 14 Lam & Koo (1983); 15 Valenzuela et al. (1985); 16 Dickson (1986); 17 Capurso et al. (1986); 18 Spencer-Mills (1986).

in suppressing 24-hour intragastric acidity (Deakin et al. 1985; Merki et al. 1987). The recommended dose of cimetidine (800mg) is therefore less potent than the marketed dose of ranitidine (300mg). Cimetidine 800mg and ranitidine 300mg given at night have not been directly compared in large healing studies, but McIsaac et al. (1987) reviewed the results of 14 endoscopically controlled double-blind trials where ranitidine 150mg twice daily was compared with cimetidine 400mg twice daily over a 4-week period. The combined healing rate with ranitidine was 11.5% higher than that for cimetidine, an advantage part of which may be due to the difference in the degree of acid inhibition by the 2 doses.

The recommended doses of famotidine and nizatidine have been shown in clinical pharmacology studies to be equipotent to those recommended for ranitidine (Dammann et al. 1989; Merki et al. 1988; Savarino et al. 1989; Thomson et al. 1989). In clinical trials, therefore, significant differences in healing rates between any of these 3 compounds would not be expected and this is essentially what has been found. A summary of the most recent studies of single daily dosing with H_2-receptor antagonists is available in Table II.

vantages to the administration of a single dose of H_2-receptor antagonist in the early evening since the antisecretory effect can be prolonged by doing this, potentially leading to better symptom control as well as increased healing rates. Administration of 300mg of ranitidine after the evening meal instead of before bed has indeed been shown to increase healing at 2 weeks from 50% to 74% and from 94% to 100% (Merki et al. 1986).

There is no proven advantage in giving a larger daily divided dose. Gitlin et al. (1987) directly compared famotidine 40mg at night with 40mg twice daily. Healing rates were equivalent at both 4 weeks (70% healing rate with the night-time dose, 75% with the twice-daily dose), and 8 weeks (83% and 82%, respectively). The timing of dosing may not be as important as presupposed, however; equivalent healing rates at 4 and 8 weeks have been demonstrated with ranitidine 300mg at night or at 0800h (Bianchi Porro et al. 1990).

Roxatidine has been approved for clinical use in some countries and will shortly be widely available on the antiulcer market (for review see Murdoch & McTavish 1991). Again the dose has been matched to give a similar antisecretory effect to

be comparable to ranitidine 150mg twice daily – 93.5% *vs* 89.2% healing at 6 weeks (Huttemann 1988). Also, as has been shown with the other H_2-receptor antagonists, equivalent healing rates are obtained with a once-daily dose and a twice-daily dose (Hentschel & Schutze 1988), and following a night-time dose of roxatidine 150mg or ranitidine 300mg (Walt et al. 1991).

1.3 Comparisons with Omeprazole

The H^+,K^+-ATPase (acid pump) inhibitor omeprazole causes achlorhydria in virtually all patients when given at a dose of 20 or 40mg (see review by McTavish et al. 1991). Duodenal ulcers, and particularly larger ulcers, heal slightly faster during omeprazole treatment and consequently early healing rates are higher than with the H_2-receptor antagonists.

Following treatment with omeprazole 20mg once daily, healing rates of 42 to 79% at 2 weeks, 82 to 97% at 4 weeks, and 88 to 100% at 8 weeks have been demonstrated (Archambult et al. 1988; Barbara et al. 1987; Bigard et al. 1987; McFarland et al. 1990; Valenzuela et al. 1991). A recent meta-analysis of studies that directly compared omeprazole and ranitidine showed an overall increase of 16.5% in the percentage of healed ulcers at 2 weeks (69.3% with omeprazole *vs* 52.8% with ranitidine); at 4 weeks, the healing rates were 92.8 *vs* 83.1% (Mulder & Schipper 1990). Omeprazole 40 mg/day also heals the majority of duodenal ulcers that do not heal following treatment with the H_2-receptor antagonists (Bardhan et al. 1991a).

1.4 Comparisons with Prostaglandin Analogues

Prostaglandin analogues were introduced into ulcer treatment because of the proposition that they would combine the benefits of gastric acid secretion inhibition with a 'cytoprotective' effect.

Table II. Percentage of patients with acute duodenal ulcers healed after 2, 4 or 8 weeks of treatment with single night-time doses of cimetidine, ranitidine, famotidine or nizatidine in double-blind, endoscopically controlled studies

Reference	No. of pts	Ranitidine 300mg	Cimetidine 800mg	Famotidine 40mg	Nizatidine 300mg
2 weeks					
Arnold et al. (1989)	367	63			57
Cherner et al. (1989)	375		33		41
Hartmann & Folsch (1988)	78		23	31	
Simon et al. (1987)	777	64			60
4 weeks					
Arnold et al. (1989)	367	90			87
Alcala-Santaella et al. (1989)	133	77		79	
Bovero et al. (1987)	165	78			78
Cherner et al. (1989)	353		67		73
Hartmann & Folsch (1988)	78		85	95	
Marks & Wright (1987)	132	78		75	
Rodrigo et al. (1989)	105		82.3	91.6	
Pace et al. (1988)	138	77.5			84.1
Simon et al. (1987)	777	80			81
8 weeks					
Arnold et al. (1989)	367	96			92
Bovero et al. (1987)	165	95			91
Cherner et al. (1989)	347		75		81
Pace et al. (1988)	138	94			92

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