PAPERS

Effect of famotidine on oesophageal sensitivity in gastro-oesophageal reflux disease

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Abstract

Gastric acid suppression could improve heartburn by healing oesophagitis or by reduction of oesophageal sensitivity to acid. To independently assess changes in oesophageal sensitivity, it would be necessary to study patients with reflux disease but no oesophagitis. The aim of this study was to investigate the effect of acid suppression on oesophageal sensitivity and to assess the time course of any measured effect. Twenty seven patients were recruited, of whom 25 completed the study (14 men and 11 women, mean (SD) age 50 (15) years). All had classic symptoms of gastro-oesophageal reflux but normal results of upper gastro-intestinal endoscopy and oesophageal mucosal histological tests. Each had abnormal 24 hour pH studies and a positive acid perfusion tests. Subjects were assigned double blind to placebo (n=11) or famotidine 40 mg twice daily (n=14) for four weeks. Acid perfusion tests were carried out at 0, 4, 5, and 8 weeks and time to heartburn recorded. Time to heartburn (mean (SEM)) was 124 (78) seconds in the famotidine and 187 (154) in the placebo group at week 0 (NS). Compared with baseline, significant increases in time to heartburn was found with famotidine at weeks 4 (383 (102), $p<0.01$) and 5 (344 (92), $p<0.01$) but not week 8 (336 (90) seconds). No significant effects were found with placebo (219 (41), 146 (23), and 144 (25) seconds for weeks 4, 5, and 8). Heartburn symptom score decreased significantly with famotidine (mean scores 3.6, 1.9, 2.1, and 2.6 at weeks 0, 4, 5, and 8 ($p=0.001$)) and showed a significant negative correlation with time to heartburn ($r_s=-0.60$; $p<0.0001$). It is concluded that oesophageal sensitivity to acid is reduced by famotidine independent of an effect on oesophagitis; the effect wanes one to four weeks after the end of treatment and correlates with change in heartburn score. (Gut 1994; 35: 447-450)

Numerous treatment studies of patients with gastro-oesophageal reflux have shown that suppression of gastric acid has a beneficial effect on symptoms¹; two early controlled studies with cimetidine showed in addition that active treatment resulted in an increase in the time to heartburn during oesophageal acid perfusion.^{2,3} Because most studies have recruited patients with endoscopic oesophagitis, however, it is

difficult to know whether symptomatic improvement is a result of improvement in the oesophagitis or some other factor. It has been shown that healing of oesophagitis is accompanied by histological improvement, including reduction in dermal papillary elongation.⁴ This is difficult to assess, as such changes, being patchy, are liable to sampling error and also occur in the distal two centimetres of the normal oesophagus.^{5,6} Nevertheless, it has been suggested that symptoms improve as a result of the increased thickness of epithelium (acting as a mechanical barrier to acid) above sensory nerve endings in the dermal papillae.⁷ Alternatively, oesophageal afferent nerves may in fact be sensitised by repeated exposure to acid. A similar phenomenon has been described in cutaneous pain receptors^{8,9} and nociceptors in other viscera.^{10,11}

It is unresolved whether symptom improvement is a result of healing of the oesophagitis or desensitisation of oesophageal sensory receptors sensitised by exposure to refluxed gastric acid. The well recorded lack of correlation between endoscopic oesophagitis¹² and symptoms together with the tendency of symptoms to recur rapidly after anti-secretory treatment has finished would favour the second. The aims of this study were therefore to examine the effects of a four week course of acid inhibition treatment with a potent H_2 receptor blocker (famotidine)¹³ on oesophageal acid sensitivity and symptoms in subjects with symptomatic gastro-oesophageal reflux but no oesophagitis and to explore the time course of any effect after treatment has finished.

Patients and methods

Twenty seven patients with typical symptoms of gastro-oesophageal reflux (retrosternal burning after meals or on stooping or lying flat, or both, pharyngeal acid regurgitation) were recruited. There were 14 men and 13 women, of mean (SD) age 50 (15) years. To be eligible for the study, all patients had to have a normal upper gastro-intestinal endoscopy and no histological abnormality on two random distal oesophageal pinch biopsy specimens taken ≥ 2.5 cm above the gastro-oesophageal mucosal junction. A normal histological result required there was no intraepithelial or submucosal polymorphs or microscopic breaches in the epithelium. Papillary length and basal layer thickness were not assessed, as these represent the mucosal

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response to reflux rather than oesophagitis and are non-specific and patchy changes.^{5,6} Additional requirements were that anti-secretory drugs had not been prescribed for at least four weeks, a positive acid perfusion test, and positive 24 hour intra-oesophageal pH monitoring. The study was approved by the local hospital ethical committee.

Acid perfusion test¹⁴ was carried out in a single blind fashion by inserting a naso-oesophageal tube with the distal margin 10 cm above the gastro-oesophageal mucosal junction whose position had been determined at endoscopy (5 cm added for nasal insertion). Perfusion was started with normal saline at a rate of 10 ml/min for 10 minutes, after which the perfusate was changed without the patient's knowledge to 0.1 N solution hydrochloric acid at the same rate for up to 20 minutes or until typical heartburn was reproduced. A positive test required reproduction of the patient's familiar heartburn by acid but not saline perfusion. The time to start of symptoms was noted.

Twenty four hour oesophageal pH monitoring was carried out using a Radiometer combined glass electrode (CK2802C) connected to a portable digital recorder (Digitrapper Mark II, Synectics Medical, Enfield). The distal point of the pH electrode was positioned 5 cm above the point of sudden rise of pH on withdrawal from stomach to oesophagus.¹⁵ Patients took the apparatus home, with instructions to return after 23 hours. They each kept a diary card recording the time and content of meals or drinks, time of retiring to bed, and time and nature of any dyspeptic symptoms. There were no restrictions of diet or activity placed on patients as in previously reported studies.¹⁶ Before and after pH monitoring, the electrode and system was calibrated in buffer solutions at pH 1 and 7. The digitised data were downloaded onto a personal computer and analysed by computer program (Gastrosoft, Synectics Medical). Abnormal pH

monitoring required either total time pH <4 for more than 7% of the total recording time¹⁷ (n=1), or a positive symptom index ($\geq 50\%$ of episodes of heartburn occurring with five minutes of an acid reflux episode¹⁸) (n=2), or both of these criteria (n=24).

These 27 patients were enrolled into the study after giving their written informed consent. They were then assigned in a double blind randomised fashion to receive famotidine 40 mg twice daily or matching placebo for a period of four weeks. Compliance was assessed by tablet counts at the end of the treatment period and patients were allowed to take antacid tablets (Rennies) if required. At the 4 week point, a further acid perfusion test was performed as described above and the time to heartburn recorded. The test was again repeated at five and eight weeks after the start of the study (receiving no treatment except ad lib antacids). At each visit, heartburn in the previous week was assessed according to the scale: 1=none; 2=occasional, not interfering with normal activities; 3=interfering with normal activities but not constant; 4=constantly interfering with normal activities.

All results (unless otherwise stated) are expressed as mean (SEM). Differences between groups were assessed by unpaired *t* test, while intragroup differences were examined by analysis of variance with localisation of significant differences by multiple range test (Scheffe). Correlation was assessed by Spearman rank correlation coefficient (*r_s*). Statistical significance required *p*<0.05.

Results

Two patients defaulted from further follow up after enrolment and could therefore not be evaluated further (both were taking placebo). This left 25 (14 famotidine, 11 placebo) who completed the study. Compliance (>95%, as assessed by tablet counts) among these 25 was excellent. The mean % total time oesophageal pH <4 during 24 hour pH monitoring was 10.7 (0.8)% (range 5.9–19) for the 25 patients who completed the study. Median (range) of symptom indices was 100 (50–100)%. Thus, all had objective evidence of gastro-oesophageal reflux induced heartburn.

Mean time to heartburn during acid perfusion (oesophageal mucosal sensitivity) was not significantly different between the active and placebo groups at any time during the study, though there was a trend at weeks 4 and 5 for a longer time in the active group (week 0: 124 (21) v 187 (46), *p*=0.2; week 4: 452 (102) v 218 (41), *p*=0.07; week 5: 346 (92) v 146 (23), *p*=0.07; week 8: 276 (90) v 144 (25), *p*=0.2 for active and placebo groups respectively). Within groups, however, there was a significant decrease in oesophageal mucosal sensitivity at weeks 4 and 5 compared with baseline in the active but not the placebo group (Fig 1). The lack of intergroup difference is explained by examining the data for individual patients (Figs 2 and 3), from which it is evident that most patients (except one) in the placebo group showed little change in time to heartburn over the eight weeks of the study,

Figure 1: Time to heartburn was significantly increased at week 4 and 5, but only in the famotidine treated group (**p*<0.01 v week 0, famotidine group only).

Figure 2: Individual data of time to heartburn in the famotidine treated group (n=14).

Figure 3: Individual data of time to heartburn in the placebo treated group (n=11).

Figure 4: Heartburn grading was significantly improved in the famotidine group.

Figure 5: Correlation between grade of heartburn and time to heartburn ($r_s = -0.6$, $p < 0.0001$, $n = 100$).

whereas among the active group, there were two apparent subsets: eight patients increased the time to heartburn while six did not.

Heartburn grading improved in the active compared with the placebo group at weeks 4 ($p < 0.01$) and 5 ($p < 0.05$), but was not different at baseline or week 8 (Fig 4). Within groups, heartburn grades improved at weeks 4, 5, and 8 compared with baseline for active ($p < 0.005$) but not placebo group (NS; Fig 4). When patients receiving active treatment were subdivided into non-responders (increase in time to heartburn at week 4 over baseline 100 seconds or less; $n = 6$) or responders (increase in time to heartburn > 150 seconds; $n = 8$), there was a significant difference mean (SEM) in heartburn grade at week 4 (non-responders 2.7 (0.5) *v* responders 1.4 (0.2); $p < 0.02$). Furthermore, patients in the active group could be subdivided into those in whom decreased oesophageal mucosal sensitivity was maintained ($n = 4$) and those in whom it was not ($n = 10$; see Fig 2). The heartburn grade at week 8 was lower in the first compared with the second (1.3 (0.3) *v* 3.1 (0.2); $p < 0.001$). There was a significant correlation between grade of heartburn and time to heartburn during acid perfusion ($r_s = -0.6$, $p < 0.0001$; Fig 5) using all 100 data points (heartburn scores and acid perfusion in 25 patients each on four occasions).

Discussion

In this study, it has been shown that in patients with symptomatic gastro-oesophageal reflux but no oesophagitis, both heartburn and oesophageal mucosal sensitivity improve with famotidine 40 mg twice daily taken for four weeks. This dose was chosen because dose ranging studies have shown that 40 mg twice daily produces a greater reduction of oesophageal acid reflux than 20 mg twice daily or 40 mg at night.¹⁹ Furthermore, famotidine at this dose has been shown to produce a significantly better reduction of heartburn than 20 mg twice daily in patients with oesophagitis.²⁰ The lack of significant difference of oesophageal mucosal sensitivity between the active and placebo groups is related to the fact that six patients in the active group did not show

any change in this parameter. There are two possible reasons for this: one might be that treatment was not continued for long enough to reach maximum effect, as symptomatic response is maximal at six to eight weeks in symptomatic patients without oesophagitis.²¹ Another reason could be that even this dose of famotidine could not reduce basal gastric acid output, a feature of patients who fail to respond to H₂ receptor antagonists.^{22,23}

We deliberately chose to recruit patients with typical symptoms, no oesophagitis, and objective evidence of gastro-oesophageal reflux disease to assess if symptom improvement could be related to a change in mucosal sensitivity to acid. Because patients did not receive another endoscopy at the end of the treatment period, we cannot be certain that some patients did not develop oesophagitis, which can occur over a six month period of observation in patients initially without endoscopic lesions.²⁴ It seems probable, however, that one month would be too short a period for this to occur. The time to heartburn seems to be reproducible, in that among the patients on placebo, values changed very little in most patients over the eight weeks of the study. This finding also suggests that antacids, which were available to both groups of patients ad libitum had little discernible effect, because it might be expected that the maximum effect would occur in patients taking placebo. The close relation between heartburn score and time to heartburn during oesophageal acid perfusion supports the hypothesis that improved symptoms of heartburn are related to decreased oesophageal mucosal sensitivity. This conclusion is supported by the findings of better heartburn improvement in the subgroups of patients receiving active treatment in whom mucosal sensitivity was decreased and in whom this decrease was maintained to the end of the study. It would be interesting in further studies to investigate if more profound acid suppression (for example, with proton pump inhibitors) both increased the proportion of patients with decreased oesophageal mucosal sensitivity and increased the proportion in whom this improvement was maintained. Although the mechanisms underlying changes in oesophageal mucosal sensitivity to acid are not well understood, increasing the proportion of patients who maintain a decreased acid sensitivity will increase the symptom remission rate and duration.

In conclusion, famotidine at a dose of 40 mg twice daily reduces symptoms of heartburn and decreases oesophageal mucosal sensitivity in patients with symptomatic gastro-oesophageal reflux disease but no oesophagitis, and suggests that, at least in this group of patients, the two are closely related.

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