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Does misoprostol given as a single large dose improve its antisecretory effect?

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SUMMARY

H_2-receptor antagonists have been shown to be effective in the suppression of nocturnal acidity. This double-blind, randomized, crossover Latin-square study of 24-h intragastric pH in 12 normal volunteers investigated the effect of large single-dose administration of misoprostol on intragastric acidity. Efficacy of 800 μg misoprostol h.s., 600 μg h.s., 400 μg h.s. and 800 μg after supper was compared to placebo and 200 μg misoprostol q.d.s. Twenty-four hour mean pH $\pm$ s.d. was placebo 2.1 $\pm$ 0.3, misoprostol 200 μg q.d.s. Twenty-four hour mean pH $\pm$ s.d. was placebo 2.1 $\pm$ 0.3, misoprostol 200 μg q.d.s. 2.2 $\pm$ 0.3, 800 μg p.m. 2.6 $\pm$ 1.1, 400 μg h.s. 2.6 $\pm$ 0.7, 600 μg h.s. 2.6 $\pm$ 0.4, 800 μg h.s. 2.6 $\pm$ 0.5. The effect of misoprostol on gastric acidity was short and limited to the nocturnal period. Only misoprostol 800 μg and 600 μg reduced 24-h acidity compared to placebo ($P < 0.04$).

INTRODUCTION

The importance of suppression of nocturnal gastric acidity in the healing of duodenal ulcer has been well established for the H_2-receptor antagonists.[1–3] Currently available short-acting H_2-receptor antagonists are more effective in the suppression of nocturnal than daytime acidity.[4] The clinical efficacy of the

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H_2-receptor antagonists has been borne out by the demonstration of a clear relationship between duodenal ulcer healing and the suppression of nocturnal acidity.[5] Misoprostol is a prostaglandin E_1 analogue, currently prescribed as a q.d.s. dose regimen for the treatment of duodenal ulcer. It is believed that this agent acts primarily through its antisecretory activity rather than its cytoprotective effect.[6] However, there is only a very weak antisecretory effect over 24 h when studied by datalogger and pH probe.[7] Thus with the increased appreciation of the importance of suppression of nocturnal acidity, it was considered important to study the efficacy of 800 μg given as a single dose in the control of nocturnal intragastric acidity in comparison with 200 μg q.d.s.

Early evening dosing after supper with ranitidine has been claimed to have a pharmacological and therapeutic advantage over nocturnal dosing with ranitidine, with a significantly greater decrease in median 24-h acidity and a longer period of suppression of nocturnal acidity.[8] This advantage has been confirmed by an early clinical healing trial.[9] We therefore also studied an early evening dose together with a dose–response profile, to determine whether a lower overall dose might be of clinical benefit.

MATERIALS AND METHODS

The study was designed as a double-blind, placebo controlled, randomized, cross-over, Latin-square experiment, in 12 healthy male volunteers; mean age 23.7 (20–30 years). All were non-smokers with no history of peptic ulcer disease. Each regimen was administered for 4 days and on the fourth day of each treatment a 24-h gastric acidity study was performed. There was a 5-day wash-out period between each treatment period and each subject underwent six individual 24-hour study periods. Written informed consent was obtained from each subject together with McMaster University Medical Center ethical committee approval. During the study period subjects were asked to adhere to the meal pattern of the study schedule (08.00, 12.00, 18.00 hours). Standardized meals were eaten and no snacks allowed on each study day (breakfast: 563 kCal, 12% protein, 25% fat, 65% CHO; lunch: 733 kCal, 21% protein, 38% fat, 43% CHO; supper: 909 kCal, 29% protein, 34% fat, 37% CHO). Subjects reported to the investigational laboratory at 06.30 hours on the study day and a 14F nasogastric tube (Salem Sump, Sherwood Medical, St Louis, USA) was placed in the stomach so that its tip lay in the most dependent position of the stomach, as indicated by the water recovery test.[10] At 07.00 hours, a 5-ml sample of gastric juice was aspirated and subsequent 5-ml samples aspirated at hourly intervals and the pH determined to the nearest 0.01 pH unit using a glass electrode (Corning 150, Medfield) and digital pH meter (Corning 150 Medfield). The electrode was calibrated with standard buffers (pH 7.0, 4.0 and 2.0) before during and after each batch of samples.

Data analysis

The data were analysed as mean and median over each of the following time periods: total (complete 24 hours study), night (22.00 hours to 07.00 hours), morning (07.00 hours to 11.00 hours), afternoon (12.00 hours to 16.00 hours) and evening (17.00 hours to 21.00 hours). The Kruskall–Wallis test was applied to determine any overall statistical significance. Multiple comparisons with placebo were tested with the Wilcoxon test. The P value was adjusted according to the number of groups compared.

RESULTS

Statistical analysis was only performed on the pH data, because examination of means and medians of H^+ activity indicated that further statistical analysis would only duplicate that already performed.

The data are represented in Table 1 graphically as notched box-whisker plots compared to placebo and in Fig. 1 and Fig. 2. A short duration of antisecretory action for 3.5 h was seen after each dose, and this study confirms that misoprostol is a weak, short-acting antisecretory drug, the effects being limited, with all doses, to the nocturnal period.

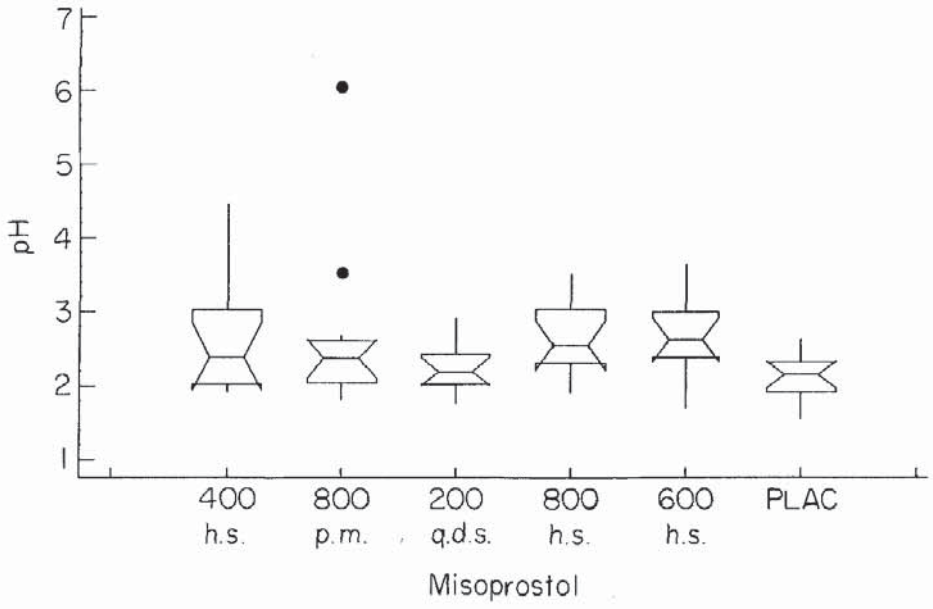

Figure 1. Box whisker plot total 24 h pH. Annotation: horizontal line inside the box indicates the median, the box the interquartile range, the notch on the box the 95% confidence limits for the median and the whiskers indicate the range of the data.

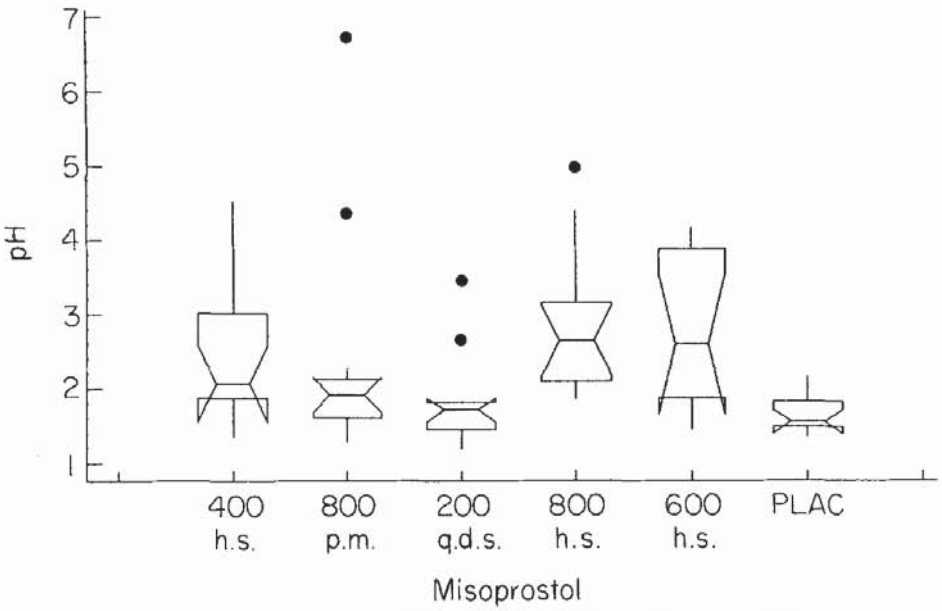

Figure 2. Box whisker plot of the night-time pH.

Table 1. Mean pH with standard deviation for each drug regime and time period

	Total (24 h)	Nocturnal (22.00–07.00 hours)	Morning (07.00–11.00 hours)	Afternoon (12.00–16.00 hours)	Evening (17.00–21.00 hours)
400 h.s.	2.6 ± 0.7	2.5 ± 1.0	3.2 ± 1.1	2.3 ± 0.6	2.5 ± 0.7
800 p.m.	2.6 ± 1.1	2.3 ± 1.5	2.9 ± 1.2	2.3 ± 0.9	3.0 ± 0.9
200 q.d.s.	2.2 ± 0.3	1.8 ± 0.6	2.9 ± 0.7	2.2 ± 0.2	2.2 ± 0.2
800 h.s.	2.6 ± 0.4	2.8 ± 0.9	3.1 ± 0.8	2.1 ± 0.3	2.2 ± 0.5
600 h.s.	2.6 ± 0.5	2.7 ± 0.9	3.1 ± 0.7	2.3 ± 0.6	2.3 ± 0.5
Placebo	2.1 ± 0.3	1.6 ± 0.2	2.7 ± 0.9	2.2 ± 0.4	2.2 ± 0.4

DISCUSSION

In this study, the placebo mean 24-h pH was high which may have made the antisecretory action of the drug appear comparatively weaker. The short duration of action of the drug is best indicated by the limited efficacy of the 800 μg early evening dose on nocturnal acid secretion compared to the bedtime doses. Overall, only the 800 μg and 600 μg h.s. doses were significantly different from placebo and these were of equal efficacy in this study.

From this study, a trial of nocturnal therapy in duodenal ulcer healing would be justified with a dose of 600–800 μg of misoprostol. Despite a better understanding of the mechanism of the antisecretory action of the prostaglandins on the parietal cell,[13] the weak antisecretory action of misoprostol, seen here, raises the question of whether the positive effects on mucosal defense, induced by prostaglandins, might

be more important for duodenal ulcer healing than has been hitherto thought. However, other drugs, also thought to act primarily by the inhibition of gastric secretion, have a weak antisecretory effect on 24-h intragastric acidity.[14, 15] Stimulation of duodenal bicarbonate secretion,[16] and an increase in thickness of the mucus gel layer[17] could perhaps be of greater importance in the prophylaxis and treatment of NSAID-induced injury,[18, 19] where antisecretory efficacy is less well understood.

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