Effect of Wy-45,727 on 24 h intragastric acidity in twenty normal volunteers

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- 1 The effects of single daily doses of 20, 50 and 150 mg of WY-45,727, a novel H₂-receptor antagonist, and placebo were compared using long term pH-monitoring in 20 male volunteers.
- 2 Intragastric acidity was measured using combined Ingold glass electrodes. Subjects underwent four studies each under identical dietary conditions. Medication was taken after the evening meal.
- 3 Median 24 h pH rose from 1.3 (1.2–1.4 interquartile range) on placebo to 1.9 (1.6–2.8) on 20 mg WY-45,727, to 3.1 (2.3–3.7) on 50 mg WY-45,727 and to 4.5 (3.7–4.7) on 150 mg WY-45,727. All three doses increased 24 h and night-time pH significantly compared with placebo ($P < 0.0001$).
- 4 The PAGE test for order effects confirmed clear dose dependent inhibition of acidity ($P < 0.0001$).
- 5 Highly consistent individual responses were found during the night following 150 mg WY-45,727.

Keywords intragastric acidity pH-monitoring H₂-receptor antagonists

Introduction

WY-45,727 is a new furan histamine H₂-receptor antagonist (Wyeth Laboratories, Philadelphia) of greater potency than ranitidine (3–10 times weight for weight in animal models). The clinical effects of H₂-receptor antagonists largely parallel their effects on gastric acidity, particularly nocturnal acidity (Jones *et al.*, 1987). We have compared the effects of different doses of WY-45,727 and placebo on 24 h intragastric acidity to show a dose-response relationship and to give an indication of reasonable dosages for clinical testing.

Methods

Acidity was measured every 5 s using miniaturised combined glass electrodes (model '440 M4',

Ingold AG, Switzerland), which provide accurate and reproducible measurements (Merki *et al.*, 1987a,b; Fimmel *et al.*, 1985). All studies were performed under hospitalised conditions: Subjects attended the investigation ward in groups of 20 at 15.00 h having fasted from noon. The electrodes were passed transnasally into the gastric corpus (approximately 8 cm below the cardia). Intragastric acidity was measured continuously from 17.00 h–18.00 h the next day. Dietary conditions were identical in timing and menu throughout. The menus for breakfast (08.00 h), lunch (12.00 h), tea (16.00 h), supper (18.00 h), snack (22.00 h) were the same as in previous studies from this unit (Merki *et al.*, 1987 a,b). Oral medication was taken at 18.30 h after the evening meal; the tablets for different doses

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were identical in size, shape, colour and taste and administration was observed. Subjects were allowed to move freely within the hospital area except for meals and at night. Ethics Committee approval for these investigations was obtained, and written informed consent was given by all volunteers.

Statistical analysis

The 5 s pH tracings were stored on solid state devices (Ingold AG, Switzerland). Non-parametric statistical tests for order effects (PAGE test) were applied to the following pre-defined time periods: 24 h (18.00–18.00 h), evening (18.00–24.00 h), night (24.00–08.00 h), and day (08.00–18.00 h). *P* values were corrected for multiple testing according to Holm-Bonferroni (Holm, 1979). Probability values of $P < 0.05$ were considered significant. For graphs, the mean pH of sixty pH readings (mean of 5 min) was calculated and smoothed by the moving average.

Results

The mean age of the 20 male volunteers was 28 years (22–38 years) and half of the subjects were

non-smokers. Clinical, haematological and biochemical examinations (including ECG) were normal in all men before the start of the study.

The median pH profiles of the 20 subjects are shown for the four treatments in Figure 1. All three doses of WY-45,727 inhibited 24 h acidity compared with placebo ($P < 0.0001$). Median 24 h pH was 1.3 (1.2–1.4 interquartile range) on placebo, and increased to 1.9 (1.6–2.8) on WY-45,727 20 mg, to 3.1 (2.3–3.7) on WY-45,727 50 mg and to 4.5 (3.7–4.7) on WY-45,727 150 mg (Figure 2). An explanation of the box-whisker-plot is shown in Figure 3.

The PAGE test was highly significant ($P < 0.0001$) confirming clear dose dependent inhibition of acidity. During the night (24.00–08.00 h) pH rose from 1.3 (1.1–1.5) on placebo to 2.4 (1.7–4.8), to 6.0 (3.3–6.5), and to 6.7 (6.5–7.0) on the 20, 50 and 150 mg doses, respectively. Figure 4 shows the frequency distribution curves for the 24 h period during all treatments. Figure 5 illustrates the consistency of response following the highest dose. No significant inhibition of acidity was found with any dose during the daytime (08.00–18.00 h).

In one subject bilirubin increased from 1.2 to 1.6 mg/dl; (normal range < 1.2 mg/dl). There were no other changes in the clinical, haemato-

Figure 1 Median 24 h pH profiles during placebo, Wy-45,727, 20 mg, Wy-45,727, 50 mg and Wy-45,727 150 mg. Meals are shown at the bottom by the arrows, D (dinner), S (snack), B (breakfast), L (lunch), and T (tea).

Figure 2 Box-whisker-plots of median pH values on all treatments during the 24 h (18.00–18.00 h). A full explanation of all symbols is given in Figure 3.

The Box-Whisker-Plots

Figure 3 Explanation of a box-whisker-plot. Reprint from Merki *et al.* (1987a,b) with permission.

Figure 4 Frequency distribution curves of pH on all treatments. The proportion of time during 24 h with pH values above any given level are shown.

Figure 5 Box-whisker-plots of median pH values on all treatments during the night (24.00–08.00).

logical and biochemical examinations at any time during treatment or within 10 days after the last dose. The drug was well tolerated and no symptoms were reported.

Discussion

A clear dose-response relationship is shown and maximal effects were seen with all doses during the night. The drug was given after the evening meal (*post cenam nocte/PCN*) because other studies have shown that gastric acidity is decreased for longer periods with most drugs given at this time rather than at bedtime (Merki *et al.*,

1987a; Coppens *et al.*, 1986; Orr *et al.*, 1987). One clinical study has also suggested that this increased inhibition of secretion is associated with faster healing of duodenal ulcer (Merki *et al.*, 1988). From the results of this study one could anticipate that duodenal ulcer healing would be accelerated by WY-45,727. We have not compared the new agent with any other H₂-receptor antagonist but these results are similar to those found with alternative drugs. However, following the 150 mg dose all subjects showed a marked and consistent response with pH rising to above 6.0 during the night-time (24.00–08.00

h). To our knowledge, such consistent individual responses have never been reported with an oral H₂-receptor antagonist before. Even though a direct prospective correlation between the degree of intraindividual reduction of acidity and duodenal ulcer healing is lacking, it is likely that the variability of individual pharmacological responses following recommended doses of H₂-receptor antagonists might account for variations in healing rates. One might expect, therefore, that clinical results with this drug would be at least as good if not better than those found with the available compounds.

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