Effect of food on \( \text{H}_2 \)-receptor blockade in normal subjects and duodenal ulcer patients

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Abstract
Two separate studies of 24 hour intragastric acidity were carried out in normal volunteers and duodenal ulcer patients to define the interaction of food and the antisecretory effects of \( \text{H}_2 \)-receptor blockers. Both investigations were double blind randomised comparisons using ranitidine 300 mg with either different meal times or \textit{ad libitum} snacks after an evening meal. Meals taken after drug administration nearly abolished measurable antisecretory effects. Median 24 hour pH was 1.3 on placebo, 2.6 when ranitidine was administered after the evening meal and 1.9 when administered before the evening meal. Snacks taken after evening dosing with ranitidine also significantly decreased pharmacodynamic efficacy. During placebo, median night-time pH was 1.3 without snacks and 1.4 with snacks. pH rose to 5.9 during ranitidine treatment when snacks were forbidden but was only 3.1 when snacks were allowed. These findings could be of therapeutic importance and should rationalise dietary advice to patients receiving \( \text{H}_2 \) blockers. The timing of drug administration can be adjusted according to individual life styles.

It has been noted that the efficacy of histamine \( \text{H}_2 \)-receptor blockers as inhibitors of gastric secretion is limited by food.1-4. Previous investigations identified this by chance and no prolonged studies have been specifically designed to measure the interaction between food and drug effect. An early study which considered a possible pharmacokinetic interaction between food and cimetidine suggested that food affected blood concentrations, but concluded that the timing of cimetidine administration was not critical because no pharmacodynamic effects were noted.1 A pharmacodynamic interaction would be of potential therapeutic importance, as it is believed that clinical efficacy parallels antisecretory potency.3 We carried out two separate studies to identify and quantify this interaction. We have previously shown that early evening dosing with an \( \text{H}_2 \)-blocker produces the best pharmacodynamic response.1 It is possible that this results from the timing of the evening meal and the subsequent interaction between food and \( \text{H}_2 \)-blockers. Many people traditionally eat late and, therefore, the validity of the previous study could be questioned. The first investigation aimed to identify whether a late meal would interfere with the pharmacodynamic effects of early drug administration. The objective of the second investigation reported here was to identify whether snacks taken after an evening meal (perhaps the commonest behaviour) interfere with the antisecretory effects of ranitidine.

Methods

PATIENTS

STUDY 1
Twelve normal volunteers (six men) of mean age 28 years (19-37 range) participated in the trial. Half of the subjects smoked regularly (>10 cigs/day). Each subject underwent three studies during which 24 hour intragastric acidity was continuously measured by indwelling glass electrode and pH measurements were stored on solid state devices (Autronicord, Autron, West Germany). The technique has previously been described in detail. The double blind studies compared, in random order, the effects of single doses of ranitidine 300 mg and placebo taken either at 1800 or at 2230 with a late evening meal (2200). The investigations started at 1600 and continued until 1600 the next day. The menus for breakfast (0800), lunch (1200), tea (1600), a snack (1800), and the late supper were identical on each day. Additional drinks of water or unsweetened black tea were allowed, but were recorded and repeated on each study day. Cigarette consumption was treated similarly.

STUDY 2
Twenty duodenal ulcer patients in whom ulcer healing had been verified within the preceding 12 months and who were in symptomatic remission (12 smokers, 10 men, mean age 39-8 years with a range of 25-66 years) were accrued. Each underwent four studies of 24 hour intragastric acidity using the Gastrograph Mark I (Medical Instruments Corporation, Solothurn, Switzerland) and combined Ingold-M4 glass electrodes. The studies compared, in random order, the effects on the fifth day of treatment with ranitidine 300 mg and placebo taken at 1830 after an evening meal, with food intake including alcohol thereafter either forbidden (two studies) or allowed ad libitum (two studies). During the first study with ad \textit{lib} snacks a record was kept and this intake was reported on the second ad \textit{lib} day. Other regular meals, drinks and cigarette smoking were standardised as in study 1. The studies all started at 1500 and continued until 1500 the next day.

STATISTICAL ANALYSIS
For study 1 the predefined interval of interest was the whole 24 hour period and Wilcoxon’s signed-rank tests were used to compare median...
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pH 7

Effect of food followed by ranitidine intake

Figure 1: Median 24-hour pH profiles in 12 normal subjects during placebo (-----), early evening ranitidine administration (1800 h) followed by late dinner (------), and ranitidine intake after the late supper (-----). Meals are shown at the bottom by the arrows, T (tea), S (snack), D (late dinner), B (breakfast), L (lunch).

24 hour pH. In study 2 the periods of interest were between 1800 and 0800 (evening and night) and 1800 to 2400 (evening) and Wilcoxon’s signed-rank tests again compared median pH during these periods. All other probability tests were considered descriptive. For confirmative testing a Holm-Bonferroni correction for multiple testing was performed. Ethical approval and written consent was obtained.

Results

STUDY 1

Three studies had to be repeated because of failure of the recording device (two studies) or electrode drift (>0.2 pH units after 24 hours). The study was well tolerated and no side effects of drug administration were noted. Median 24 hour pH was 1.30 (1.25–1.50 Interquartile Range, IQR) on placebo, 1.85 (1.65–2.20 IQR) on early ranitidine intake, followed by a late evening meal, and was 2.57 (2.05–2.90 IQR) on ranitidine administered after the late supper (p<0.02). Overnight pH (2200–0600) was 1.2 (1.10–1.45 IQR) on placebo, 1.80 (1.50–2.25 IQR) on early evening ranitidine administration and was 3.70 (3.40–4.65 IQR) on late drug intake (2230) (p<0.002). Figure 1 shows the 24 hour median pH profiles during the three studies. The late evening meal almost abolishes the measurable effect on the $H_2$ receptor blocker administered at 1800 hours.

STUDY 2

All patients completed the four study periods without adverse events. When food was allowed ad libitum (1830–2400) the mean extra caloric intake was 737 kcal (range 243–1884). [Carbohydrates: 73.5 g (mean), protein: 19.65 g (mean), fat: 30.32 g (mean), fibre: 3.83 g (mean)]. Mean intake of alcohol in nine patients drinking alcoholic beverages was 25 g.

Figures 2 and 3 show median 24 hour pH profiles and frequency distribution of pH during the four study periods. The effect of ranitidine is clearly attenuated by ad lib food. Median night time pH (1800–0800) was 5.9 (4.1–6.8 IQR) on ranitidine when food was forbidden and 3.1 (2.1–4.0 IQR) on ranitidine when food was allowed ad lib (p<0.0002). During placebo treatment median night time pH was 1.25 (1.20–1.45) and 1.35 (1.20–1.55) when food was forbidden or allowed, respectively (p=0.63). Figure 4 shows box whisker plots of the night time and 24 hour acidity results.

Discussion

These two investigations confirm that the effects of $H_2$-receptor blockers are affected by food intake. In the first study the late supper nearly abolished the measurable effect of ranitidine on overnight and 24 hour acidity. The drug was clearly active before the meal (Fig 1) but pH fell postprandially, nocturnally to near normal levels. In contrast, when ranitidine was taken at the end of supper, gastric pH rose and high levels were maintained throughout the night. The second study corroborated these results. The efficacy of ranitidine in reducing both nighttime and 24-hour acidity is greatly diminished by late snacks (Fig 2).

Food intake is known to stimulate acid secretion by several means, some of which are not primarily effected through $H_2$-receptor pathways – for example, the cholinergic system activated during the cephalic phase of feeding. Gastrin release is provoked by more than one stimulus intra- and postprandially. These regulatory mechanisms presumably overcome the antiserocatory action of ranitidine after food intake.

Gastric motility is changed by feeding and this may in itself modulate the absorption of ranitidine, although this was discounted in a study by Louis and coworkers. If general advice on the timing of drug administration is to be given to
duodenal ulcer patients it is important to consider their normal patterns of eating. Food taken as desired after drug administration more closely reproduces normal habits.

In this and many previous studies, breakfast abruptly abolishes any measurable changes in acidity after either evening or bedtime administration of H₂ blockers. This further illustrates the ability of food to overcome the effect of H₂ receptor blockade, particularly when plasma concentrations can be expected to be low.

These results may be extrapolated to all the currently available H₂-receptor blockers and it is also seen with high doses of the most potent agents when given intravenously. The action of other, non-surmountable or even more potent and long-acting members of this class may not be so affected.

These findings are of clinical importance and may have some bearing on the number of patients whose ulcers fail to respond to H₂-blocker therapy. One previous clinical study has shown that patients with ‘resistant’ ulcer respond well to ranitidine if food is withheld. Our data can be used to provide rational recommendations for the timing of H₂-receptor blocker administration, providing patients’ eating habits are considered.

The general advice of withholding food after taking the tablets is valid. Patients whose last meal is in the early evening and who do not have subsequent snacks would benefit from early evening dosing, whereas those who eat late or have snacks before bed should take their medication after the last meal.

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