Ranitidine bismuth citrate and ranitidine do not affect gastric emptying of a radio-labelled liquid meal

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Ranitidine bismuth citrate, a new chemical entity which is a salt complex of ranitidine and bismuth citrate, is being developed for the treatment of relapse of benign gastric and duodenal ulcer and eradication of *Helicobacter pylori*. The aim of the present study was to establish whether ranitidine bismuth citrate (800 mg) or ranitidine hydrochloride (300 mg) have any effect on gastric emptying of a liquid meal using gamma scintigraphy. On three separate occasions, each of twelve subjects received a single oral tablet of 800 mg ranitidine bismuth citrate, 300 mg ranitidine hydrochloride or placebo in random order. Thirty minutes after dosing each subject was given 375 ml of 99mTc-DTPA (diethylene triaminepentaacetic acid) labelled Clinifeed-ISO. The primary endpoint was the time to 50% gastric emptying (t50%). The proportion of the meal remaining was summarised by weighted mean proportion of the meal remaining in the stomach over 0–60 min and 0–180 min, separately. No differences were observed for t50%, weighted mean 0–60 min, and weighted mean 0–180 min between any two treatments. In man, we have detected no significant effect of single oral doses of ranitidine bismuth citrate 800 mg or ranitidine hydrochloride 300 mg on the rate of gastric emptying of a liquid meal when compared with placebo.

**Keywords** ranitidine bismuth citrate ranitidine hydrochloride gastric emptying gamma scintigraphy liquid meal man

**Introduction**

Ranitidine bismuth citrate, a new chemical entity which is a salt complex of ranitidine and bismuth citrate, is being developed for the treatment of relapse of benign gastric and duodenal ulcer and eradication of *Helicobacter pylori*. This agent inhibits gastric acid secretion [1], protects the gastric mucosa from aspirin-induced injury [2] and suppresses *H. pylori* [3].

Previous studies of gastric emptying with ranitidine hydrochloride have shown conflicting results [4–11]. Therefore, the aims of this present study were to establish whether ranitidine bismuth citrate or ranitidine hydrochloride had any effect on gastric emptying of a liquid meal and to compare gastric emptying of a liquid meal between ranitidine bismuth citrate and ranitidine hydrochloride using gamma scintigraphy.

**Methods**

**Subjects**

Twelve healthy males of Caucasian origin, aged between 21 and 37 years (mean age 26.1 years, mean weight 72.7 kg and mean height 174.8 cm) participated in this randomised, double-blind, placebo-controlled, three-way crossover study. All subjects gave written informed consent, and the study was approved by South Glamorgan Local Research Ethics Committee and granted approval from the Administration of Radioactive Substances Advisory Committee (ARSAC).
Protocol

On three separate occasions, after an overnight fast, each subject received a single oral tablet of either 800 mg ranitidine bismuth citrate, 300 mg ranitidine hydrochloride or placebo (taken with 100 ml water), followed 30 min later by a radiolabelled liquid meal (3 MBq $^{99m}$Tc-diethylene triaminepentaacetic acid (DTPA)) mixed with 375 ml Clinifed Iso (Roussel-Energy—375 kcal, containing 10.5 g protein, 15.4 g fat and 49.2 g carbohydrate) taken over 2 min.

Immediately after consuming the test meal, anterior and posterior views (30 s acquisition) of the stomach were recorded using a gamma camera (GEC Maxicamera 400A) fitted with a low-energy parallel hole collimator and coupled to a Sun SPARC station IPX computer operating commercial software (MAPS 10000; Link Medical Systems). Further views were taken at 5 min intervals during the first hour then every 15 min thereafter up to 3 h after the meal was consumed.

Measurement of gastric emptying

The geometric mean counts in a region defining the stomach were calculated from pairs of anterior and reflected posterior images after correction for background radiation. Following correction for natural decay the geometric counts at each time point were expressed as a proportion of the original activity remaining in the stomach and used to form a gastric emptying time profile. From the mean gastric emptying time curves (mean proportion of meal remaining) the following parameters were calculated for each treatment group: $t_{50\%}$ (time taken for 50% of the radiolabelled liquid to be emptied) was calculated by linear interpolation.

Weighted mean proportion of meal remaining over 1 h and weighted mean proportion of meal remaining over 3 h were derived by calculating the area under the response-time curve and then dividing by the relevant time.

Statistical analysis

Twelve evaluable subjects gave this study approximately 80% power to detect a 13% decrease or a 15% increase between any pair of treatments, assuming significance was declared at the two-sided 5% level.

All of the derived parameters were log transformed prior to analysis, and were analysed using analysis of variance. There was consistent evidence of carry-over. Therefore, the analysis of variance model allowed for effects owing to subject, period, treatment and carryover. Tests of treatment by period interaction were also carried out. Estimates of pairwise differences were obtained, together with 95% confidence intervals.

Results

Figure 1 illustrates the mean gastric emptying time curves obtained after single oral doses of 800 mg ranitidine bismuth citrate, 300 mg ranitidine hydrochloride or placebo.

There was no statistically significant difference between any two treatments, for any of the derived parameters (Table 1).

Discussion

Gastric emptying studies after administration of ranitidine hydrochloride performed in healthy subjects and patients with duodenal ulcer [4–11] have yielded contradictory results. This may be attributed to the different doses, duration of dosing, and route of administration of ranitidine; and also the radiolabelled test meal used and whether the study was placebo-controlled or not.

Corinaldesi et al. [5] showed that a single intravenous bolus dose of ranitidine (150 mg) significantly delayed emptying of both a radio-labelled liquid and a solid meal in healthy volunteers. However, repeated administration of ranitidine, 150 mg twice daily orally for 2 weeks, had no significant effect on gastric
emptying of either a liquid or a solid meal in patients with duodenal ulcer. The delay in healthy subjects was postulated to be due to an increase in duodenal motility [12] which was only observed following the intravenous dose of ranitidine [5] and which was supposed to be independent of histamine H2-receptor blockade. Therefore, it was unlikely that similar delays in gastric emptying would be observed following an oral dosing regimen. In addition, a comparison between panels of healthy volunteers and patients with duodenal ulcer may be misleading.

Houghton & Read [4] showed that after a single oral dose of ranitidine (300 mg), there was no effect on the rate of gastric emptying following a solid meal but an acceleration following a liquid meal. The increase in rate of emptying following a liquid meal was suggested to be a result of a potentiating effect of ranitidine on the contractions induced by acetylcholine [13] since ranitidine, has been shown to increase fundal and antral contractility [14, 15].

Jonderko [8] assessed gastric emptying of a radio-labelled solid meal using a randomised blinded but not placebo-controlled design and confirmed a significant dose-related delay in gastric emptying with ranitidine, which was more profound in patients with duodenal ulcer than in healthy subjects. This could be ascribed to the rapid basal gastric emptying of a subgroup of patients with an active duodenal ulcer [17, 18]. The design of this study, however, poses difficulties in interpretation since, for ethical reasons, a placebo phase was not included in the study design.

In the present study, neither ranitidine bismuth citrate nor ranitidine hydrochloride proved to have an effect on gastric emptying of a liquid meal. The design of the present study cannot preclude a potentiating effect of ranitidine or ranitidine bismuth citrate on the cholinergic input to gastric motility [13] and, if it were to occur, it would have no significant functional implications in terms of gastric emptying because of the interaction of fundic tone and pyloric resistance [19].

References

8 Jonderko K. Influence of oral cimetidine and ranitidine

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