

Influence of acid-pepsin secretion on gastric emptying of solids in humans: studies with cimetidine

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Abstract

The commonly accepted model for gastric emptying suggests that the 'antral mill' is responsible for the trituration and subsequent emptying of solid food from the stomach. Little is known about the contribution to solid emptying made by other digestive mechanisms such as acid-pepsin secretion. We have investigated the effect of inhibiting gastric secretion on the rate at which a solid test meal emptied from the stomach. Using a radiolabelled beefburger, we performed paired gammacamera studies on consecutive days in 10 fasted, healthy volunteers to compare gastric emptying of the test meal with and without oral cimetidine (400 mg 1 hour before the test, 800 mg at the start of the meal). Inhibition of acid-pepsin secretion by cimetidine was associated with an appreciable delay in the rate of emptying of the burger from the stomach (T_{50} cimetidine 187 (16) min (mean (SEM); T_{50} no cimetidine 146 (15) min; $p < 0.01$, paired t test). This delay was related to a change in the slope of the emptying profile and was not associated with a prolonged lag phase. These results may be explained by the relative achlorhydria and reduced pepsin activity induced by cimetidine impairing the breakdown of solid food into particles small enough to leave the stomach.

Studies carried out in dogs and humans suggest that digestible solids must be reduced to particles less than 1 mm in diameter before they will empty from the stomach.^{1,2} This process of trituration is usually ascribed to the mechanical action of the 'antral mill,' although it is possible that acid and pepsin in gastric secretions also help to fragment solid food particles by breaking down connective tissue proteins. The H_2 receptor antagonist cimetidine inhibits gastric acid and pepsin secretion³⁻⁵ and might therefore affect gastric emptying of digestible solids by delaying disruption of large fragments of chewed food into a fine particulate suspension. To test the hypothesis that gastric secretions have a physiological role in the breakdown and emptying of solid food, we have measured the rate at which a radiolabelled beefburger emptied from the stomach before and after acid secretion had been blocked by cimetidine.

Methods

Studies were carried out in 10 healthy volunteers (five men, five women) aged 18-34 years, each of whom had given written informed consent. This

study received approval from the local Sheffield Hospitals Ethical Sub-committee.

Paired gastric emptying studies, one with cimetidine and one without, were performed in a random order on consecutive days in semi-recumbent, fasted subjects using a gammacamera (Model 1201 Pho-gamma III, Nuclear-Chicago, Europa NV, Amsterdam, The Netherlands) positioned anteriorly over the abdomen. The oral dose of cimetidine (Tagamet, Smith Kline and French, Philadelphia PA, USA) used to suppress acid secretion was 1.2 g (400 mg given one hour before the study and 800 mg with the meal, to ensure that reduced gastric secretion was maintained throughout the study). In an attempt to standardise the size of swallowed food particles subjects were fed 1 cm cubes of radiolabelled beefburger over a five minute period. The burger weighed approximately 130 g (20 g fat, 23 g protein, 8 g carbohydrate, 1.5 g sodium chloride) and was labelled with 1 MBq technetium-99m sulphur colloid bound to egg, which was incorporated into the raw meat. Results of *in vitro* studies of ^{99m}Tc binding have confirmed the reliability of this labelling technique, with less than 2% of the isotope dissociating from the meal when incubated with saline at 37°C for three hours. More isotope (up to 15%) leached out of the burger when gastric juice was substituted for saline, but this was almost certainly the result of peptic digestion since the incubate became noticeably turbid.⁶

Images of the distribution of radioactivity in the abdomen were collected at five minute intervals for 3.5 hours and stored on a microcomputer for later analysis. The position of the stomach was identified from an integrated image of the first five frames after the meal had been ingested and then outlined with a cursor. The counts within this gastric region of interest were corrected for decay and plotted to yield a profile of gastric emptying. From this profile the following values were obtained: (i) the time taken for 50% of the isotope to leave the stomach (T_{50}); (ii) the amount of isotope remaining in the stomach at 30 minute intervals after the meal was ingested; (iii) the duration of the lag phase, defined as the time from ingestion of the meal to when isotope first appeared in the duodenum; (iv) the time taken from the onset of emptying to the point at which 50% of the burger had left the stomach (T_{50} -lag), which provided an index of the emptying phase.

STATISTICS

As each subject acted as his or her own control,

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Accepted for publication
7 February 1991

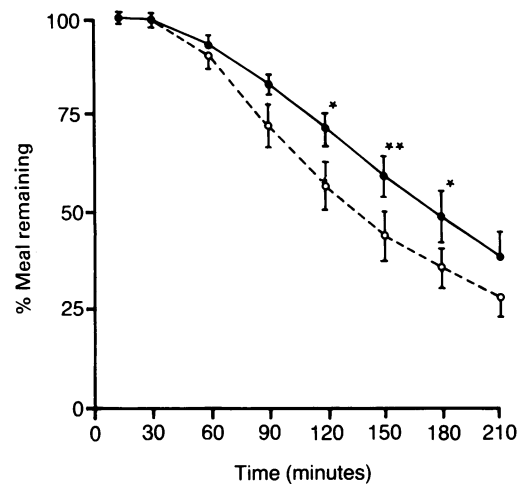


Figure 1: Gastric emptying profiles of subjects with (●) and without (○) cimetidine. Each point represents the percentage of the test meal remaining in the stomach at 30 minute intervals after ingestion (mean (SEM) of 10 studies). * $p < 0.04$; ** $p = 0.02$.

the significance of differences in gastric emptying in each subject was assessed using a paired *t* test.

Results

The profiles of gastric emptying of the test meal in the presence or absence of cimetidine are shown in Figure 1. Very little solid left the stomach during the first 60 minutes of either study, but once emptying began it occurred significantly more slowly when the subject had received cimetidine. This difference was particularly noticeable in the second postprandial hour and resulted in a significantly prolonged half-emptying time after cimetidine administration (Fig 2) (T_{50} cimetidine 187 (16) min (mean (SEM)); T_{50} no cimetidine 146 (15) min; $p < 0.01$). Interestingly, the duration of the lag period was identical in the two studies (43 (5) min in each), indicating that the retarded gastric emptying induced by cimetidine was entirely due to a shift in the slope of the emptying curve. This is supported by the observation that the time taken from the onset of emptying to the point at which half of the meal had left the stomach (T_{50} -lag) was significantly longer after cimetidine ingestion (Fig 2) (T_{50} -lag cimetidine 144 (17) min; T_{50} -lag no cimetidine 102 (14) min; $p = 0.006$).

Discussion

The results of this study show that oral administration of cimetidine slows the emptying of digestible solid food from the stomach. We know from human and canine studies that during the postprandial period solids are retained by the stomach until they have been reduced to a slurry of particles most of which are less than 1 mm in diameter.¹² Although trituration is thought to come about largely through the action of vigorous antral contractions, surgical studies in the dog have indicated that an intact 'antral mill' is not essential for this process,¹⁷ and it is therefore likely that other mechanisms may also contribute to the disruption of gastric solids. Our results suggest that peptic digestion in the stomach may

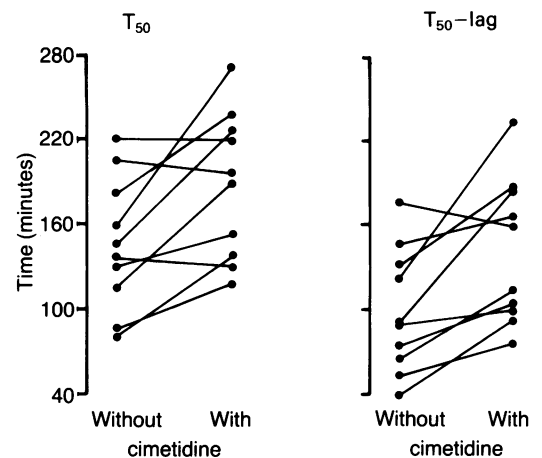


Figure 2: T_{50} and T_{50} -lag in individual subjects with and without cimetidine. T_{50} cimetidine v no cimetidine, $p < 0.01$ (paired *t* test); T_{50} -lag cimetidine v no cimetidine, $p = 0.006$ (paired *t* test).

be an important factor in this respect. When the contribution of peptic digestion to the trituration process was reduced by ingestion of cimetidine, the rate at which food was evacuated from the stomach was significantly delayed, presumably because the time taken to reduce it to particles of a sufficiently small size to leave the stomach was increased.

This delay in solid emptying resulted from a decrease in the slope of the emptying curve; ingestion of cimetidine did not alter the duration of the lag phase. Recent studies have indicated that the lag phase probably represents a period in which food is redistributed from the antrum to the fundus,⁸ and that it is terminated by the onset of coordinated antroduodenal contractility propelling chyme into the duodenum.⁹ It is an oversimplification to view this period as merely the time taken for the process of trituration to occur. It seems more logical that particle disruption is a continuous process which occurs throughout the postprandial period; if this process of digestion is impaired – for example, by the reduction in meal stimulated secretion associated with ingestion of cimetidine – the slope of the emptying curve would be expected to alter, rather than lag time increase, which is precisely what we observed.

Could there be an alternative explanation for our findings? Cimetidine also reduces the volume of gastric secretion,^{10,11} which could affect gastric emptying by altering the meal volume and the viscosity of the gastric contents.¹²⁻¹⁴ But if this volume effect was of major importance, emptying would be expected to be more rapid when subjects had received cimetidine, because smaller volume meals empty more quickly.^{15,16} Significant volume changes after cimetidine would also be expected to have a profound effect on the emptying of liquids, which is reported to be normal in human subjects receiving this drug.¹⁷⁻²⁰ Moreover, the normal pattern of liquid emptying after cimetidine also implies that the inhibitory effect of H_2 receptor blockade on gastric emptying of solids is unlikely to be due to a direct action on either fundic tone or antral contractility, both of which also contribute to liquid emptying.^{13,21,22} This argument against a direct effect of cimetidine on gastric

motility is supported by a recent preliminary report indicating that the H+K+ATPase blocker RU749 (which exerts an antisecretory effect independent of H₂ receptor antagonism) produces similar alterations in gastric emptying to those induced by cimetidine in the present study.²³ Although both cimetidine and H+K+ATPase blockers are associated with increased postprandial gastrin concentrations,^{18 20 24 25} physiological doses of naturally occurring gastrin-17 do not seem to affect gastric emptying.²⁶

Previous studies of the effects of cimetidine on gastric emptying of solid meals in humans have yielded conflicting results, some investigators reporting accelerated gastric emptying,²⁰ while others maintain that emptying is unaffected.^{17 18 27-29} Some of these discrepancies have almost certainly arisen because gastric emptying was measured in different groups of subjects – for example, patients with duodenal ulcers or normal volunteers – under unphysiological conditions²⁸ and using radioisotopes bound to indigestible markers.^{18 20} While the reduction in peptic activity induced by cimetidine might alter the emptying profile of isotope bound to digestible solids such as our beefburger test meal, it may have little or no effect on the emptying of indigestible markers. Moreover, cimetidine is unlikely to affect gastric emptying of easily disruptible test meals,¹⁷ or meals which stimulate acid secretion only weakly.

We believe that the results of this study suggest that gastric secretions have a physiological role in facilitating emptying solids in humans, probably by enhancing the disruption of digestible food into particles which are small enough to pass the pylorus.

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