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Omeprazole Causes Delay in Gastric Emptying of Digestible Meals

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We have studied gastric emptying of a solid, realistic meal (800 cal, 15% protein, 45% fat, 40% carbohydrate) in 21 healthy subjects twice, with and without a four-day pretreatment with 40 mg omeprazole. The last dose of the drug was taken 24 hr before the test, to avoid hypothetical nonsecretory side effects of the drug. Gastric emptying was measured by ultrasound of antral diameters. The results show that basal and maximal postprandial antral cross-sectional areas were the same during the two tests. A greater residual distension of the antrum was present throughout the study after the omeprazole treatment, the difference being significant at time 120 and 240. Omeprazole induced a highly significant delay in gastric emptying [control 199.6 (12.6) vs omeprazole 230.9 (12.7) min, mean (1 SEM); $P < 0.003$]. The delay was not due to a prolonged lag phase, but rather to an effect on the slope of the emptying curve. This study shows that in normal subjects omeprazole delays gastric emptying of a digestible solid meal.

KEY WORDS: gastric emptying; omeprazole; acid secretion; motility; ultrasound.

The gastric emptying of liquids is delayed when exogenous acids are added to the meal (1, 2). The effect of the inhibition of acid secretion by H_2 blockers is controversial. Different authors have reported delayed (3, 4), normal (5–8), or accelerated (9, 10) emptying of liquids, and delayed (11–13), normal (5, 8, 12, 14), or accelerated (15, 16) emptying of solids. Many hypotheses have been proposed to explain these discrepancies: use of radioactive meals that are digestible or undigestible by peptic juice; different efficacy of H_2 blockers against meal-stimulated acid secretion; and acid responses elicited by various meals in different subjects, e.g., healthy controls or ulcer patients. Other possibilities include the techniques employed or the H_2 blockers themselves. The measurement of gastric emptying is subject to many different factors. The applied potential tomography method (17) is influenced by acid secretion, and its results (4) must be accepted with caution. Even scintigraphy, which is the consensus standard for gastric emptying studies, is biased by chloridopeptic juice, which causes an elution of the marker from the labeled solid constituent (18).

H_2 blockers may alter gastric emptying by mechanisms other than the inhibition of gastric secretion. H_2 receptors present in the gastric muscular layer stimulate gastric emptying (19). Most H_2 blockers also have a vagal action due to acetylcholinesterase inhibition (20–23), which explains their direct stimulatory effect on antral motility and on gastric emptying (24, 25). The effect of H_2 blockers on gastric emptying is therefore probably the algebraic result of these contrasting actions, rather than simply the effect on acid secretion.

The methodological problems related to the drugs may in large part be offset by the use of the proton pump inhibitor omeprazole. After oral intake, the

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drug is concentrated in the intracellular canaliculi of parietal cells, where the highly acidic environment transforms it into the active protonated form (26, 27). This metabolite binds irreversibly to the canalicular Na^+, K^+-ATPase, enabling its antisecretory action to last 24–72 hr (28), which is much more than the time necessary for the complete clearance of the drug from all other body tissues (29). One may therefore study the gastric effects of acid inhibition at a time when other possible pharmacological effects of the drug should have vanished. Few scintigraphic data are available on the effects of omeprazole on gastric emptying. An early report that a single 80-mg dose did not affect gastric emptying (30) has been contradicted by other studies (presented only in abstract form) (31, 32) claiming a delayed emptying after proton pump inhibitor administration.

Ultrasound has recently been suggested as a valid alternative to scintigraphy (3, 34). This technique cannot discriminate between the emptying of solid and liquid components of the meal, but it gives an accurate overall evaluation of the emptying of complex meals. The aim of this study is to clarify the effect of hydrochloric acid inhibition on the gastric emptying of a mixed realistic meal in normal asymptomatic subjects.

MATERIALS AND METHODS

Subjects. Twenty-one healthy asymptomatic members of the medical and technical staff of our hospital (17 men, 4 women; age range 28–41 years), taking no drugs, volunteered for the study after giving informed consent. None of them had had abdominal surgery, apart from appendectomies. Women were always studied during the preluteal part of their menstrual cycle.

After an overnight fast, all subjects ate the same two-course test meal, on two different days. It consisted of 60 g of "macaroni alla bolognese" with 70 g of meat sauce and then 50 g of ham, 50 g of soft fatty cheese, one roll, and 250 ml of water. The total caloric content was 800 kcal (15% protein, 45% fat, 40% carbohydrate). The subjects were instructed to eat in 20 min, chewing as they wished. One of the two emptying studies, randomly chosen, was preceded by a four-day course of omeprazole, 40 mg in the morning. The last dose was taken 24 hr before the study.

Gastric Emptying Studies. Real-time ultrasonography was used to measure gastric antrum diameters (33) before the meal (basal), immediately after it (time 0) and at 30, 60, 120, 180, 240, and 300 min. All measurements were performed by the same operator (G.C.), blinded to the treatment given the control subjects.

There was no difference in gastric emptying time when antral sections were measured either every 30 or every 60 min (unpublished observations). The mean of three readings was calculated at each time during interperistaltic relaxation. The antral cross-sectional area was calculated assuming an elliptical shape. Ultrasound measurement of complete gastric emptying of a liquid meal has been reported to parallel the result of the scintigraphic method (35). After a solid meal, gastric emptying behaves differently. The time required for the return of antral size to the baseline as measured by ultrasound (total emptying time) can be divided into two periods: in the first the antral sections remain fairly constant (lag-phase), in the second they gradually decrease to the baseline. This behavior resembles the scintigraphic sequence of solid emptying, but it mirrors different aspects of gastric emptying. The lag phase at ultrasound does not represent the period before emptying begins, as it does in scintigraphic studies, but rather a period during which the antrum is already transporting gastric contents but maintains its size because it is continuously fed by the fundic reservoir. This view is confirmed by the simultaneous measurement of gastric emptying of a solid meal with scintigraphy and with ultrasound in nine patients; we used the same meal as in the present study, but substituting 20 g of ham with 50 g of ^{99m}Tc-labeled chicken liver. There was an almost perfect correspondence between the ultrasonographic measurement of total emptying time (calculated as described later on) and the time necessary for a 95% reduction of the radioactive counts on the gastric region. However, whereas the scintigraphic counts on the gastric region of interest continuously decreased from the maximum value toward the baseline, after a very short lag phase, the antral sections remained fairly stable at ultrasound for 30–90 min, and then gradually returned to the basal value (personal unpublished data).

The following parameters were considered in the present study: basal and maximal antral cross-sectional area, percent residual distension of the antrum at hourly intervals, time required for total emptying, slope of the emptying curve, and lag phase. The percent residual distension of the antrum at each time interval was calculated by relating the increase above the basal value of cross-sectional area to its maximal postprandial increase above the basal value. The total emptying time was calculated by the regression equation of antral sections with time, considering only the values from the maximal section to the return to the baseline (36, 37). This method allowed a more accurate and objective quantitation of the emptying times than the simple consideration of the moment when baseline values were reestablished. It was also on a continuous scale. The slope of the emptying curve was obtained by the same regression equation. The time before the onset of the rapid emptying (lag phase) was calculated by extrapolating the regression line to the antral section at time 0, as suggested for the scintigraphic method (38).

The interassay variation of the different parameters was evaluated by repeating the test twice after a standard meal in nine controls and calculating the mean coefficient of variation. The latter was found to be 6.7% for the maximal section, 9.1% for the basal section and the total emptying time, and 16.3% for the percent residual distension of the antrum after 120 min.

Statistics. Results are given as mean ± SEM. The paired difference between the results is given as mean [95% confidence interval (CI)]. The statistical significance of the differences was calculated using the Student's *t* test for paired data.

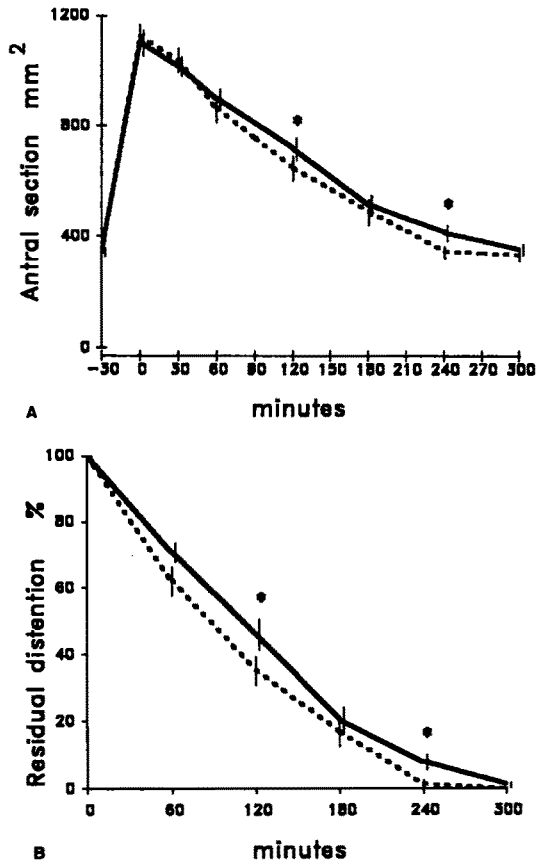

Fig 1. Variation in time of the antral cross-sectional areas (A) and the percent residual distension of the antrum (B) during the study period during the control test (dotted line) and after the omeprazole treatment (continuous line). Vertical bars represent 1 SEM. *$P < 0.05$.

RESULTS

Figure 1A shows the variation in time of the antral sections and Figure 1B that of the percent residual distension of the antrum. Basal and maximal postprandial antral sections were similar after the two meals [basal section: 343 ± 19.9 vs 345.6 ± 18.5 mm^2 after the control meal (C) and the omeprazole period (Om), respectively; paired difference 2.5 mm^2 (95% CI: −29.8 to 34.7), P = NS; maximal postprandial section: C 1165 ± 41.5 vs Om 1132 ± 43.5 mm^2; paired difference −32.1 mm^2 (95% CI: −126.7 to 62.4), P = NS]. A significant difference in antral sections between the two tests was found at time 120 (C 648.4 ± 45.8 mm^2 vs Om 719 ± 43.0, $P < 0.05$) and at time 240 (C 346.5 ± 24.8 mm^2 vs Om 415.0 ± 31.1, $P < 0.03$). A greater residual distension of the antrum was found throughout the study after the omeprazole

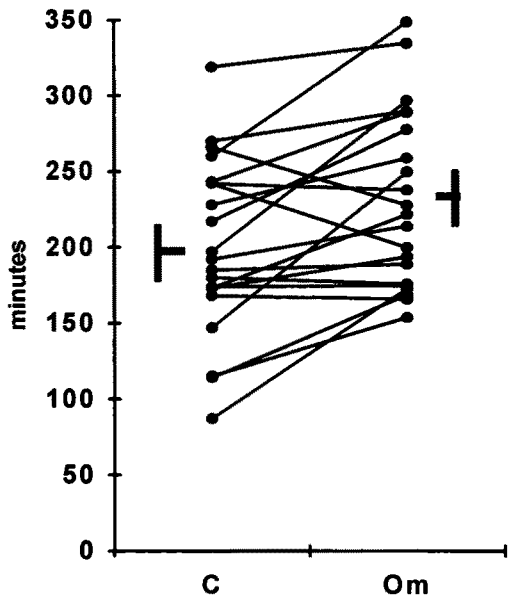

Fig 2. Time required for total gastric emptying of the test meal after the control and the omeprazole test in the individual patients. The vertical bars represent mean ± 1 SEM. The difference between the two tests was highly significant ($P < 0.003$).

treatment, the difference again being significant at time 120 and 240 min.

Figure 2 shows the total emptying time after the two tests. All subjects had a control emptying time within our normal range (less than 330 min). Omeprazole induced a highly significant delay in gastric emptying [C 199.6 ± 12.6 vs Om 230.9 ± 12.7 min; mean paired difference 31.3 min (95% CI: 12.3–50.3); $P < 0.003$]. This delay was not due to a prolonged lag phase (C 21.4 ± 6.1 vs Om 24.5 ± 7.7 min, NS), but rather to an effect on the slope of the rapid phase of the emptying curve (C 4.38 ± 0.28 mm^2/min vs Om 3.6 ± 0.23, $P < 0.03$). The apparent discrepancy in timing between Figures 1 and 2 (a longer emptying time would be anticipated when looking at Figure 1) is due to the fact that once the antral section has returned to its basal value, no further decrease occurs. The basal value for the whole group will therefore be attained only when the last patient's stomach is empty. Therefore, Figure 2 provides a better representation of the real behavior of gastric emptying.

DISCUSSION

This study shows that omeprazole delays gastric emptying of a digestible solid meal. In a previous study on the effect of omeprazole on gastric emptying,

no difference was found in emptying rate after a single, although rather high, dose of omeprazole (80 mg per os) (30). This discrepancy in results is due to the fact that the antisecretory effect of omeprazole progressively increases during the first five to seven days of treatment. The single dose used in that study may not have elicited a clinically relevant acid inhibition.

In our opinion, the delay caused by omeprazole is probably mediated by an inhibition of acid and pepsin secretion. A direct effect of the drug or its metabolites on gastric muscular cells is most unlikely, because of the long time interval that elapsed between the last administration of omeprazole and the test and the rapid clearance of the drug from the circulation and from body tissues other than the gastric parietal cells. In rats, 16 hr after administration of [^{14}C]omeprazole, the only residual radioactivity was found within the secretory canaliculi (29). Even in man, [^{14}C]omeprazole is rapidly cleared from the body, apart for the fraction bound to the canalicular Na^+, K^+-ATPase within the parietal cells (39).

We do not believe that our results could be due to a placebo effect. In fact, all our subjects were asymptomatic, and therefore they did not expect any beneficial result from treatment. The only possible interfering effect may be due to a better confidence with the ultrasound test in the second study, but this was avoided by random application of the two studies.

The hypergastrinemia caused by the omeprazole treatment is not a likely explanation for our results. In fact, our subjects were studied after a very short treatment, which had been stopped as long as 24 hr before the study. Under the same experimental conditions, it has been reported that gastrin levels only marginally increase (40) and are already reverting toward normal values (41).

Digestible solids are reduced to small particles before they can be emptied (42), mainly by the mechanical action of the antral mill, but also by the lytic action of acid and pepsin on structural proteins of food (11, 18). The delay we observed was associated with a reduction of the slope of the curve of antral size vs time, whereas the lag phase was not affected. This apparently contrasts with the hypothesis of a delayed food grinding induced by omeprazole, since it is generally assumed, at least for scintigraphy, that the lag phase represents the time interval necessary for antral grinding of the meal to begin (42). A drug impairing grinding should therefore make the scintigraphic lag phase longer. We have already explained why the ultrasonographic lag phase represents a different phenomenon. Moreover, the solid–liquid discrimination is not an all-or-none phenomenon, and relatively larger unground particles may also empty from the stomach, although at a slower rate than smaller particles (43). It is therefore not surprising if a drug that ideally delays antral grinding causes a reduction of the emptying slope rather than a lengthening of the lag phase.

In our study antral sections (both basal and postprandial) were not different after the two tests. This apparently contrasts with the fact that larger acid volumes should be secreted after the control meal, and with the recent report of a linear correlation in each subject between volume of gastric contents and ultrasonographic measurement of antral volumes (44). However, our finding is in line with the long-held notion that the reservoir region in the stomach is mainly the body–fundus; the antrum can adapt only to a limited extent (45). This view is confirmed by our finding that, when two of our volunteers ate increasing quantities of chocolate pudding, the antral cross-sectional areas increased linearly to a maximum, reached after meals 400–500 ml in volume; no further increase in antral sections was observed after larger meals (like the one used in the present study) (personal unpublished data).

Our results confirm the physiologic relevance of acid secretion on the digestion of meals. The clinical meaning of a delayed gastric emptying caused by acid inhibition in asymptomatic subjects is not clear. A delayed gastric emptying has been claimed in half of nonulcer dyspepsia patients (33), in whom antisecretory drugs represent a common form of treatment. On the other hand, a high gastric emptying rate in duodenal ulcer patients may increase the acid load to the duodenum, and this may play a role in the pathogenesis of the disease. The possible effect of antisecretory drugs on gastric emptying in these patients and in patients with gastric hypersecretion should be considered.

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