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Effects of antacid formulation on postprandial oesophageal acidity in patients with a history of episodic heartburn

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SUMMARY

Background: Heartburn self-treatment with antacids is extremely common. If the oesophagus is the primary site of antacid action, chewable antacids might raise the oesophageal pH more effectively than swallowable tablets.
Aim: To establish a model to assess postprandial acid reflux and to compare the onset and duration of action on oesophageal pH of different antacid formulations.
Methods: Twenty subjects with a history of episodic heartburn underwent eight pH monitoring sessions each for 5.5 h postprandially. One hour after consuming a meal consisting of chilli, cheese, raw onions and cola, subjects received 750 mg, 1500 mg and 3000 mg of either chewable or swallowable $CaCO_3$ tablets, an effervescent bicarbonate solution or placebo. Oesophageal and gastric pH data were collected.
Results: Mean intra-oesophageal pH remained lower than baseline for more than 1 h (pH range 5–5.5) postprandially, indicating reflux of somewhat acidic intragastric contents into the oesophagus. The onset of action on oesophageal pH was similar for all antacids (30–35 min). The duration of action on pH varied: chewable tablets and effervescent bicarbonate had relatively long durations of action (oesophagus, 40–45 min; stomach, 100–180 min); swallowable tablets had little effect.
Conclusions: The meal model used in this study dependably produced acidic gastro-oesophageal reflux. Antacids increased oesophageal pH independent of gastric pH, demonstrating that chewing antacids controls oesophageal acidity more effectively than swallowing antacid tablets.

INTRODUCTION

Heartburn occurs intermittently in more than 30% of otherwise healthy individuals and is almost always associated with acidic gastro-oesophageal reflux.[1–3] In addition, heartburn and related symptoms can be produced by certain 'provocative' foods[1, 4, 5] or by overindulgence in food and drink.[6]

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Antacids are popular 'over-the-counter' preparations for the relief of episodic heartburn, and have been assumed to assuage heartburn by neutralizing gastric acid, thus preventing subsequent acidic gastro-oesophageal reflux.[7, 8] With large antacid doses (e.g. 156 mmol), fed subjects demonstrate significantly elevated gastric pH.[2] However, more recent studies have indicated that usual doses of antacids are primarily active in the distal oesophageal lumen[9, 10] rather than by neutralization of intragastric contents. If this is indeed the case, chewable antacids should rapidly increase and sustain the elevated intra-oesophageal pH better than swallowable antacids.

The use of standardized meals eliminates a significant variable in reflux and heartburn studies. In a previous

comparative study of three meals (hamburger, chilli and sausage-biscuit),[11] the chilli meal induced more reflux episodes and more severe heartburn over the initial 45 min postprandially, as measured on a 100-point visual analogue scale, compared to the other meals.

In order to verify the site(s) of action of antacids and to determine the effects of various antacids on oesophageal and gastric pH, increasing doses of swallowable and chewable calcium carbonate tablets were studied using a refluxogenic chilli meal previously demonstrated to produce consistent effects on intragastric and intra-oesophageal pH.[11]

METHODS

This study had two goals: (i) to validate the consistency of a model designed to assess postprandial acid reflux; and (ii) to use this model to compare the onset and duration of action of acid neutralization of various antacid formulations.

Subjects

Twenty otherwise healthy subjects, 18 years or older, with a history of episodic heartburn on three or more days per week of at least 2 months' duration, were recruited.

Study design

The protocol was approved by the independent national Western Institutional Review Board of Olympia, Washington, and all subjects signed informed consents prior to the study. Subjects taking antisecretory or motility drugs within 1 week prior to study entry were excluded. Normal physical examinations and laboratory screening tests were required, including a negative pregnancy test in women of childbearing potential. The study was a single-centre, randomized, crossover, placebo-controlled study with each subject acting as his/her own control. Subjects randomly received the following eight study treatments, with study periods separated by at least 24 h:

(a) Calcium carbonate ($CaCO_3$) 750 mg chewable tablets (Tums E-X tablets, GlaxoSmithKline, UK); acid neutralizing capacity (ANC), 16 mmol;
(b) $CaCO_3$ 1500 mg chewable tablets as above; ANC, 32 mmol;
(c) $CaCO_3$ 3000 mg chewable tablets as above; ANC, 64 mmol;
(d) $CaCO_3$ 750 mg swallowable tablets (Glaxo-SmithKline, UK); ANC, 16 mmol;
(e) $CaCO_3$ 1500 mg swallowable tablets as above; ANC, 32 mmol;
(f) $CaCO_3$ 3000 mg swallowable tablets as above; ANC, 64 mmol;
(g) Na^+/K^+ bicarbonate effervescent solution with 32 mmol ANC (the effervescent bicarbonate solution) as Alka-Seltzer Gold tablets (Bayer Corporation, Consumer Care Division, USA);
(h) placebo tablets identical to the swallowable tablets.

A description of the study protocol is shown in Figure 1. Each subject remained confined to the research unit throughout each study day. Subjects consumed breakfast by 08.00 h. From 08.00 h to 12.00 h, only water was permitted. Subjects fasted from 12.00 h until the refluxogenic meal at approximately 18.00 h. At approximately 17.00 h, subjects were intubated transnasally with a dual antimony pH electrode catheter (15 cm spacing between electrodes) (Medtronics Synectics, Shoreview, MN, USA), placed to position the proximal electrode 5 cm above the upper margin of the manometrically identified lower oesophageal sphincter. All pH data were stored every 4 s for approximately 5.5 h using a portable digital recorder (Mark III Gold, Medtronic Synectics, Shoreview, MN, USA). Electrodes were calibrated to pH 1.07 and 7.01

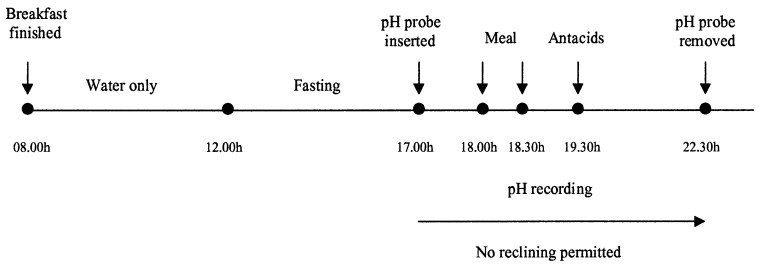

Figure 1. Diagrammatic example of the protocol for the study.

with solutions composed of 59 mM KNO_3, 27 mM KCl (pH 1.07) and 16.5 mM Tris buffer, 40 mM KNO_3, 96 mM KCl (pH 7.01). Stored data were processed in DOS mode using temperature-compensating pH recording software (Polygram for Windows, Version 2.0, Medtronic Synectics, Shoreview, MN, USA).

One hour after intubation, at approximately 18.00 h, a refluxogenic meal was consumed over 30 min.[11] The meal consisted of at least 227 g of Wendy's™ chilli supplemented with half a cup of cheddar cheese and half a cup of chopped raw onions and 340 mL Coke™ Classic cola.

Additional portions of chilli and cola were allowed (in half portions), but each subject was required to consume the same amount at each subsequent study session.

The study medication was administered 1 h postprandially at 19.30 h. Tablets were chewed, swallowed whole with water or dissolved in water and the liquid swallowed, according to the randomization treatment code. Three hours after administration of the study medication (at 22.30 h), pH recording was terminated and the pH electrodes were removed. During the 5-h observation period, subjects did not recline at an angle of more than 30° from upright.

Untoward events were monitored for safety (none occurred).

Study analyses

Intragastric pH. Intragastric pH was recorded every 4 s. All data points between 0 and 5 min (75 values) were used to calculate the mean pH for this time point. For each treatment and each subject, 5-min average oesophageal and gastric pH values were calculated and the 5-min pH averages were computed over the entire study period. These mean pH values were then averaged for all subjects at the specified time points (every 5 min) and over the specific time periods as described below. For each subject, the difference was calculated between 5-min averages for each active treatment and placebo. These differences were tested for normality using the Shapiro–Wilks procedure.[12] The differences were then analysed using a paired *t*-test if the normality assumption was not rejected, or a Wilcoxon signed-rank test if the normality assumption was rejected.

The onset of action, duration of action and mean intragastric pH over specific time periods were all computed as described below.

Onset and duration of action. Analyses were carried out separately for intragastric and intra-oesophageal pH, producing estimates of the onset and duration of action for each active treatment in the stomach and in the oesophagus. The onset of action is the time from dosing to the first statistically significant difference vs. placebo ($P < 0.05$). The offset time is the time to the first non-significant difference following the onset time. The duration of action is defined as the offset time minus the onset time.

Specific time periods before and after dosing. For each pre-treatment and post-treatment time interval, oesophageal and gastric pH averages were calculated. Mean pre-treatment pH was calculated for two time periods: 5–60 min after intubation (i.e. −145 to −90 min) and the 60 min before administration of the study medication (i.e. −60 to 0 min).

Mean pH was calculated for four post-treatment time periods: 0–30, 0–60, 0–90 and 0–120 min post-dosing. Each mean pH was calculated for intra-oesophageal and intragastric pH. Mean pH values were compared using univariate analysis of variance (ANOVA) with the factors sequence, period and treatment. All pairwise treatment comparisons were then made using Fisher's least significant difference procedure.

RESULTS

Demographics

Twenty subjects (11 males, nine females) completed all eight treatments. The mean age was 44 years, with a range of 24–63 years. At the time of study initiation, 15 of 20 subjects were using antacids for the treatment of heartburn. Ten were taking calcium-rich Rolaids and five were using the antacid Mylanta. These pre-study medications were deemed to have no significant effect on subsequent study results and all such medications were discontinued for the duration of the study period.

Pharmacodynamic data: intra-oesophageal and intragastric pH profiles

The mean 5-min oesophageal and gastric pH values over the 5.5-h study period are presented in Figures 2 and 3, respectively. Statistical analyses showed that there were no significant differences within dosage forms (i.e. various chewable doses vs. the swallowable

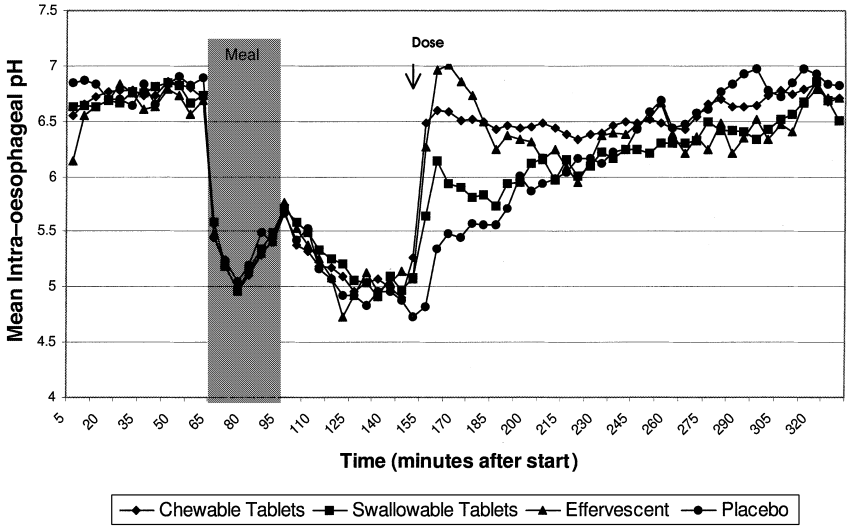

Figure 2. Plot of mean intra-oesophageal pH/5 min during the entire recording period. Subjects consumed the refluxogenic meal from 60 to 90 min after the start of the study (shown by the shaded area). Antacids or placebo were given at 150 min after the start of the study (Dose). Data for swallowable tablets and for chewable tablets have been combined.

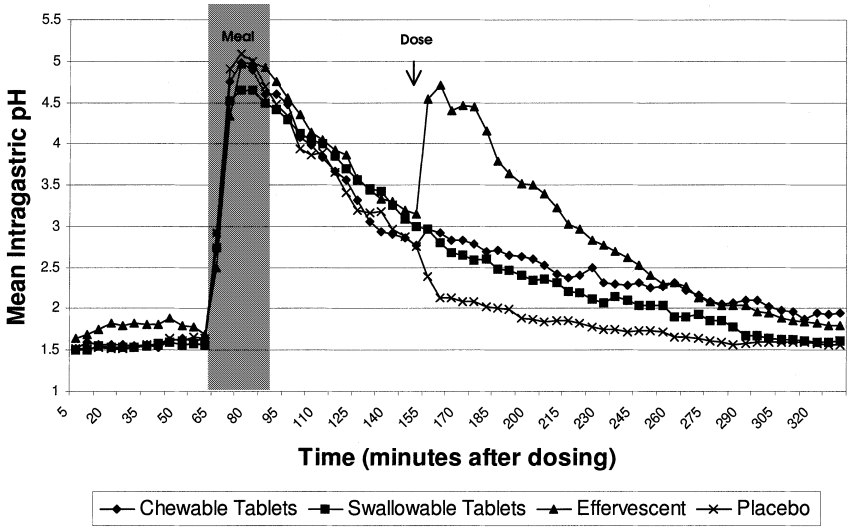

Figure 3. Plot of mean intragastric pH/5 min during the entire recording period. Subjects consumed the refluxogenic meal from 60 to 90 min after the start of the study (shown by the shaded area). Antacids or placebo were given at 150 min after the start of the study (Dose). Data for swallowable and for chewable tablets have been combined.

dosage levels). Therefore, the data for chewable tablets and for swallowable tablets have been combined for display in these figures. The 5-min oesophageal and gastric pH averages for 1 h after dosing are presented for each dosage form in greater detail in Figures 4 and 5, respectively.

Overall, effervescent bicarbonate rapidly elevated oesophageal pH compared with the other active treatments, and chewable $CaCO_3$ formulations sustained pH elevation vs. swallowable $CaCO_3$ (Figures 2 and 4; Table 1). Chewable calcium carbonate tablets and the effervescent antacid solution more effectively raised oesophageal pH than any of the swallowable formulations. In the stomach, only the effervescent bicarbonate and higher doses of chewable $CaCO_3$ appeared to reliably elevate pH compared with the other antacid treatments and placebo (Figures 3 and 5; Table 1).

Figures 4 and 5 show the 5-min means for oesophageal and gastric pH during the first hour after dosing. Figure 4 shows that, within 5 min of dosing, the effervescent solution and chewable calcium carbonate tablets produced a rise in pH in the oesophagus to above 6.5 that was sustained for up to 60 min. Swallowable calcium carbonate tablets produced a slower and less marked rise in pH that was not sustained over this period. Figure 5 shows a marked increase in intragastric pH only with the effervescent bicarbonate solution. There were less marked and inconsistent increases in intragastric pH with the swallowable and chewable forms of calcium carbonate.

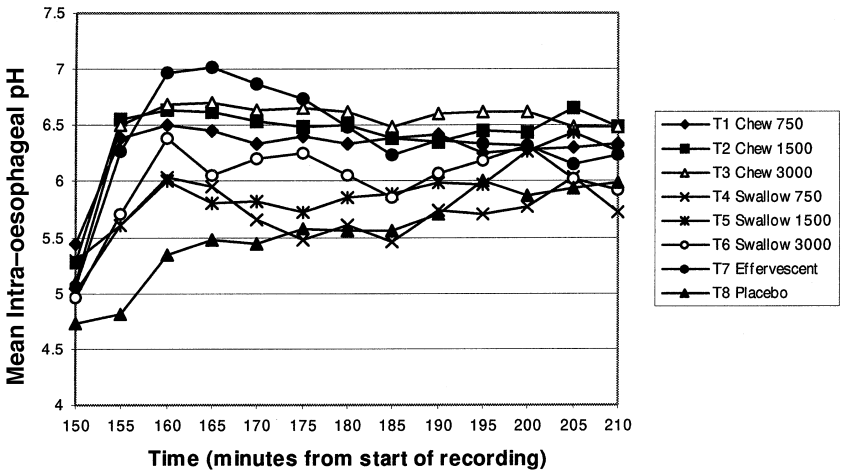

Figure 4. Mean intra-oesophageal pH during the first hour after dosing (at 150 min). Symbols for each individual treatment are shown in the diagram; Chew, chewable tablets; Swallow, swallowable tablets; Effervescent, effervescent solution.

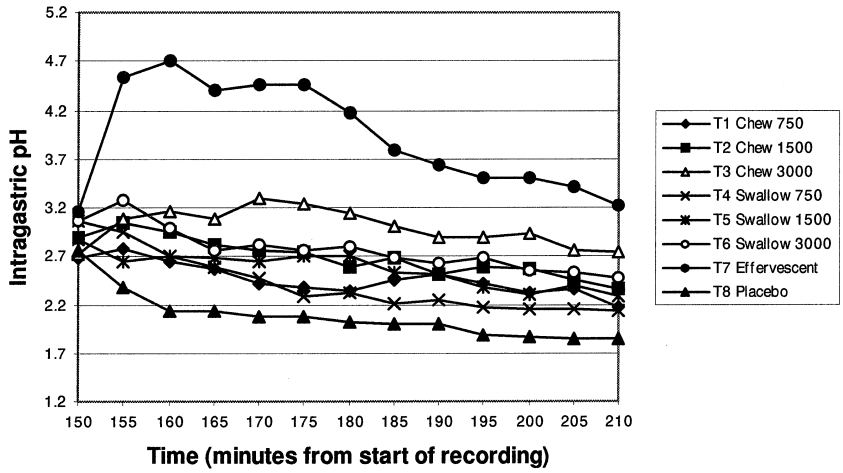

Figure 5. Mean intragastric pH during the first hour after dosing (at 150 min). Symbols for each individual treatment are shown in the diagram; Chew, chewable tablets; Swallow, swallowable tablets; Effervescent, effervescent solution.

Table 1. Mean intra-oesophageal and intragastric pH with calcium carbonate formulations, effervescent bicarbonate solution or placebo for the period 0–60 min after dosing ($n = 20$)

			Chew			Swallow		
	Placebo	Effervescent	750 mg	1500 mg	3000 mg	750 mg	1500 mg	3000 mg
Oesophageal pH	5.12	5.88*†	5.71*†	5.76*†	5.89*†	5.42*	5.38	5.56
Gastric pH	2.58	3.89*†	2.78	2.93*	3.01*	3.01*	2.92	3.10*

*$P < 0.05$ vs. placebo.
†$P < 0.05$ vs. swallowable 750, 1500 mg.

Effects of the refluxogenic meal

A previous study demonstrated that a chilli meal reliably produces reflux and heartburn in this population.[11] The present study verified the refluxogenic nature of a chilli meal. The analysis of intra-oesophageal and intragastric pH after meals is often difficult due to the inherent variability of pH: the ingested food buffers and dilutes gastric acid against a background of rapidly rising stimulated acidity as the stomach empties. However, the following generalities can be made regarding the effects of this meal on intra-oesophageal and intragastric pH.

Before test meal ingestion, the intra-oesophageal pH remained stable with a value of approximately 6.7 (mean values for all treatment groups were in the range 6.68–6.88). This fell to a value of approximately pH 5 during meal ingestion (see Figures 2 and 4, 0–60 min).

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