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ORIGINAL ARTICLE

A Glass of Water Immediately Increases Gastric pH in Healthy Subjects

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Abstract Onset of action of antisecretory agents is of pivotal importance for patients with gastroesophageal reflux disease (GERD) treated "on-demand." *Aim* To study the acute effect of acid-inhibiting drugs and water administration on gastric pH. *Method* A cross-over study was performed in 12 *H. pylori* (-), healthy subjects (6 men; mean age: 26 years). A single oral dose of the following agents was received with a wash-out period between each study: a glass of water (200 ml), antacid, ranitidine, omeprazole, esomeprazole, and rabeprazole. Gastric pH was recorded for 6 h after drug intake. *Results* Water increased gastric pH >4 in 10/12 subjects after 1 min. The time (median) needed to pH >4 was for: antacid 2 min, ranitidine 50 min, omeprazole 171 min, esomeprazole 151 min, and rabeprazole 175 min. Gastric pH >4 lasted for 3 min after water and for 12 min after antacids; it remained >4 until the end of recording in: 4/12 subjects with ranitidine, 11/12 with rabeprazole, and all with omeprazole and esomeprazole. *Conclusion* Water and antacid immediately increased gastric pH, while PPIs showed a delayed but prolonged effect compared to ranitidine.

Keywords Water antacids · PPIs · Ranitidine · Gastric pH · Onset of action

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Introduction

Up to 20% of the general population has heartburn at least twice a week [1], while 1–4% of the Western population consumes acid-suppressive drugs, most often for gastroesophageal reflux disease (GERD) [2].

The majority of symptomatic GERD patients have non-erosive reflux disease (NERD) and require treatment with acid suppressive drugs for symptom relief [3]. However, GERD is a chronic disease, and relapse of symptoms occurs frequently. Studies have shown relapse rates in up to 70–80% in patients with NERD after they finish an initial course of therapy [4, 5]. Therefore, maintenance therapy is often required for ongoing symptom control.

Treatment to relieve symptoms as they occur may be the best way to manage NERD patients. In the on-demand approach, symptoms are allowed to recur, and patients take an acid-suppressing drug when symptoms arise [6]. Since reflux symptoms are often transient, medication for on-demand therapy should have a rapid onset of action for prompt symptom relief and act long enough to prevent recurrent symptoms. Many agents are currently available for the treatment of heartburn, including antacids, H_2-receptor antagonists (H_2RAs), and proton pump inhibitors (PPIs) [7]. PPIs have been established to be potent inhibitors during chronic administration [8]; however, H_2RAs are reported to have a faster onset of antisecretory activity than that of PPIs [9–11].

We have observed that many patients with heartburn report immediate relief after drug administration. The majority of patients take acid-suppressive drugs with tap water, which usually has an alkaline pH. Thus, we hypothesized that the water could be the putative factor of the early post-administartion effect, whereas the active drug results in the later and prolonged action.

The aims of our prospective study on healthy subjects were: (1) to compare the acute effects (onset and the duration) on intragastric pH of antacids and acid-inhibiting drugs (H_2RAs and PPIs) and (2) to investigate the effect of water administration on gastric pH.

Materials and Methods

Subjects

Subjects were 12 (6 men; mean age: 26 years, range 21–30) healthy volunteers with no symptoms of gastrointestinal or other disease. None of the subjects was receiving any acid-suppresive medications or medication likely to interact with acid secretion. Volunteers with a negative ^{13}C-urea breath test for *Helicobacter pylori* infection were included in the study. All subjects were doctors or nurses of our unit and medical students who volunteered to participate in the experiments. Written informed consent was obtained from each volunteer, and the study was carried out in accordance with the Helsinki Declaration.

Study Design

The study was an open-label, randomized, crossover trial. The volunteers were fasted overnight before treatment, and study medications were randomly given in the morning. A single oral dose (swallowed with 15 ml of water) of each of the following medications was received with a washout period of at least 2 days between each study [12]: aluminium hydroxide plus magnesium oxide 400 mg, ranitidine 150 mg, omeprazole 20 mg, rabeprazole 20 mg, and esomeprazole 40 mg. Moreover, administration of 200 ml (a glass) of water was studied in all subjects. All subjects underwent pH monitoring on 6 separate days, and they were blinded for the administered drug.

Each study drug was administered 5 min after an intragastric pH value of 1–3 was continuously recorded for 5 min. Gastric pH monitoring was continued for 6 h after intake of the medication. Smoking and ingestion of food or liquids were prohibited during the pH recording periods.

Measurement of Intragastric pH

Gastric pH data were collected using an antimony pH catheter with external reference (Synectics Medical Inc.), which was inserted transnasally under local anesthesia (xylocaine spray 2%). The catheter was calibrated before insertion using standard buffer solutions of pH 1.0 and 7.0 at room temperature. It was positioned 10 cm below the proximal border of the lower esophageal sphincter (LES), and a pH value of 1–3 was recorded for 5 min. The location of LES was determined by stationary esophageal manometry.

Values for intragastric pH were recorded on a Digitrapper Mk III (Synectics Medical, Stockholm, Sweden) every 5 s. At the end of pH monitoring, the recorded data were uploaded from the data logger to a computer and were analyzed using a commercially available software program (Polygram NET, Medtronic, Denmark).

In Vitro Experiment

Gastric juice was obtained from one healthy fasting volunteer. In 20 ml of the sample of gastric juice (pH 1.3), we added different volumes (50, 100, and 200 ml) of tap water, distilled water, and two commercially available bottled mineral waters (Table 1). The pH of the used bottled water is into the range (from 6.0 to 7.9) of that characterizing nearly all the worldwide bottled mineral water.

Further Experiments with Water Administration

Further intragastric pH studies were performed in five subjects. This ancillary study was performed to clarify the early effect of water volume on the gastric pH. Each volunteer drank 50, 100, and 200 ml of water in a random order with a washout period of 60 min between each study.

Study End Points

The effects of each medication and of water were compared for the time (in minutes) required for pH to increase to >4 after their ingestion. The time for which intragastric pH remained above 4 during the 6-h monitoring period after taking the study drug and water was also measured.

Statistical Analysis

Results in the text and tables are expressed as median with ranges. Statistical analysis of paired data was performed

Table 1 In vitro experiment: effect of different volumes of various types of water on 20 ml gastric juice

Gastric acid juice pH (1.3) plus water			
	50 ml	100 ml	200 ml (a glass of water)
Tap water (pH 5.9)	1.9	2.9	5.3
Distilled water (pH 6.4)	2.1	3.1	5.4
Bottled water (Korpi) (pH 7.2)	2.2	3.1	5.6
Bottled water (Vikos) (pH 7.4)	2.3	3.2	5.8

using non-parametric tests as appropriate. A P-value <0.05 was considered significant.

Results

Time Until Intragastric pH Rises >4

Figure 1 shows the median time taken for gastric pH to increase >4 for all study drugs. Water administration immediately increased gastric pH >4 in 10/12 subjects. Antacids increased gastric pH >4 within 2 min (Fig. 2). The onset of antisecretory action of the remaining study drugs occured in the majority of subjects within 2 h of drug administration. Ranitidine provided faster increase in time to pH >4 (median: 50 min) compared to omeprazole (median: 171 min, $P < 0.05$), rabeprazole (median: 175 min, $P < 0.05$), and esomeprazole (median: 151 min, $P < 0.05$). No significant difference was found among omeprazole, rabeprazole, and esomeprazole.

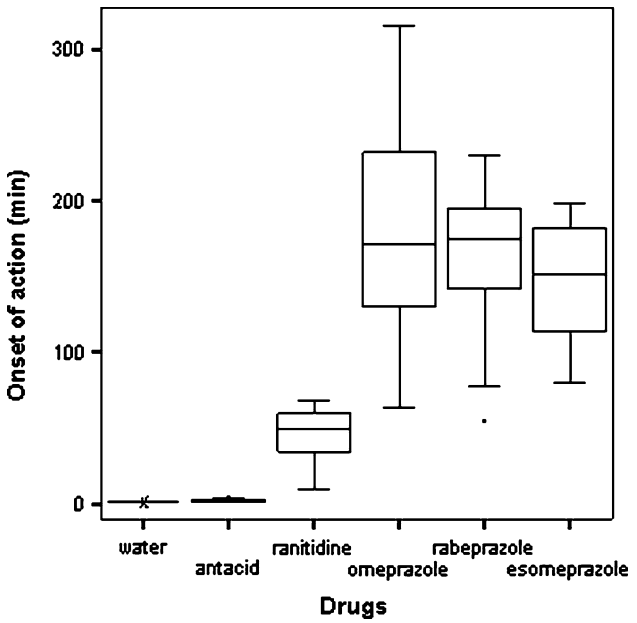

Fig. 1 Time taken until pH rise >4 (median, 25th–75th percentile and 9th–95th percentile)

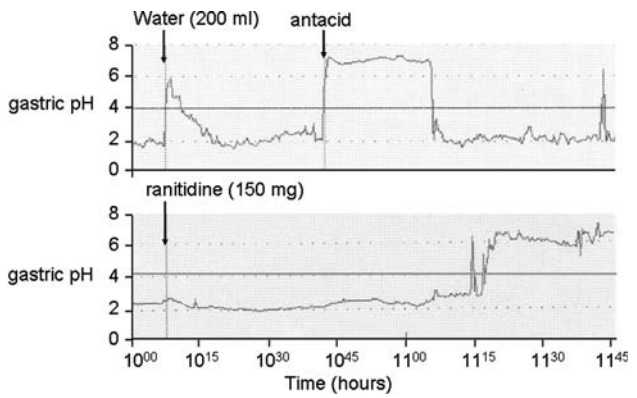

Fig. 2 Intragastric pH after administration of a glass of water and of antacids

Duration for Which pH Remained >4

Administration of water and of antacids provided a short duration of pH control (median: 3 and 12 min, respectively). Figure 3 shows median time that gastric pH remained >4. A sustained pH >4 was observed until the end of the 6-h study period in 4/12 subjects on ranitidine, in 11/12 subjects on rabeprazole, and in all subjects on omeprazole and esomeprazole. The pH was maintained >4 for shorter periods with ranitidine when compared with omeprazole, rabeprazole, and esomeprazole (median: 65 vs. 189, 185, 209 min, respectively; $P < 0.05$). No significant difference was found among omeprazole, rabeprazole, and esomeprazole.

In Vitro Experiment

Changes of fasting gastric juice pH after administration of different volumes of tap, distilled, and mineral bottled water are shown in Table 1. We observed that by increasing the volume of added water, intragastric pH increased. This increase also depended on the initial pH of the type of added water (Table 1).

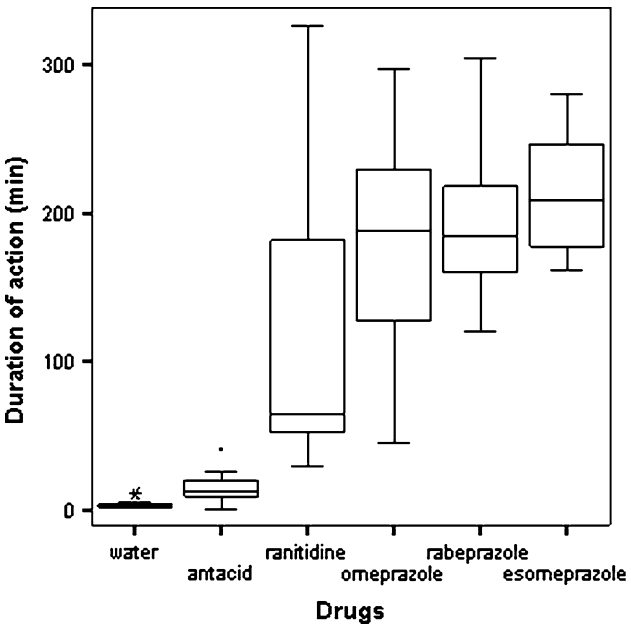

Fig. 3 Duration for which pH remained >4 (median, 25th–75th percentile and 9th–95th percentile)

Intragastric pH after Water Administration

Gastric pH remained below 4 after administration of 50 and 100 ml of water in all volunteers. In contrast, administration of 200 ml of water induced increase of pH >4 in all subjects after a median time of 1.5 min (range: 1–3). The pH remained above 4 for a short period of time (median: 2, range: 1–4 min).

Discussion

Our study investigated the acute effect on intragastric pH of water and of the early phase following an oral single dose of antisecretory drugs. Water intake and antacids showed an immediately increase of gastric pH that lasted for a few minutes. Ranitidine showed a faster onset of action than did PPIs (omeprazole, rabeprazole, and esomeprazole). In contrast, maintenance of a gastric pH above 4 was longer with all PPIs compared to ranititidine during this early period.

Although PPIs are the antisecretory drugs of choice for GERD, they are not considered good candidates for treatment of very short episodes because of the rather long lag time needed to increase intragastric pH >4 [13]. Indeed, our study showed that PPIs required longer time to increase gastric pH above 4 compared to ranitidine, and this finding is compatible with results reported by others [9– 12, 14–16]. However, our results are in contrast to studies showing that gastric pH failed to rise above 4 in the majority of subjects after PPI treatment during a 6-h period [9, 13]. We found that although PPIs required more time to start being effective, gastric pH above 4 was achieved in all subjects within a period of approximately 3 h after drug administration. Our results support the findings of a previous study showing that the onset of antisecretory action for PPIs occured within 2 h of drug administration [17].

We also found that high intragastric pH with PPIs was maintained for a longer period of time than with ranitidine. Gastric pH remained above 4 at the end of the study in all subjects with omeprazole and esomeprazole and in all except one with rabeprazole, while only four subjects with ranitidine sustained a pH >4. This finding was unexpected because previous studies have shown that during the early postadministration period, H_2RAs had a greater long-standing effect on gastric pH compared to PPIs [9–12, 14–16]. All studies were carried out in healthy, *H. pylori* (-) subjects; thus, we can speculate that differences either in doses and formulations of the drugs or in fasting status of the subjects could explain this discrepancy.

An important finding of our study was the fact that in the majority of our subjects, administration of a glass of water resulted in a rapid increase of gastric pH, comparable to that observed after antacids intake. A putative mechanism for such a phenomenon is that the water as a substance with alkaline pH eliminates gastric acid similarly to the action of antacids. Moreover, water could increase the total volume of gastric fluid, decreasing the concentration of acid in the gastric fluid. In other words, water administration seems to have a dilution effect on H^+ ions. The latter is supported by the in vitro experiments and our ancillary study. We showed that only the administration of a glass of water (200 ml) induced an increase of gastric pH above 4, whereas the smaller water volumes usually used during drug consumption are inadequate to induce an effect on gastric pH. Although a dilution effect could be an important factor for gastric pH increase, other factors might also be involved. Indeed, in our in vitro studies, we observed a large increase of pH (e.g., from 1.4 to 5.4) with the addition of 200 ml of tap water to 20 ml of gastric juice sample. Thus, on the basis of dilution alone, one would predict that the $[H^+]$ of the sample would decrease 11-fold, the dilution factor, from 40 mM to 3.6 mM, or to pH 2.4. The finding that water increased the pH to 5.4 suggests that the tap and mineral water used also had a high buffering capacity. This buffering effect might be partly explained from the presence of component elements, such as ions, acting as bases.

Keeping in mind that antacids are provided as rescue therapy in patients receiving on-demand PPI therapy [18], administration of a glass of water is likely to be clinically meaningful. Water had a rapid onset of action comparable to antacids and should be efficacious in relief of symptomatic heartburn episodes. Our study has a preliminary nature as it was performed in healthy subjects. Therefore, further studies in patients with heartburn are needed to confirm the effect of water on gastric acidity and to support a potential role of water as rescue therapy for episodic reflux symptoms during non-continuous treatment for GERD.

In conclusion, we showed that in healthy subjects, similarly to antacids, a glass of water (200 ml) increases gastric pH immediately. Although heartburn is usually associated with acidic esophageal pH and not with intragastric drop in pH <4, we could hypothesize that an increase of intragastic pH >4 is likely to contribute to the improvement of heartburn. Thus, patients who with "on-demand" therapy for episodic heartburn should swallow the pill with at least a glass of water, as this may immediately relieve GERD symptoms.

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