Alimentary Pharmacology & Therapeutics

Continuous distal oesophageal acidification decreases postprandial gastric acidity in healthy human subjects

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Publication data
Submitted 12 October 2008
First decision 1 November 2008
Resubmitted 3 November 2008, 23 November 2008
Accepted 25 November 2008
Epub Accepted Article 28 November 2008

SUMMARY

Background
Previously, we hypothesized that exposing the distal oesophagus to acid signals the stomach to decrease gastric acidity.

Aim
To test the hypothesis that exposing the distal oesophagus to acid signals the stomach to decrease gastric acidity.

Methods
Twenty-two healthy humans ingested a standard meal containing [^{14}C]octanoic acid and [^{13}C]glycine over 30 min on 2 separate occasions. Gastric pH was measured for 90 min before and 240 min after the meal. 10 mM HCl was infused continuously at 1 mL/min into either the distal oesophagus or stomach in a 2-way crossover fashion for 60 min before and 240 min after the meal. Gastric emptying of solid and liquid were determined with breath tests.

Results
Compared to gastric infusion, oesophageal infusion significantly decreased gastric acidity after the meal, but not before the meal and the magnitude of the decrease varied directly with gastric acidity. Gastric emptying of solid or liquid with oesophageal infusion was not significantly different from that with gastric infusion.

Conclusions
These findings support the hypothesis of the existence of a physiological oesophago-gastric feedback mechanism that might contribute to regulation of postprandial gastric acidity. Oesophageal acidification might decode gastric information and signal the stomach to decrease gastric acidity. Further studies are needed to assess the characteristics of such feedback mechanism in-patients with gastro-oesophageal reflux disease (GERD).

doi:10.1111/j.1365-2036.2008.03907.x

INTRODUCTION

The pathophysiology of gastro-oesophageal reflux disease (GERD) is multifactorial, including gastric motility and secretory factors, anatomical and functional alterations at the oesophago-gastric junction, oesophageal motility disorders, mucosal defense failure and altered perception of oesophageal exposure to gastric contents.[1] Gastro-oesophageal reflux is most frequent in the postprandial period and the characteristics of the refluxate depend on the volume, distribution and acidity of gastric contents.[1]

Postprandial gastric acidity is influenced by gastric acid and bicarbonate secretion and the distribution, composition and buffering capacity of the ingested meal and gastric emptying.[2] During meal ingestion, maximal acid secretion may be achieved by removing the inhibitory influence of somatostatin on G and ECL cells and directly stimulating acid and gastrin secretion.[2] When food enters the stomach, the protein component stimulates the antral G cells to release gastrin, which circulates and stimulates the proximal body region to secret acid. The amount of gastrin released by the antral G cells is regulated by intragastric pH and this serves as a negative feed-back control to prevent hypersecretion of acid. When the pH of gastric juice falls, this inhibits further release of gastrin. This inhibitory influence of intragastric acid is mediated by stimulating the release of somatostatin from the D cells situated close to the antral G cells. The buffering effect of the meal is not homogeneous throughout the stomach. Pull-through gastric pH measurements have demonstrated a short gastric segment not buffered extending 2 cm below the LES, the so called the 'acid pocket'.[3] As the meal empties the stomach, a number of paracrine and neural pathways are activated to restore the inhibitory influence of somatostatin in the fundus/body and antrum and hence restrain acid secretion.[2]

A limited amount of postprandial gastro-oesophageal reflux is considered a physiological phenomenon that can be observed at all ages.[4] The role of such 'physiological' reflux remains unknown. In a previous study, it was observed that the fractal pattern of both oesophageal pH and gastric pH over time is self-similar across at least 3 orders of magnitude in that the pattern appears approximately, but not exactly, identical at different scales. Moreover, the fractal scaling properties of oesophageal pH and gastric pH in subjects with GERD at baseline or after treatment with a proton pump inhibitor were essentially the same as those in normal subjects.[5] This study[5] also posed the hypothesis that these fractal patterns might encode information regarding the acidity of the gastric contents and that the physiological function of gastro-oesophageal reflux might be to inform the oesophagus regarding gastric acidity. If gastric acidity is high, the oesophagus might decode the fractal information and then through a negative feedback action on the stomach, cause a decreased gastric acidity.

The present study was designed to test this hypothesis by continuously infusing HCl into the distal oesophagus of healthy human subjects and measuring gastric pH and gastric emptying of solid and liquid. The present study found that oesophageal acidification decreased postprandial but not basal gastric acidity with no change in gastric emptying of solid or liquid.

METHODS

The study was conducted at the UZ Gasthuisberg Leuven and the Center for Gastroenterological Research, K.U.Leuven, Belgium. Subjects were 24 healthy adult males, aged 19–44 years with no gastrointestinal symptoms. The study was approved by the Ethics Committee of University of Leuven, Leuven, Belgium. All subjects enrolled in this study gave written informed consent.

Exclusion criteria were: no blood donation within 6 weeks of the study; no gastric antisecretory medication (including OTC antisecretory medication), agents that affect gastric motility or antacids within 14 days of the study and no alcohol consumption within 24 h of the study.

Sample size was determined from previous measurements of gastric pH in healthy subjects. With a type I (alpha) error of 0.01, a type II (beta) error of 0.10, a standard deviation for time for postprandial gastric pH < 2 of 52 min and a correlation coefficient of 0.60, a sample size of 20 subjects would be sufficient to detect a difference between time for postprandial gastric pH<2 of 42 min employing a randomized, 2-way crossover design.

Study design

An infusion catheter, external diameter 2 mm, was placed 5 cm above (oesophageal infusion) or 12 cm below (gastric infusion) the manometrically defined upper border of the lower oesophageal sphincter. A gastric pH recording electrode was placed 10 cm below

the manometrically defined upper border of the lower oesophageal sphincter.

The sequence of events for each subject was as follows.

T = 0 minutes: begin gastric pH recording.

T = 30 minutes: begin infusion of distal oesophagus or upper stomach with 10 mM HCl at a rate of 1 mL/minute (Peristaltic Perfusion Pump, IVAC, San Diego, CA USA).

T = 30 minutes: collect 2 sequential 15-minute baseline breath samples.

T = 90 minutes: ingest standard meal containing [^{14}C]octanoic acid plus [^{13}C]glycine over 30 minutes and suspend infusion.

T = 120 minutes: resume infusion and collect sequential 15-minute breath samples to measure [$^{13}CO_2$, $^{14}CO_2$]. Excretion of [$^{13}CO_2$] will reflect gastric liquid emptying and excretion of [$^{14}CO_2$] will reflect gastric solid emptying.

T = 360 minutes: stop infusion, gastric pH recording and collection of breath samples.

Each subject was assigned to undergo oesophageal or gastric infusion in a randomized, two-way cross-over fashion with at least 7 days between infusions.

Measurement of gastric pH

Gastric pH data were recorded using a disposable pH catheter (Medtronic Synectics, Shoreview, MN, USA) with a single antimony pH electrode and external reference. The electrode was calibrated to pH 1.07 and 7.01 using solutions (obtained from Medtronic Synectics) composed of pH 1.07, 59 mM KNO_3, 27 mM KCl and pH 7.01, 16.5 mM Tris, 40 mM KNO_3, 96 mM KCl. The pH catheter was connected to a portable data storage unit (Ambulatory UPS 2020, MMS, Enschede, The Netherlands) that recorded gastric pH every 5 s. Data were transferred from the portable data storage unit and processed using software designed for pH recordings (MMS). All pH values were adjusted for the difference between the temperature at which the electrodes were calibrated (25 °C) and the recording temperature (37 °C).

Measurement of gastric emptying

Gastric emptying of solids and liquids was determined using the [^{14}C]octanoic acid and [^{13}C]glycine breath tests.[6–10] The test meal included an egg, the yolk of which contained 74 kBq of [^{14}C]octanoic acid sodium salt (DuPont, NEN Research, Boston, MA, USA) and 300 mL of water in which 100 mg [^{13}C]glycine (99% enrichment; Isotec, Miamisburg, OH, USA) was dissolved. Breath samples were obtained before the meal and at 15-min intervals for a period of 240 min postprandially. At each sample time, the subject exhaled into two different containers for measuring exhaled ^{13}C and ^{14}C. One was a liquid scintillation vial containing 2 mL of 1 M hyamine hydroxide and 2 mL of ethanol together with one drop of thymolphtalein solution. This amount of hyamine is neutralized by 2 mM of CO_2. The end point of neutralization is indicated by decolouration of the indicator. After decolouration, 10 mL of scintillation cocktail (Hionic Fluor, Packard, Meriden, CT, USA) was added and ^{14}C was determined by liquid scintillation counting (Packard Tri-Carb Liquid Scintillation Spectrometer, model 3375, Packard Instrument Company, Downers Grove, IL, USA). For [^{13}C]O_2 measurements, breath was collected by blowing directly into a tube. The ^{13}C breath content is determined by on-line gas chromatographic purification-isotope ratio mass spectrometry (ABCA, Europe Scientific, Crewe, UK).[6–10]

Standard meal

The standard meal consisted of 125 g steak, 200 g cooked potatoes, 200 g carrots, 50 g lettuce, one scrambled egg, 300 mL water, 200 mL pudding (skim milk with sugar). It contained 606 kcal, 47.8 g protein (32%), 9.1 g fat (13%) and 83.3 g carbohydrate (55%).

The meal was homogenized and titrated to pH 2 with 0.1N HCl as described previously.[11] The mean pH of the homogenized meal was 6.27 $\pm$ 0.09 (mean $\pm$ s.d.; n = 4) and the amount of acid required to decrease the pH of the meal to pH 2 was 157 $\pm$ 15 mmol.

Analytical procedures

Median gastric pH was calculated for each minute of the 360-min recording period and these values were used to calculate median gastric acid concentration (mM) using the equation 1000×10^{-pH}. Although we refer to the current measurements as acid 'concentration', the pH electrode actually measures hydrogen ion 'activity'. Others have documented the extent to which hydrogen ion concentration can differ from hydrogen ion activity, particularly in the presence of other ions and have developed methods to adjust hydrogen ion activity to hydrogen ion concentration.[12, 13]

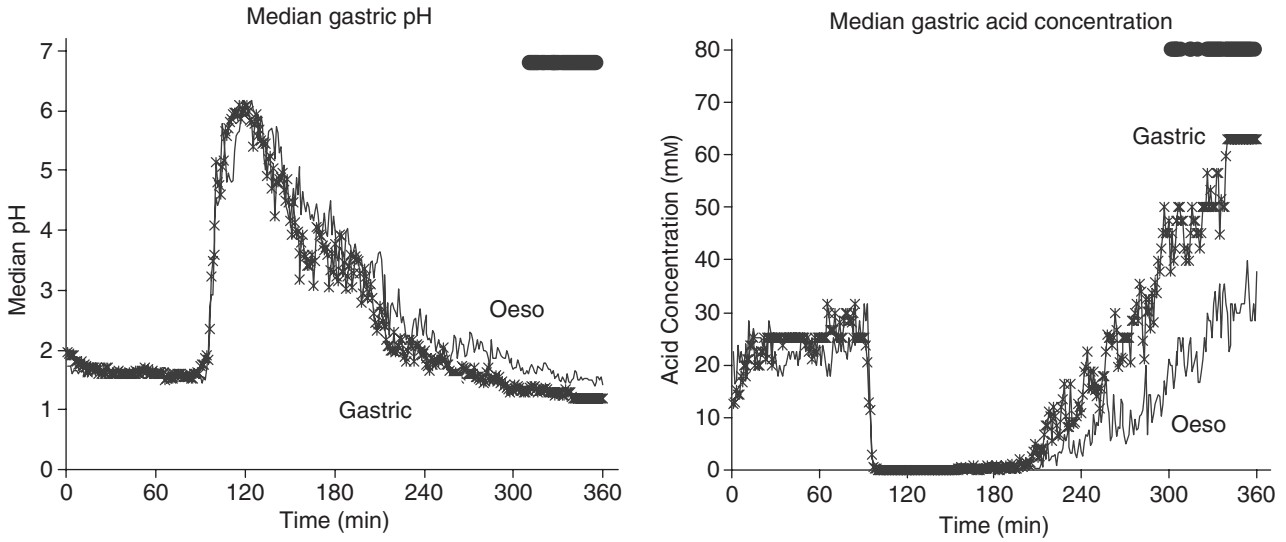

Figure 1. Gastric pH and gastric acid concentration with oesophageal or gastric infusion of 10 mM HCl. Median gastric pH and acid concentration were calculated for each minute of the 360-min recording period. The solid symbols in the upper right of each panel indicate times when values are significantly different by paired *t*-test at $P < 0.01$. Results given are from 22 subjects. In the left panel, the upper curve represents oesophageal (Oeso) acidification, while the lower panel represents gastric acidification. In the right panel, the upper curve represents gastric acidification, while the lower curve represents oesophageal acidification.

We calibrated the electrodes to pH 1 and 7 using polyelectrolyte solutions provided by the manufacturer, which results in measured hydrogen ion activity more closely approximating the hydrogen ion concentration. We did not adjust the measured hydrogen ion activity. Integrated gastric acidity, which is the time-weighted average of the gastric acid concentration, was calculated as described previously.[14] Values for integrated acidity were summed cumulatively every 5 s and the resulting value is expressed as mM × time, i.e. mmol.h/L. Meal-stimulated gastric acid secretion was determined as described previously[11] and was calculated from the amount of acid needed to titrate the homogenized meal to pH 2 *in vitro* (157 mmol) and the time required for the pH of the meal to decrease to pH 2 *in vivo*.

Results of the $^{13}CO_2$ and $^{14}CO_2$ breath tests for gastric emptying were expressed as the percentage $^{13}CO_2$ and $^{14}CO_2$ excreted per hour as described previously.[6–10] For both carbon labels, CO_2 production was assumed to be 300 mmol/m^2 of body surface per hour. Three parameters were derived from $^{13/14}CO_2$ excretion curves: the gastric emptying coefficient (GEC), a global index for the gastric emptying rate, the half emptying time (*T*1/2) and the lag phase (Tlag).

Statistical analyses

Statistical analyses were performed using Microsoft Excel or GRAPHPAD for Windows software.

RESULTS

Two subjects withdrew from the study, one because of heartburn with oesophageal acid infusion and the other because of difficulty tolerating intubation. The following analyses are based on results from 22 subjects.

Figure 1 illustrates that during the basal period, gastric acidity with oesophageal infusion of HCl was not significantly different from that with gastric infusion of HCl. After the meal, however, gastric acidity with oesophageal infusion of HCl was significantly lower than that with gastric infusion of HCl beginning at approximately 300 min or 180 min after the end of the meal.

Figure 2-left plots the number of subjects with a higher median gastric pH with oesophageal infusion than with gastric infusion for each minute of the study period. During the 90-min basal period, more subjects tended to have higher median gastric pH with gastric infusion than with oesophageal infusion. In contrast,

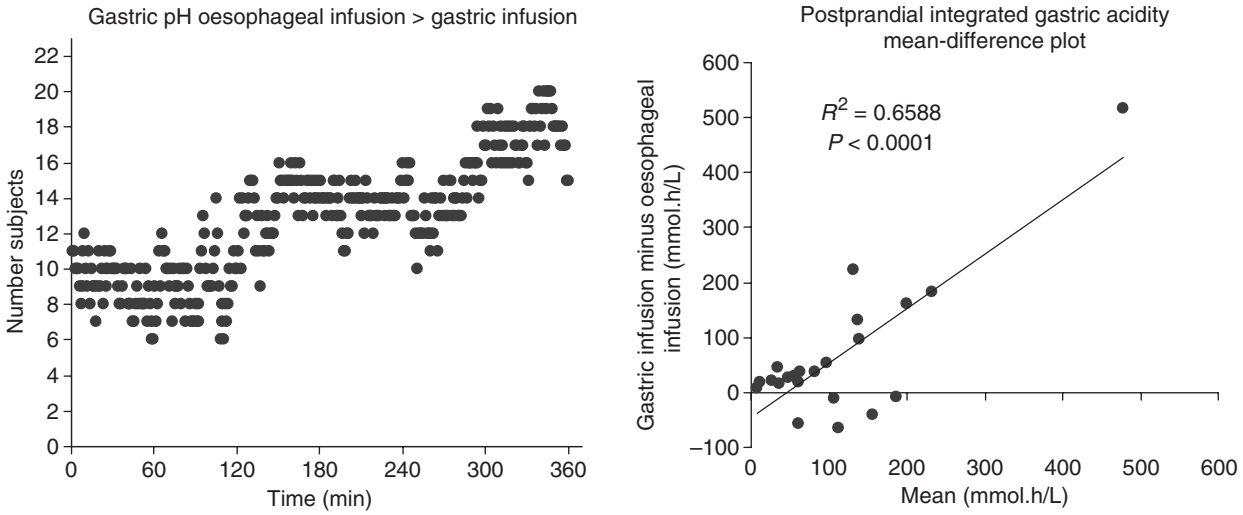

Figure 2. Number of subjects with higher gastric pH during oesophageal infusion than during gastric infusion (left panel) and mean-difference plot of integrated gastric acidity during the 240-min postprandial infusion period (right panel). In the left panel, median gastric pH was calculated for each minute of the 360-min recording period. In the right panel, the solid diagonal line is the least-squares regression line. Results in both panels are from 22 subjects.

after the meal (120–360 min), more subjects tended to have higher median gastric pH with oesophageal infusion than with gastric infusion. Using a flat prior probability that considered all values from 0 to 1.0 to be equally probable,[15] the Bayesian posterior probability that a distribution of 16:6 subjects is different from 11:11 is 0.977. Figure 2-left shows that a clear majority of subjects have a higher gastric pH with oesophageal infusion during the last hour of the study period in agreement with the data in Figure 1.

Figure 2-right is a mean-difference plot that makes it possible to examine the relationship between the magnitude of an effect (the difference) and the magnitude of the values (the means). Figure 2-right shows that 17 of the 22 subjects had lower postprandial integrated gastric acidity during oesophageal infusion than during gastric infusion (the values above zero on the vertical axis). Moreover, there was a clear relationship between the magnitude of the difference in integrated acidity with the two infusions and the magnitude of the mean of the two values for integrated acidity. That is, the higher the value of integrated gastric acidity, the greater the reduction in gastric acidity produced by oesophageal acid infusion.

Figure 3-left is a Kaplan–Meier plot of the time at which gastric pH decreased to pH 2 after the meal. The median time with gastric infusion was 289 min and with oesophageal infusion was 349 min – a difference of 60 min (P = 0.001; log-rank test). Previously,[11, 16] we reported that meal-stimulated gastric acid secretion can be calculated from the time required for the pH of a meal to decrease to 2 and the amount of acid required to decrease the pH of the meal to 2 *in vitro*. In Figure 3-right, meal-stimulated gastric acid secretion with oesophageal infusion is plotted vs. meal-stimulated gastric acid secretion with gastric infusion. Values below the identity line indicate that acid secretion with oesophageal infusion is lower than the corresponding value with gastric infusion and the vertical distance from the identity line indicates the magnitude of the difference between the two values. Meal-stimulated gastric acid secretion with oesophageal infusion was significantly less than that with gastric infusion (P = 0.0015; Wilcoxon matched-pairs test). We recognize that some of the values for meal-stimulated gastric acid secretion with gastric infusion are in the range usually only seen in Zollinger–Ellison Syndrome. These high values were associated with the most rapid decreases in postprandial gastric pH, but because the pH recordings were technically satisfactory, we included the data in the analyses. As illustrated in Figure 3-left, six subjects failed to decrease gastric pH to below pH 2 after the meal with oesophageal infusion and one subject with gastric infusion. In calculating results in Figure 3-right we assumed that gastric pH in these subjects first decreased to below pH 2 at 360 min. Thus, we overestimated meal-stimulated gastric acid secretion in these subjects and the

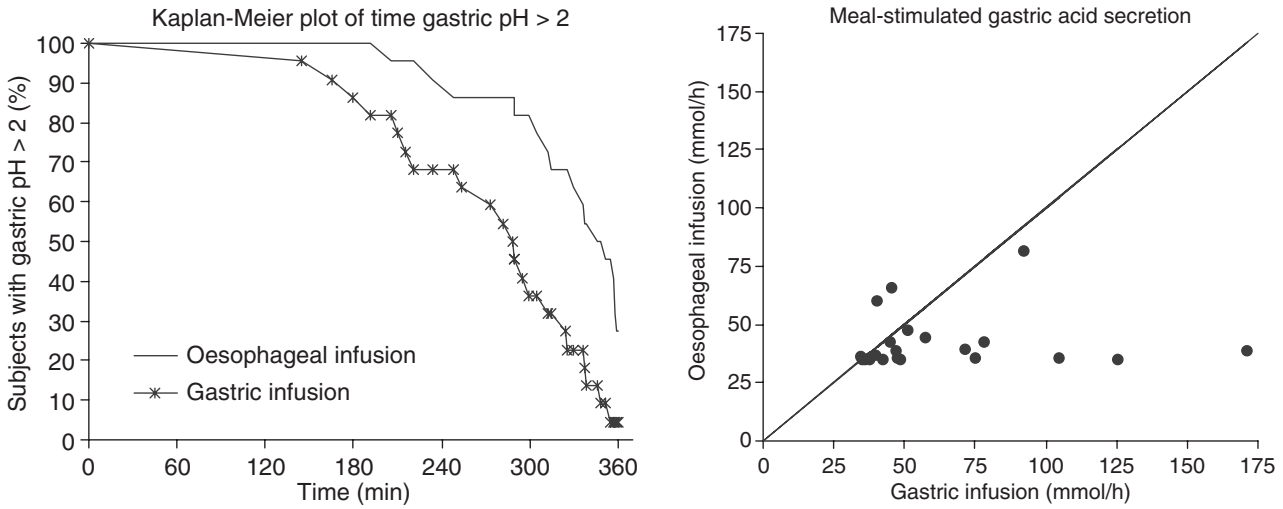

Figure 3. Kaplan–Meier plot of time to gastric pH < 2 (left panel) and meal-stimulated gastric acid secretion (right panel). In the left panel, results are for the time at which postprandial gastric pH first remains below 2 for the remainder of the recording. In the right panel, gastric acid secretion was calculated by dividing 157 mmol (the amount of acid required to decrease the pH of the standard meal to pH 2 *in vitro*) by the number of hours after the beginning of the meal that gastric pH first remained below 2 for the remainder of the recording. The solid diagonal line is the identity line. Values that are lower with oesophageal infusion will lie below the line and vice versa. Results in both panels are from 22 subjects.

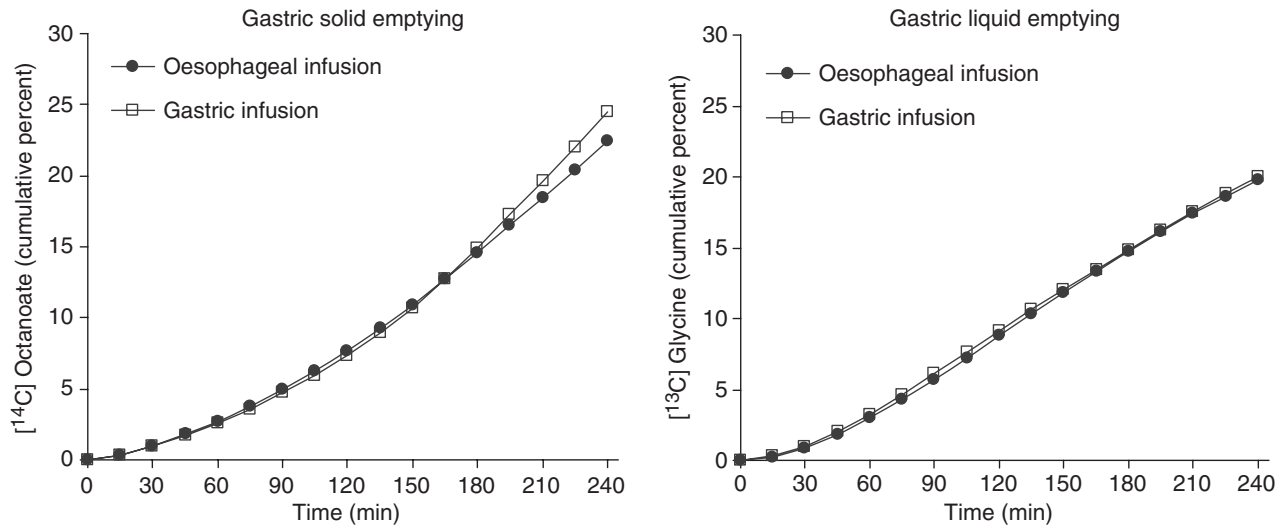

Figure 4. Gastric emptying of solids or liquids with oesophageal or gastric infusion of 10 mM HCL. Results given are means from 22 subjects.

difference between values with oesophageal and gastric infusion is likely to be greater than that illustrated in Figure 3-right.

The results in Figure 4 and Table 1 show that gastric emptying of solid or liquid with oesophageal infusion did not differ significantly from that with gastric infusion.

Figure 1 illustrated that postprandial gastric pH with oesophageal acid infusion was not significantly different from that with gastric acid infusion until approximately 180 min after beginning the infusion. We considered the possibility that this delay was due to the buffering effect of the meal on gastric pH, not a delayed onset of the effect of oesophageal infusion. To

Table 1. Parameter values for gastric emptying of solid and liquid with oesophageal or gastric infusion of HCl

	Solid emptying		Liquid emptying	
	Oesophageal infusion	Gastric infusion	Oesophageal infusion	Gastric infusion
GEC	1.45 (0.17)	1.33 (0.15)	2.16 (0.05)	2.10 (0.07)
T1/2 (min)	290 (24)	291 (25)	140 (13)	160 (17)
Tlag (min)	177 (17)	195 (16)	–	–

There was no lag phase for liquid emptying. Results are means (S.E.M.) from 22 subjects. None of the parameter values with oesophageal infusion differed significantly from corresponding values with gastric infusion ($P > 0.35$ by paired t-test).

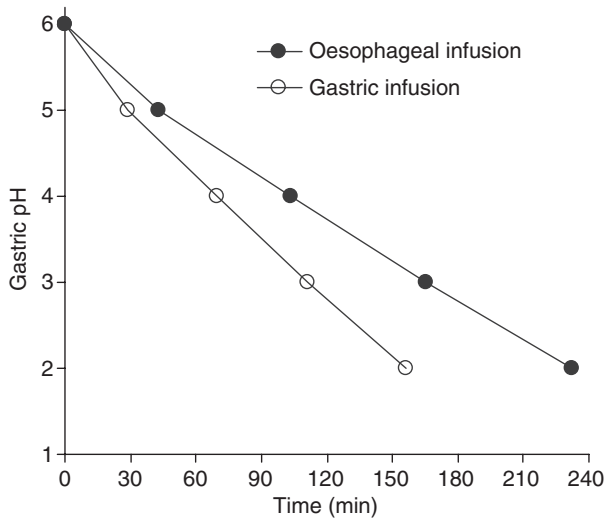

Figure 5. Theoretical effects of oesophageal and gastric infusion of 10 mM HCl on gastric pH *in vivo*. Results were calculated using the mean values for meal-stimulated gastric acid secretion given in Figure 3-right (62 mmol/h with gastric infusion and 42 mmol/h with oesophageal infusion) and the amount of HCl required to titrate a homogenized meal *in vitro* from pH 6 to 5 (30 mmol), 5 to 4 (42 mmol), 4 to 3 (43 mmol) and 3 to 2 (47 mmol). The theoretical calculations assumed that gastric secretion remained constant over the 240-min period and ignored gastric emptying.

examine this possibility, we used data from *in vitro* titration of a meal that was similar in composition to the one ingested by subjects in this study and values for meal-stimulated gastric acid secretion with oesophageal and gastric infusion illustrated in Figure 3-right to calculate theoretical values for the time as which gastric pH would reach pH 5, 4, 3 and 2. As an example of how the data in Figure 5 were calculated, the gastric secretory rates were 62 mmol/h with gastric infusion and 42 mmol/h with oesophageal infusion. *In vitro*, 30 mmol of HCl are required to decrease the pH of the meal from 6 to 5. Thus, with gastric secretion of 62, the meal would reach pH 5 after 30/62 or 0.48 h (29 min) and with gastric secretion of 42, the meal would reach pH 5 after 30/42 or 0.71 h (43 min). The theoretical values in Figure 5 illustrate that the two curves for gastric pH become more separated over time and offer support for the explanation that the 180-min delay before values are significantly different with the two infusion results from the buffering effect of the meal on gastric pH. Our theoretical calculations ignored emptying of the meal; however, as emptying was the same with the two infusions, it would be unlikely to influence the differences in theoretical results. We also assumed that gastric acid secretion was constant over the 240-min postprandial period. In one study[17] in which meal-stimulated gastric acid secretion in healthy subjects was measured by intragastric titration of a steak meal, acid secretion increased and became maximal at 90 min and then decreased progressively so that by 240 min, secretion was still approximately 25% of maximal. Using values for gastric acid secretion measured by intragastric titration and assuming a constant 32% decrease in secretion with oesophageal infusion, theoretical values for gastric pH showed the same pattern for the difference between oesophageal and gastric infusion as that illustrated in Figure 5.

DISCUSSION

This study was designed to test the hypothesis that exposing the distal oesophagus to a high acid concentration will decrease gastric acidity. We considered

three possible mechanisms by which oesophageal acid exposure might decrease gastric acidity: by increasing gastric emptying, by decreasing gastric acid secretion or by increasing gastric bicarbonate secretion. Our results exclude increased gastric emptying, because with oesophageal acid infusion, gastric emptying of solid or liquid was the same as with gastric acid infusion. Oesophageal acid infusion decreased gastric acidity after a meal but not during baseline. It may be that the effect of oesophageal acidification is specific in some way for the postprandial period. On the other hand, it may be that the effect is simply not of sufficient magnitude to alter baseline gastric pH. If so, the effect would resemble that of proton pump inhibitors on gastric pH in that they have little or no detectible effect on fasting gastric pH,[18, 19] but substantial effects on postprandial gastric pH (e.g.[20]). We have interpreted the effects of oesophageal acid infusion on gastric acid concentration as reflecting decreased meal-stimulated gastric acid secretion. This should be understood, however, to mean 'net' gastric acid secretion, because our results cannot distinguish between increased secretion of bicarbonate and decreased secretion of hydrochloric acid.

We considered the possibility that gastric acidity is lower with oesophageal infusion than with gastric infusion because gastric infusion of acid itself increases gastric acidity. We believe that there are several findings that argue against this possibility. First, the amount and rate of acid entering the stomach are the same with the two different infusions - the only difference is the site of initial administration. Second, the fasting stomach contains approximately 50 mL of fluid at pH 1.2 (3.15 mmol).[21, 22] Infusing 0.6 mmol of HCl during a 60-min period would not be expected to produce an important effect on basal gastric pH. In addition, the infused HCl would be expected to increase basal gastric pH, not decrease it, because the pH of the infusate (pH 2) is higher than the pH of the gastric fluid (pH 1.5 in Figure 1-left). Third, the standard meal has a volume of approximately 800 mL and after homogenization has a pH of 6.27 and requires 157 mmol of HCl to decrease the pH to pH 2. Postprandial gastric acid secretion is approximately 500 umol/min[11, 16] and infusing 2.4 mmol of HCl over a 240-min period (10 umol/min) would not be expected to produce an important effect on postprandial gastric pH.

The present results are consistent with the hypothesis that one of the physiological functions of gastro-oesophageal reflux might be to inform the oesophagus regarding gastric acidity. If gastric acidity is too high, the oesophagus decodes the information encoded in the fractal pattern of gastric pH described previously[5] and decreases net gastric secretion, thereby decreasing gastric acidity. This hypothesis is also consistent with our finding that the greater the magnitude postprandial integrated gastric acidity, the greater the decrease in integrated gastric acidity caused by oesophageal acidification. The stomach secretes sodium bicarbonate as well as hydrochloric acid and decreased gastric acidity could be produced by increased bicarbonate secretion or decreased hydrochloric acid secretion.[23]

Other reflexes triggered by oesophageal acidification are consistent with our findings. Acid perfusion of the distal oesophagus in humans, increases bicarbonate secretion from the salivary gland and this effect can be blocked by a muscarinic cholinergic receptor antagonist.[24, 25] Furthermore, patients with GERD sometimes experience 'water brash', a sudden, profuse salivary secretion of water and bicarbonate associated with acid reflux. Interestingly, one subject in the present study spontaneously reported increased secretion of saliva with oesophageal HCl infusion, but not with gastric HCl infusion. Finally, *in vivo* ligation of the abdominal oesophagus in rats has been reported to decrease gastric acidity.[26]

One limitation of this study is that the continuous infusion of 10 mM HCl into the distal oesophagus does not reproduce the physiological conditions with spontaneous gastro-oesophageal reflux. Typically after a meal, distal oesophageal pH fluctuates between 1.5 and 6.5 instead of being exposed to a constant pH of 2 as in this study.[27, 28] In fact, postprandial oesophageal pH values have a power-law distribution with pH 2 occurring at a very low frequency.[27] We chose continuous exposure of the distal oesophagus to 10 mM HCl, however, because we wanted to make sure that we would not miss an effect of oesophageal acidification because of insufficient stimulus. In view of our present findings, one might consider examining the effect on gastric acidity of abolishing oesophageal acid exposure by repeating this study using 10 mM $NaHCO_3$ in place of HCl.

Another limitation of this study is that we measured gastric pH in the main body of the stomach. After a meal, however, there is a pocket of acid in the upper portion of the stomach at and just below the gastro-oesophageal junction that escapes the buffering effect of the ingested meal.[3, 28] This pocket is the likely source of acid that refluxes into the oesophagus after a meal; however, the relationship between gastric acid

secretion and the acidity in the pocket is not known. If the physiological function of gastro-oesophageal reflux is to signal the stomach to decrease gastric acid secretion, one would expect that this hypothetical signal would decrease acidity in the acid pocket. Our theoretical calculations illustrate that the buffering effect of a meal can attenuate the effect of inhibition of gastric acid secretion on gastric pH. Thus, inhibition of gastric acid secretion might produce a greater increase in the pH in the unbuffered acid pocket than in the pH in the main body of the stomach.

If limited postprandial gastro-oesophageal reflux has a physiological function that contributes to regulation of gastric acidity, GERD subjects might have an impaired regulatory feedback mechanism that results in increased gastric acid that can reflux from the stomach into the oesophagus. In this regard, previous studies have shown that postprandial integrated gastric acidity in GERD subjects is significantly higher than that in normal subjects.[16]

ACKNOWLEDGEMENTS

Declaration of personal interest: Dr Gardner is President of Science for Organizations, Inc., a company that provides consulting services to pharmaceutical and biotechnology companies (http://www.scifororg.com). *Declaration of funding interests*: This research was conducted with support from the Investigator-Sponsored Study Program of AstraZeneca.

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