

# Duodenal pH in health and duodenal ulcer disease: effect of a meal, Coca-Cola, smoking, and cimetidine

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**SUMMARY** Intraluminal duodenal pH was recorded using a combined miniature electrode and logged digitally every 10 or 20 seconds for five hours (basal/meal/drink) in eight control subjects and 11 patients with duodenal ulcer (five on and off treatment with cimetidine). Over the whole test there were no significant differences in duodenal mean pH or log mean hydrogen ion activity (LMHa) between control subjects and patients with duodenal ulcer, but there were significantly longer periods of duodenal acidification (pH <4) and paradoxically more periods of duodenal alkalinisation (pH >6) in the duodenal ulcer group compared with controls. After a meal duodenal mean pH and LMHa fell significantly in both controls and patients with duodenal ulcer, with more periods of duodenal acidification and alkalinisation in the duodenal ulcer group. An exogenous acid load (Coca-Cola) significantly increased the periods of duodenal acidification, and reduced alkalinisation, in both groups. Cimetidine significantly increased mean pH and LMHa and abolished the brief spikes of acidification in four of five patients with duodenal ulcer. Peak acid output (but not basal acid output) was significantly correlated with duodenal mean pH and LMHa but not with the periods of duodenal acidification. Smoking did not affect duodenal pH in either group.

The role of gastric acid hypersecretion in duodenal ulcer disease is well established,<sup>1</sup> but the relative importance of acid load and acidity at the site of ulceration within the duodenum<sup>2</sup> remains poorly documented, largely because of technical and methodological problems.<sup>3,4</sup> A reliable method of digitally recording intraluminal duodenal pH, under near normal conditions, has been developed<sup>5,6</sup> and used in control subjects and patients with duodenal ulceration.

## Methods

### PH DATA LOGGING SYSTEM

Full details of the electrode characteristics, stability of the electrode position, the electronic data logging system, the calibration and correction techniques have been published in detail elsewhere.<sup>5,6</sup> In brief, two miniature combination pH electrodes

(Beckman-RIIC Ltd, Glenrothes, Scotland\*), attached to 2.5 mm × 3 m wires, were positioned in the antrum of the stomach and the duodenal bulb. The distal electrode was tethered by a thin silk thread to a mercury-weighted balloon positioned just caudal to the duodenojejunal flexure. The wires passed out through the mouth and were fixed by a ribbon gauze tape tied around the head. The position of the electrode assembly was maintained by this tape and by constant distal traction from peristalsis acting on the mercury balloon.

In this paper records from the gastric electrode have not been analysed in detail, but acted as a confirmation of electrode position within the duodenal bulb by constant comparison of the two electrode readings – continuous recordings of similar pH from the two electrodes was found to be indicative of proximal electrode displacement.<sup>6</sup> The electrodes were connected *via* a switch unit to a

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\* Beckman Cecar electrode now discontinued. Electrode with equivalent specifications available from WA Scott (Scientific Instruments), 9 Almond Way, Glenrothes, Scotland.

standard digital pH meter and the binary coded decimal output was sampled by an electronic logic unit at 10 or 20 second intervals (for the duodenal electrode). Once in a suitable format, the digital data were stored on punched paper tape. The entire data logging system was mounted on a transportable trolley which could be wheeled to the bedside.

The electrodes were calibrated in standard pH buffers (pH 2, 4 and 7) in a water bath at 37°C at the start and end of each test. The electrodes were then positioned in the stomach and duodenum, with the mercury balloon in the upper jejunum, using fluoroscopic control. The electrode position was similarly checked at the end of the test. The electrode wires were long enough to allow the subject some mobility when linked to the trolley so that he could lead a nearly normal life. Events during the study period were recorded by the investigator, or by the subject, from an incremental reading counter which was updated after the logging of each pH reading on the punched tape.

#### SUBJECTS

Patients and volunteers gave their full and informed consent to these tests which were approved by the Medical Ethics Committee of Hammersmith Hospital and the Royal Postgraduate Medical School.

Eight normal healthy men with a mean age of 31 years (range 25–44 years) were studied together with 11 men with duodenal ulcer disease (mean age 41 years; range 22–57 years). In each patient an ulcer had previously been seen endoscopically but their disease activity (active or healed) was not determined in relation to the timing of the pH studies. Basal acid output and peak acid output to pentagastrin were assessed on a separate day in seven of the eight normal controls and 10 of the 11 patients with duodenal ulcer using a standardised gastric function test with corrections for pyloric loss of gastric acid and for duodenogastric reflux.<sup>7</sup> The median basal acid output of the control group was 1.9 mmol/h (range 0.5–4.2) and was 5.7 mmol/h (range 0.7–18.5) in the patients with duodenal ulcer: the corresponding mean peak acid outputs were 43.0 mmol/h (SD 7.0) and 52.9 mmol/h (SD 12.6) respectively. Fortunately, the gastric secretory capacity of the control group more closely resembled the acid output levels of a duodenal ulcer population,<sup>1</sup> so that patients with duodenal ulcer were compared with normal subjects of similar maximal secretory capacity.

#### PROTOCOL

A standard five hour meal test was used in all subjects. After an overnight fast and intubation with

the electrode assembly duodenal pH was recorded at 10 or 20 second intervals for one hour in the basal state. The subject was then given a standard breakfast meal which started with a drink of orange juice (120 ml, pH 3.2) followed by three eggs scrambled with bacon (28 g), two slices of bread and butter, a portion of marmalade (40 g), and a drink of tea or coffee (180 ml) made with cream (28 g) and sugar to taste (total content – 70 g carbohydrate, 78 g fat, 50 g protein, total calories 1147). Three and a half hours after the start of the test the subjects drank an exogenous acid load consisting of 300 ml Coca-Cola (pH 2.5, titratable acid load 25 mmol – fresh from can). After four hours smokers were allowed to smoke their usual brand of cigarette and at five hours the test was concluded.

An identical protocol was followed in five of the 11 patients with duodenal ulcer who underwent paired studies while on treatment with cimetidine (minimum time after start of treatment one week). The patients took their usual oral dose of cimetidine (usually 200 mg) one to three hours before the start of the test and again a second dose at one hour with the start of the meal. This ensured that both basal and meal stimulated periods were covered by adequate levels of cimetidine. All studies in patients off treatment took place more than 48 hours after the last dose of cimetidine or before beginning treatment.

#### ANALYSES

In five normal subjects and eight patients with duodenal ulcer duodenal pH was recorded every 20 seconds throughout the five hour test meal (450 readings). In the remaining three normal subjects and three patients with duodenal ulcer duodenal pH was recorded at 10 second intervals (900 readings over five hours). The analyses of data were the same irrespective of sampling rate. The raw pH data from the punched paper tape were transferred onto magnetic tape and subsequent analysis performed on an IBM 1800 computer. Each individual pH reading throughout the test was mathematically corrected for linear deviation from standard pH buffer values using scaling and shift factors derived from the start and end calibrations.<sup>5</sup> *In vitro* studies have shown that these techniques of electrode calibration and mathematical correction provide pH data which have a maximum error from true buffer pH of less than 0.3 pH units and a maximum variation over 24 hours of  $\pm 0.1$  pH units.<sup>6</sup> The chosen block of corrected pH data was analysed in three ways: (1) mean pH: the arithmetic mean of the corrected pH data; (2) log mean hydrogen ion activity (LMHa): the arithmetic mean of the antilog of the corrected pH data converted back to the more

familiar pH terminology by taking the log of the mean value; (3) pH levels: the percentage of the total number of readings in the corrected data block more acid than pH 4 and more alkaline than pH 6.

A computerised x-y plot could also be obtained of the corrected pH data for the entire test.

For parametric data, comparison of means have been performed using a Student's *t* test or paired *t* test. Non-parametric data have been analysed using a Mann-Whitney U test or Wilcoxon's sign ranked test.

## Results

Analyses of duodenal pH for the entire five hour test meal in eight control subjects and 11 patients with duodenal ulcer showed no significant differences in mean pH, 6.07 (SD 0.68) and 6.01 (SD 0.76) respectively, or LMHa, 4.74 (SD 1.10) and 3.97 (SD 1.05) respectively, between the two groups. The LMHa was always lower than the calculated mean pH because of the mathematical weighting effect of the logarithmic increase in hydrogen ion activity of the more acidic pH values. Over the five hour period, however, patients with duodenal ulcer had significantly longer periods of duodenal acidification with 11.8% of readings more acid than pH 4 (controls 6.2% readings <pH 4,  $p < 0.01$ ), and paradoxically significantly more readings, 63.3%, more alkaline than pH 6 (controls 57.9% >pH 6,  $p < 0.01$ ).

When the five hour test is broken down into basal, meal and drink periods (Table 1), there were no significant differences in duodenal pH between

Table 1 Analysis of duodenal pH in eight control subjects (C) and 11 patients with duodenal ulcer (DU) during the basal, meal and drink periods of the five hour test meal – using *t* test, paired *t* test, Mann-Whitney U tests, and Wilcoxon's matched pairs sign ranked test. There were no significant differences between controls and patients with duodenal ulcer in any period of the test

	Basal		Meal		Drink	
	C	DU	C	DU	C	DU
Mean pH	6.81	6.72	6.12*	6.04*	5.41†	5.51
SD	0.67	0.64	0.60	0.85	0.97	0.97
CV%	9.8	9.5	9.8	14.1	17.9	17.6
LMHa	5.81	5.80	5.52	5.09*	4.53†	4.29†
SD	1.03	1.32	0.66	1.27	1.06	1.28
CV%	17.7	22.8	12.0	25.0	23.4	29.8
% Readings						
<pH 4	2.4	4.7	2.0	9.5*	16.6†	17.8†
>pH 6	79.1	87.3	57.0	59.2*	33.6†	42.4†

\*  $p < 0.05$ , basal vs meal/drink.

†  $p < 0.05$ , meal vs drink.

control subjects and patients with duodenal ulcer in any period for any of the analyses. The non-linear nature of the hydrogen ion activity led to an increase in variation (coefficient of variation, CV – Table 1) of the LMHa results. The meal caused a significant fall in mean pH, LMHa, the periods of duodenal alkalinisation and an increase in duodenal acidification in patients with duodenal ulcer. These changes, however, were only significant for mean pH in control subjects. The acid drink produced significant changes in mean pH, LMHa and the percentage of readings less than pH 4 and greater than pH 6 in both groups.

A typical profile of duodenal pH and simultaneously recorded gastric pH during the five hour test meal is shown in the Figure (a). Although this patient was in the duodenal ulcer group, the pattern of changes in response to the meal and drink was characteristic of control subjects and patients with duodenal ulcer. The rise in gastric pH due to the buffering effect of the meal were less marked, however, and by contrast the brief spikes of duodenal acidification (falls in duodenal pH down to and below pH 4) were more frequent, in patients with duodenal ulcer.

Tests for correlation were performed in a combined group of seven normal subjects and 10 patients with duodenal ulcer who underwent both acid and pH studies. There was no significant correlation between basal acid output and either mean pH, LMHa or the percentage of readings less than pH 4 using a Spearman's rho test. There was a significant correlation between peak acid output to pentagastrin, however, and mean pH ( $r = 0.484$ ,  $p < 0.05$ ) and LMHa ( $r = 0.578$ ,  $p < 0.05$ ), but not with the percentage readings less than pH 4.

Treatment of patients with duodenal ulcer with cimetidine (1 g/day in four patients and 2 g/day in one patient) produced an overall reduction in basal acid output of 55% and peak acid output of 31%, and also increased the values for mean pH (5.61 to 6.33,  $p > 0.2$ ), LMHa (3.88 to 6.30,  $p < 0.02$ ) and the percentage of readings greater than pH 6 (52.5% to 78.5%,  $p < 0.03$ ) to values higher than that in the control group during the five hour test period. There were also significantly fewer readings (from 18.9% to 6.1%) more acid than pH 4 during treatment with cimetidine and these periods of duodenal acidification during treatment were comparable with the control group (6.2%). Cimetidine significantly increased basal LMHa and reduced the periods of duodenal acidification during basal, meal and drink periods (Table 2). The five hour duodenal and gastric pH profiles in a patient receiving cimetidine (2 g per day) whose basal acid output was reduced by 85% and peak acid output by 23% are shown

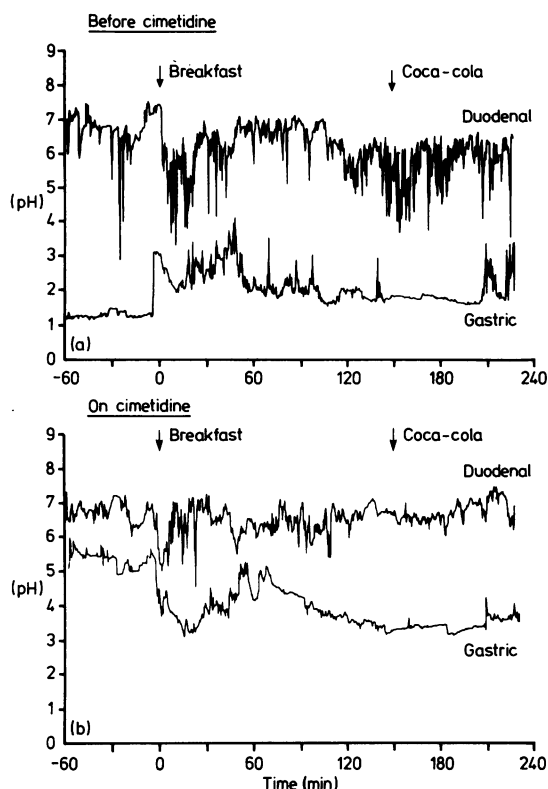


Figure Computer generated plot of 450 corrected duodenal pH and 450 gastric pH readings fasting, after breakfast and a drink of Coca-Cola in a 26 year old patient with duodenal ulceration before and during treatment with cimetidine. Acid data before treatment: BAO 18.5 mmol/h, PAO 54.3 mmol/h; duodenal pH – mean 6.43, LMHa 5.32, readings <pH 4 1.0%, readings >pH 6 78.5%. Acid data on treatment: BAO 2.8 mmol/h, PAO 41.7 mmol/h; duodenal pH – mean 6.87, LMHa 6.58, readings <pH 4 0%, readings >pH 6 96.1%.

Table 2 Analysis of duodenal pH in five patients with duodenal ulcer off and on treatment with cimetidine during the basal, meal and drink periods of the five hour test meal – using paired t and sign tests

	Basal		Meal		Drink	
	Cimetidine Off	Cimetidine On	Cimetidine Off	Cimetidine On	Cimetidine Off	Cimetidine On
Mean pH	6.60	7.03	5.57	6.37	5.02	5.80
SD	0.68	0.36	0.95	0.38	1.14	1.14
LMHa	5.17	6.81*	4.55	6.06	3.83	5.48
SD	1.60	0.72	1.38	1.38	1.31	1.93
% Readings						
<pH 4	7.4	1.9*	17.5	0.6*	28.9	17.8*
>pH 6	83.8	95.7	55.7	79.9	43.2	64.9

\* p<0.05, off vs on treatment.

before and after treatment in the Figure (a and b respectively). Intra-gastric acidity had been reduced to such a degree by cimetidine that drinking and eating caused a rise in acidity, together with a brief fall in duodenal pH. The repeated spikes of duodenal acidification down to pH 4 and below before treatment, however, were abolished completely by cimetidine. Cimetidine reduced the peak acid output in each patient with duodenal ulcer and completely abolished duodenal pH readings more acid than pH 4 in four of the five patients.

The effect of smoking on duodenal pH was studied by comparing the duodenal pH readings 30 minutes before, and 30 minutes after, starting a cigarette. Twenty eight cigarettes were smoked by seven subjects (both control subjects and patients with duodenal ulcer). There were no significant changes in either mean pH, LMHa or the percentage of readings more acid than pH 4 (Table 3).

### Discussion

#### JUXTAMUCOSAL PH

In the past remote reference electrode sites were used so that a pH electrode recorded both acidity and gut mucosal potential difference. We now use combined pH electrodes (such as Beckman Cegar and Scott) with no appreciable separation of the glass and reference electrode elements, and both immersed in the same fluid under investigation. Although combination electrodes have been available for 40 years,<sup>8</sup> the importance of the immediate proximity of the glass and reference electrode has not been fully appreciated.

Does it matter if the electrode touches, and becomes buried in, the mucosal folds? We believe contact is relevant and not a drawback because ulcers occur at this mucosal/lumen interface.

#### ELECTRODE SITING

Our twin electrode assembly suggested that the distal electrode was in the duodenum when its

Table 3 Effect of smoking on duodenal pH in seven subjects (controls and patients with duodenal ulcer) smoking 28 cigarettes

	Mean pH (SD)	LMHa (SD)	% Readings <pH 4
30 min before cigarette	5.79 (0.97)	4.89 (1.11)	9.1
30 min after cigarette	5.87 (0.73)	5.07 (0.97)	7.6
p	NS	NS	NS



recordings were different from those of the more proximal antral electrode.<sup>9</sup> The characteristics of duodenal pH (fluctuating) and gastric pH (steady acid) are recognisable,<sup>4</sup> and we have always found an antral/duodenal pH gradient in many thousands of simultaneous recordings. The stability of the duodenal electrode position, even with a big meal, has been confirmed by elaborate fluoroscopic techniques.<sup>5</sup>

#### CALIBRATION

Digital recording permits calibration and drift corrections of pH readings and improves the accuracy.<sup>6</sup> The logarithmic nature of the pH scale is a longstanding problem.<sup>10</sup> It is not known whether mucosal biological systems respond to the hydrogen ion activity or to changes in the tenth power of that activity (pH). We have therefore analysed acidity by calculating both mean pH and the mean derived from its arithmetic equivalent (log mean hydrogen ion activity: LMHa), even though the two calculations lead to similar conclusions.<sup>11-13</sup>

#### DUODENAL ULCER

The five hour test meal results showed no difference between the mean pH or LMHa of the normal control group and the duodenal ulcer group of comparable gastric acid secretory capacity. There were significant increases in the duodenal ulcer group, however, during the periods of duodenal acidification (pH <4) and of duodenal alkalinisation (pH >6). The first part of the duodenum in normal subjects was more acid than pH 4 for only 6% of the test, supporting the concept that the acidified gastric contents entering the duodenum are normally rapidly buffered and emptied until the pH is safely neutral. In patients with duodenal ulcer the processes by which acid is neutralised or removed from the duodenum may be inadequate. Nevertheless, although there are increased periods of duodenal acidification in patients with duodenal ulcer, the duodenum is also alkaline for significantly longer than normal. This increased alkalinisation is not sufficient in quantity or immediacy to prevent excess periods of duodenal acidification, perhaps because patients with duodenal ulcer appear not to use this neutralising capacity fully, although the maximal bicarbonate secretion available to enter the duodenum from the pancreas, bile and mucosa is adequate.<sup>14</sup>

#### DUODENAL BULB

Data from true combination pH electrodes are to be preferred to aspiration techniques which may alter local physiology. The duodenum has been found to

be highly acid or alkaline.<sup>8</sup> Rhodes and Prestwich<sup>15</sup> showed a marked pH gradient from the base to the apex of the duodenal bulb in both control subjects and patients with duodenal ulcer, with the pH of the upper third of the second part of the duodenum comparable with our results. These higher acidities in the first part of the duodenum have been confirmed,<sup>16</sup> with more acid mean pH values after a meal in the second part of the duodenum.<sup>17</sup> At first Rune's group found no significant difference in duodenal acidity between normal subjects and patients with duodenal ulcer. They did detect abnormally high mean activities recently<sup>4, 13</sup> in the duodenal bulb of patients with duodenal ulcer, both fasting and after a meal, probably because of more frequent pH recording (120 readings per minute against three to six per minute) which may pick up more brief spikes of duodenal acidification.<sup>13</sup> These brief periods of duodenal acidification and their importance in duodenal ulcer disease may be linked<sup>18, 19</sup> by simultaneous measurements of plasma secretin, characterised by short lived rises in plasma secretin associated with falls in duodenal pH.

#### COCA-COLA

This drink was chosen as a physiological exogenous acid load drunk by millions of people every day. Its carbonic and phosphoric acid buffering capacity might absorb unbuffered hydrogen ions in the stomach and decrease the unbuffered hydrogen ion load being delivered to the duodenum. Both in our control<sup>19</sup> and the present studies, however, Coca-Cola produced a marked fall in duodenal mean pH, considerably increased the percentage readings more acid than pH 4, and significantly reduced the periods of duodenal alkalinisation, all compatible with the theory Cola type drinks could predispose to duodenal ulceration.<sup>20</sup>

#### CIMETIDINE

In the only report of duodenal pH on and off cimetidine,<sup>18</sup> four normal subjects were studied for two hours after a meal. The brief spikes of duodenal acidification in the second part of the duodenum were abolished by cimetidine. We found more dramatic changes in the duodenum than those in the stomach. Four of the five patients with duodenal ulcer had no readings more acid than pH 4 throughout the whole five hours of the test meal. Only one patient, who had the highest stimulated acid output in the duodenal ulcer group (72.4 mmol/h), had any periods of duodenal acidification, and these were reduced by 50% compared with the test performed off cimetidine. Cimetidine increased the periods of duodenal alkalinisation to more than normal levels.

## ACID OUTPUTS

Rune<sup>21</sup> found a significant correlation between duodenal pH and basal acid output but we and others did not.<sup>22-24</sup> We found a significant correlation between stimulated acid output and duodenal pH (and LMHa), as have some,<sup>9 21 25 26</sup> but not others.<sup>22 23 27 28</sup> Many of these reports, however, are observational rather than statistical.

## SMOKING

Smoking and duodenal ulcer have been linked epidemiologically.<sup>20 29 30</sup> Smoking inhibits pancreatic bicarbonate secretion<sup>31-33</sup> but its effect on gastric acid is uncertain.<sup>34-36</sup> Murthy's smokers<sup>37</sup> had significantly lower duodenal pH's with more consistently prolonged bulbar acidity. Murthy's results<sup>37</sup> differ totally from ours even when analysed for 30 minutes before and after a cigarette. They used a Beckman Cekar electrode without a stabilising balloon so nicotine may have increased gut motility sufficiently to displace the untethered electrode back into the stomach: this small distance may not have been detected by an injection of contrast. Such displacement could explain why plasma secretin failed to rise, despite up to 60% of pH readings more acid than pH 3.5.

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