Gut, 1988, **29**, 1035–1041

Measurement of gastrointestinal pH profiles in normal ambulant human subjects

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SUMMARY **Gastrointestinal (GI) pH has been measured in 66 normal subjects using a pH sensitive radiotelemetry capsule passing freely through the gastrointestinal tract. Signals were recorded with a portable solid state receiver and recording system, enabling unconstrained measurements with normal ambulatory activities for up to 48 h during normal GI transit. Capsule position in the gut was monitored by surface location using a directional detector. Gastric pH was highly acidic (range 1·0–2·5) in all subjects. The mean pH in the proximal small intestine was 6·6 (0·5) for the first hour of intestinal recording. By comparison the mean pH in the terminal ileum was 7·5 (0·4) ($p<0·001$). In all subjects there was a sharp fall in pH to a mean of 6·4 (0·4) ($p<0·001$) as the capsule passed into the caecum. Values are means (SD). pH then rose progressively from the right to the left colon with a final mean value of 7·0 (0·7) ($p<0·001$).**

In recent years there has been increasing interest in the pH of the contents of the gastrointestinal tract. Previous measurements using aspiration or discrete sampling from the stomach or the rectum[1,2] are unsatisfactory because of the problems of pooled measurements and also of the relative inaccessibility of other parts of the gastrointestinal tract.

Previous workers have attempted to identify gastrointestinal pH profiles using a pH sensitive radiotelemetry capsule. Bown *et al*[3] and Meldrum *et al*[4] used a pH telemetry capsule to plot pH profiles in the GI tract. At the time, however, capsules were relatively unreliable, suffering from severe drift problems and a short life span.[5] Although this work is of interest as a guide line to the present study, the results must be viewed with some caution because of the doubt about the accuracy of the radiocapsules which were used.

With the advent of a new stable, reliable, pH sensitive capsule with a longer usable life[6] it is now possible to monitor pH in the gastrointestinal tract with a greater degree of accuracy than was previously possible. Additionally, with the introduction of portable receiving apparatus[7] it is also possible to measure GI pH whilst patients are carrying out normal daily activities, this being desirable to ensure that measurements are recorded under physiological conditions in ambulant subjects.

The aim of our present study was to investigate the range of GI pH profiles in a representative group of normal subjects in order to establish a base line for future reference.

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Received for publication 19 February 1988.

Methods

SUBJECTS

A total of 72 subjects (51 men) median age 26 years, range 20–83 years, with no previous or current gastrointestinal disease were recruited for the study over an 18 month period. The project was approved by the Nottingham Medical School Ethical Committee and all subjects gave written, informed consent before the study.

Subjects were not restricted to any dietary control either before or during the study. This was intentional in order to establish a base line from a mixed group of normal individuals with a wide age range and a mixed European diet. All subjects were interviewed before the study and questioned regarding dietary habits. Any subject found to have unusual

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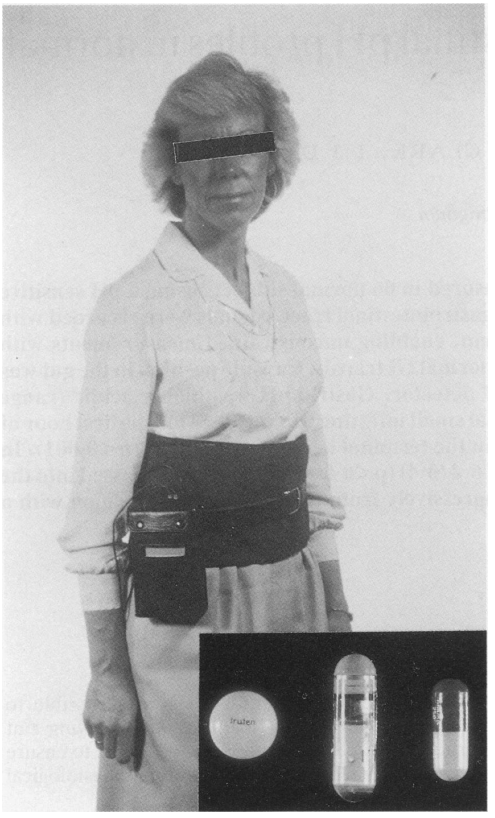

Fig. 1 *The pH sensitive radiopill (inset) and portable solid state recording equipment. The aerial array is worn around the abdomen inside a cloth band.*

eating patterns – for example, vegetarian or ethnic diets – was excluded from the study.

Gastrointestinal pH was measured using a freely moving pH sensitive radiotelemetry capsule (RTC), (Remote Control Systems). The capsule consists of a glass electrode with integral reference cap and battery which has already been widely evaluated in measurements in the oesophagus[8,9] (Fig. 1). This device enables continuous measurement of pH as the RTC passes through the GI tract, it is cable free and non-invasive. Signals from the capsule are detected by an aerial band worn around the abdomen recording on to a portable solid state receiver (John Caunt Scientific, Oxon), (Fig. 1). The recorder samples the pH from the capsule at 12 sec intervals thus enabling continuous totally ambulant monitoring for up to 48 hours.

Before swallowing, the RTC was calibrated in buffers pH 4 and pH 9·2 at 37°C. Transit of solids through the GI tract varies widely between individuals but in most cases the 48 hour recording time was sufficient to record pH from the stomach to the rectum. At the end of the study the RTC was collected in the faeces using a specially designed frame. The RTCs were cleaned and resterilised after performing a check for pH drift in the calibration buffers.

Data were replayed on a dedicated microprocessor controlled replay unit to give a hard copy of pH against time. The data were also transferred to an ICL2900 mainframe computer *via* a BBC B microcomputer and 13·3 cm floppy discs. Group analysis of the data could then be done automatically using standard programming packages.

The data transfer *via* a British Telecom land line was facilitated using Decce and Kermit software,[10,11] this enabling a continuous accurate flow of data to a large database without line errors. As each recording used approximately 70 kbytes of computer memory, mainframe storage was essential in order to compare data from a large group of subjects.

LOCALISATION OF RTC

The capsule was localised in the GI tract utilising two distinctive changes during transit.

First, in order to identify the transition of the capsule from the stomach to the small intestine the sharp rise in pH signified by the capsule leaving the highly acidic environment of the stomach into the relatively alkaline environment of the duodenum was used as a marker.

Second, in order to locate the transit of the RTC into the caecum and its subsequent passage distally, the following method was used.

The surface position of the RTC was located over the abdomen using a highly directional aerial probe connected to a portable radiotelemetry receiver tuned to the capsule frequency (Remote Control Systems, London). The position of the capsule was assessed to be where the maximum signal strength of transmission was received by the probe. This position was recorded on a body map divided into nine sections over the abdomen at two to four hourly intervals, by the subjects during the study period (Fig. 2). The position of the capsule on arrival in the caecum was always found to be in the right iliac fossa. The capsule then moved round the abdomen from the right to the left side during its passage through the colon.

This method has been validated by us using radio isotopically labelled capsules and a gamma scintigraphy technique. The GI tract was outlined in six volunteers with 100 ml water labelled with 10 MBq

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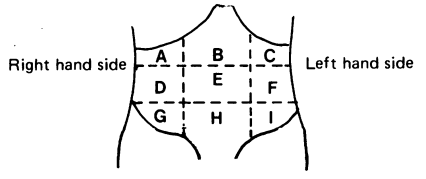
Surface map – Gastrointestinal pH studies

Name J SMITH
Date 21-7-86 Study No 046
Sex M Age 37 Study group NORMAL

Please record surface position every 2 hours during the daytime. You should record the date and time in the first two columns and the recorder reading in column 3 with the anatomical zone (see diagram) in the last column.



Date	Time	pH value	Zone
21-7-86	09·00	1·5	B
"	11·05	6·5	D
"	13·12	7·4	H
"	15·00	7·9	H
"	17·03	6·2	G

Fig. 2 *Body map used to aid localisation of the RTC as it passes through the GI tract.*

technicium 99m and the RTC labelled with indium[111]. pH and surface position were continuously monitored during the passage of the RTC through the small intestine. In all cases the RTC was seen to enter the caecum as outlined by the marker at the same time as localisation in the right iliac fossa. Characteristic pH changes were also noted and subsequently used in the identification of the important ileocaecal transition.

SIGNAL LOSS

Periods of signal loss are not uncommon from radiocapsules because the rf emission from this type of transmitter is highly directional. Studies involving free transit through the GI tract are therefore more likely to incur greater signal loss than in studies using tethered capsules,[12] which have been reported at 10% or less. Improvements in aerial design and electronic aerial switching units[13 14] have been incorporated into the solid state recorder and thus signal loss has been reduced to an acceptable level for GI transit studies. In these studies periods of signal loss of greater than 75% of the total recording were excluded from the analysis.

STUDY PROTOCOL

At 8 30 am on the morning of the study after an overnight fast subjects swallowed the RTC with a small quantity of water. The recording equipment was applied and the recordings started immediately. Subjects were required to remain in the laboratory until the RTC had left the stomach, this being indicated by a rapid rise in pH from approximately pH 1·5 to a pH sustained at greater than 5. After gastric transit subjects were allowed to eat and drink normally. Subjects were fasted before the study in order to prevent delay of transit of the capsule from the stomach as it is known that large particles are retained in the stomach when associated with a meal.[15]

During its passage through the GI tract the RTC was localised using the method previously described. Subjects were required to do this at approximately two hourly intervals to give an accurate location of the capsule. Normal food and drink were allowed throughout the study and the subjects were permitted to leave the laboratory for the remainder of this period. At night subjects removed the recording equipment but continued to wear the aerial around the abdomen to facilitate continuous recording without interrupting sleep. At the end of the study period recordings were replayed on to the Oxford replay unit to give a hard copy of the results and also transferred to the mainframe computer as previously described.

ANALYSIS

pH was sampled at 12 second intervals for the total recording period of up to 48 hours during the passage of the RTC through the gastrointestinal tract. Thus a total of 14 400 data points were possible from each subject. In order to analyse data from specific parts of the gut the real time clock incorporated in the recorder was utilised to define the time periods when the RTC was passing through these areas.

Six specific periods were assessed.

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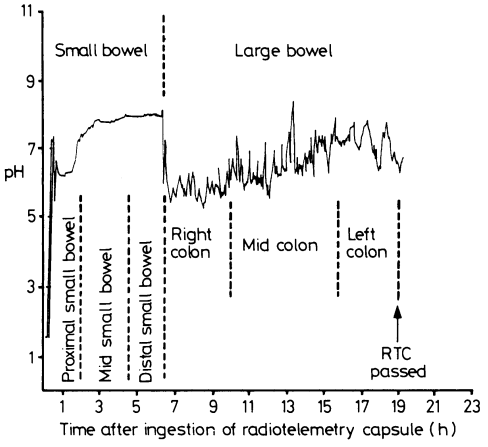

Fig. 3 *Gastrointestinal pH profile from a normal subject. The position of the capsule in specific areas is labelled accordingly.*

1 Proximal small bowel
The first hour of recording after the RTC had left the acidic environment of the stomach.

2 Distal small bowel
The last hour of the recording before the RTC was assessed to be in the caecum. Ileocaecal transition was associated with a sharp fall in pH from a relatively high stable ileal level (Fig. 3), together with a simultaneous surface location over the right iliac fossa.

3 Mid small bowel
The time period between 1 and 2 above.

4 Right colon
The four hour period after transition of the RTC into the caecum.

5 Left colon
The four hour period immediately preceding passage of the RTC from the rectum, or the last four hours of the study period providing the RTC was located in the left iliac fossa.

6 Mid colon
The period between 4 and 5 above.

A Fortran 77 program has been developed to calculate the mean pH from the six epochs. The use of mean values was justified as there was a minimum of 300 data points for each epoch for each subject. A normal distribution was confirmed by an initial test of skewness ($g1<0{\cdot}05$ in all cases). The means were grouped, from all the subjects and compared statistically using the Student's *t* test for unpaired data.

Results

All subjects completed the study without difficulty or complications and were not aware of the capsule within the GI tract. Four tests failed because of excessive pill drift >1·0 pH and two tests failed because of excessive signal loss leaving a total of 66 studies suitable for analysis.

SIGNAL LOSS

Small bowel signal loss accounted for the majority of the losses and was greater than 75% in 14 studies. These values were not included in the final analysis.

Median signal loss due to the movement of the capsule was 20·4% (range 6·9–64·1%). In these studies where multiple measurements were made in each bowel segment these signal losses were considered acceptable.

PILL DRIFT

A post calibration check for pill drift was only possible in 38 of the 72 studies carried out where the RTCs were retrieved at the end of the recording period. In the remaining studies the RTC remained in the colon or rectum beyond the 48 hour study period and a post calibration was not considered feasible when the capsules were finally retrieved.

After superficial cleaning in running water the RTCs were recalibrated in the two standard buffer solutions. The measured values after the tests can be seen in Table 1.

The RTC passed through the small bowel and entered the caecum in all 66 subjects but in 16 the capsule failed to reach the left side of the colon within the 48 hour recording period and so no left sided recordings were obtained for these subjects.

Figure 3 shows a typical pH profile of the GI tract in a normal subject. The transition from the acid to alkaline environment is clearly seen as the capsule passes from the stomach to the small intestine; another distinct change can be seen as the RTC moves from ileum to caecum.

Table 1 *pH drift as measured by a post test calibration*

Initial buffer pH (n=38)	*Median post calibration pH*	*Median drift in pH*
4·0	4·00 (3·6–4·8)	0·2 (0–0·6)
9·2	9·40 (9·0–10·2)	0·3 (0–1·0)

1 Proximal small bowel
The RTC's passage from the stomach to the duodenum was associated with a rapid rise in pH to a near neutral level. The mean pH in the proximal small intestine for the first hour of transit was pH 6·6 (0·5) for the whole group (Table 2).

2 Distal small bowel
The RTC spent a variable period in the right iliac fossa before transit into the caecum, typically in zone H (Fig. 2). This period was always associated with a relatively high value and with little overall fluctuation from a stable level (Fig. 3). The mean pH in this area was pH 7·5 (0·5). This was significantly higher than the proximal small intestine ($p<0·001$) and was typical for all subjects studied (Table 2).

3 Mid small bowel
The period analysed for this segment was necessarily of variable duration as it was derived by subtraction of the start and end time of periods of 1 and 2 above. Thus the period of analysis for each individual varied by the total transit of the RTC through the whole small bowel (that is, small bowel transit – two hours). The mean pH in the mid small bowel was pH 7·4 (0·4). This was significantly higher than pH in the proximal small bowel ($p<0·001$) but was not different from the distal recording.

4 Right colon
pH in the right colon was measured as the mean of the first four hours of colonic recording defined by the crieria of surface mapping and pH profile.

The pH in the right colon showed more coarse fluctuations with a significantly lower value than that measured in the ileum. The mean pH in the right colon was 6·4 (0·6) for the group, this was significantly lower than the distal small bowel ($p<0·001$) (Table 2).

5 Left colon
Left colonic pH was calculated from the 50 subjects where the RTC had migrated into the distal colon before the end of the recording. In 32 of the subjects the RTC was passed per rectum by the end of the recording period. In the remainder, the RTC was surface located in zone J (Fig. 2), this denoting sigmoid colon or rectal positioning. In both groups therefore pH could be calculated from the final four hours of the recording period.

The mean pH in the left colon was 7·0 (0·7) for the 50 subjects. This value was significantly higher than in the right colon ($p<0·001$) (Table 2).

6 Mid colon
Mid colonic pH, calculated as described had a mean value of 6·6 (0·8). This was significantly higher than the left colonic value ($p<0·01$), but similar to the pH in the right colon.

Table 2 *Results and statistics of pH measurements in normal subjects*

Site	*n*	*Mean pH*	*Std dev*
Jejenum	55	6·63	0·53
Mid SB	52	7·41	0·36
Ileum	58	7·49	0·46
Right colon	66	6·37	0·58
Mid colon	51	6·61	0·83
Left colon	50	7·04	0·67
Whole SB	51	7·30	0·34
Whole colon	48	6·63	0·67

Statistical analysis (Student's t test)

Group	*Group*	*df*	*t*	*p<*
Jejenum	Mid SB	105	8·9	0·001
Mid SB	Ileum	105	1·0	nsd
Ileum	Right colon	122	11·8	0·001
Right colon	Mid colon	115	1·8	nsd
Mid colon	Left colon	99	2·8	0·01
Right colon	Left colon	114	5·1	0·001
Whole SB	Whole colon	97	6·3	0·001

TRANSIT TIME
The mean RTC transit through the small intestine was 5·7 hours (2·04) hours. This compares well with other methods of small bowel transit methods[15] and confirms the validity of the ileo-caecal transition.

Whole gut transit of the RTC was calculated in the 32 subjects where the capsule was passed before the study end. The mean whole gut transit for the capsule was 23·3 hours (8·16).

Discussion

This study has evaluated a new method of measurement of pH in the gastrointestinal tract in ambulant subjects using an improved pH sensitive radiotelemetry capsule and portable receiving system. pH profiles were measured in a group of normal subjects in order to establish base lines for comparative studies. All studies were completed without difficulty, the majority being available for analysis. In some cases the pH pill was retained in the right colon until the end of the study period, thus demonstrating the wide variety of transit in normal, asymptomatic subjects. All capsules were eventually passed without complications.

The pH measured by the RTC is that of the intraluminal contents in direct contact with the electrode. It is not the mucosal pH which is being

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measured but that of the luminal contents which is in direct contact with the mucosa. In the fluid or semifluid of the small bowel the pH profile will reflect the homogeneity of the environment. This is similarly the case even in the solid or semisolid of the distal colon where there was considerable local variation in measured pH. If the electrode were to become embedded in solid matter in the distal colon then the pH recording would become static which was a phenomenon not seen in our studies.

Meldrum *et al*[4] carried out similar studies in only two normal controls and seven patients with miscellaneous GI disorders. pH profiles were similar to those found in our study although some of the extreme values of their measurements were outside those found by us. This may be due either to their capsule instability or the population sampled.

A major problem in the methodology in this type of study has been the difficulty of location of the RTC in the bowel lumen, especially in the less well definable loops of the small intestine. We found that by classifying the gut into zones which were positively identifiable and with the added evidence from surface location and pH, measurements could be relied upon as accurate.

The significance of gastrointestinal pH levels is as yet not clear. Intraluminal contents of the GI tract may well influence the development of diseases such as inflammatory bowel diseases or tumour formation. Thornton[16] postulated that intraluminal colonic pH might be important in the development of colonic neoplasia. Epidemiological evidence[17] and laboratory studies[18–20] suggest that degradation of metabolites of digestion may be carcinogenic. As these reactions are enzymic and pH dependent then pH in the colon may be an important factor in neoplastic development.

Further evidence of the association between cancer incidence and colonic effluent has come from faecal pH measurements in low and high risk populations[21] although faecal pH measurements may not be the most accurate means of assessment of colon pH. Furthermore the measurement of faecal pH gives no information about pH in the right side of the colon. As colorectal neoplasia is found in 90% of cases in the distal left colon[22] then differences from right to left may be important. Obviously a free moving radiopill would give this information and studies are underway[23] to assess differences in right and left sided pH in patients with colorectal neoplasia, different dietary groups and low and high risk populations.

If GI pH be a dynamic measurement influenced by diet and lifestyle then one might expect not only differences between individual dietary groups but also changes during dietary fibre manipulation. Bown *et al*[3] investigated the effects of lactulose, an undigestible disaccharide, on colon pH in volunteers. They used an early version of the pH capsule similar to Meldrum, but in non-ambulant subjects. The results from their studies showed similar trends to our own in control studies and a significant acidification in the right colon between lactulose and controls, but less so on the left side.

In a recent study in our department[24] a similar effect was demonstrated using Fybogel (Reckitt and Colman), a colonic bulking agent. In this study, however, pH was altered significantly in both proximal and distal colon. If, therefore, it is easily possible to alter pH in the large bowel and bowel pH is subsequently shown to be important as a protection against neoplasia then it would be highly desirable to know which substances are most efficient in altering pH in the colon.

There is increasing interest in the development of enteric coatings of drugs[25,26] in order to deliver topically acting substances to the distal gut to improve efficiency and efficacy. Many of these coatings have a pH dependent dissolution, thus it becomes important to know not only the pH profile along the GI tract, but also whether there are any differences in disease states, such as inflammatory conditions, in order to target the drugs correctly.

There is also some evidence to suggest that there are substantial changes in GI pH associated with malabsorption in cystic fibrosis.[27] Such changes may therefore exist in other chronic bowel disorders such as ulcerative colitis and Crohn's disease. These questions as well as many others concerning the influence of gut pH remain unanswered. The methodology described in this paper may be helpful in the search for such information.

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