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pH-Profile and regional transit times of the normal gut measured by a radiotelemetry device

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SUMMARY

The pH of the gut lumen was measured in 39 healthy persons using a pH-sensitive, radiotransmitting capsule. Thirteen persons were studied twice. The location of the capsule was determined by X-ray. The pH rose from 6.4 in the duodenum to 7.3 in the distal part of the small intestine. In 17 persons the pH dropped by 0.1–0.8 pH units during the last hours of the small intestinal transit. The pH was 5.7 in the caecum, but rose to 6.6 in the rectum. Gastric residence time was 1.1 h, small intestinal transit was 8 h, and colonic transit time was 17.5 h (median values). The results provide a firmer basis for prediction of the level, and the rate of release of active substance from pH-dependent sustained-release oral preparations.

INTRODUCTION

The biological availability of a tablet is influenced by a variety of factors including regional intestinal pH and regional intestinal transit times. These factors are of particular importance for the effect of some newly developed sustained-release 5-aminosalicylic acid preparations designed for the treatment of chronic inflam-

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matory bowel diseases.[1–3] These tablets release their active substance in a pH-dependent manner. Other tablets use similar pH-dependent release mechanisms,[4–6] and several of these tablets remain intact during a large part of their passage through the gut.

A precise knowledge of intestinal pH and the transit times of a tablet through the gut is necessary to predict where these tablets will release their active content. This is important as the absorption of drugs from different parts of the gut varies widely.[7,8] Detailed information is available concerning pH of the stomach and the duodenum,[9] but less is known about pH of the small intestine and the colon. The development of small, radiotransmitting, pH-sensitive capsules has provided a method which permits measurement of intestinal pH under almost physiological conditions.

Various methods of measuring small intestinal transit time[10,11] and colonic transit time[12,13] have been developed, but all have potential drawbacks. Some of the methods may themselves induce changes in the measured transit time.[14] Repeated determinations of the location of an ingested pH capsule from ingestion to recovery in the stool would give an insight to the transit times of a non-degradable tablet in the intestines.

We have determined pH and regional intestinal transit times using pH capsules in 39 normal volunteers. Thirteen subjects were studied twice in order to determine day-to-day variation.

PATIENTS AND METHODS

Thirty-nine persons without symptoms of gastrointestinal disease were studied. Eighteen were males and 21 females; age range from 18 to 65 years (median 33 years). Thirteen persons (seven males and six females) were studied twice.

All volunteers gave informed consent and the study protocol, containing an estimate of the amount of radiation expected to be used, was approved by the local ethics committee.

pH measurements

The pH capsules (Remote Control Systems Ltd, London, UK) are small encapsulated transmitters measuring 7 mm in diameter and 24 mm in length. Before use the capsules were activated, allowed to stabilize in water at 37 °C for 10–14 h, and then calibrated with pH 1.0 and 9.0 buffer solutions.

After an overnight fast the study subjects swallowed the capsule. The pH was measured every 15 min until it was above 5, indicating that the capsule had left the stomach. The subjects continued to fast until this had occurred. The pH was hereafter determined every half hour until the capsule had reached the caecum. The intervals between measurements were then increased to 2 h.

Each investigation lasted from 08.00 hours on day 1 to 23.00 hours on day 2 (39 h): no determinations were made between 23.00 hours on day 1 and 08.00 hours on day 2. All stools were examined until the capsule was recovered. The

capsule was recalibrated on recovery and pH calculations were corrected for frequency drift occurring during the study. In each person the median pH values for each segment of the gut measured were calculated. The 10, 25, 50, 75, and 90 percentiles for all pH measurements were also calculated.

When the capsule had left the stomach the subjects were allowed to have a breakfast (for example, coffee or tea, bread, butter, cheese, marmalade). At 12.00 hours a light lunch was offered (for example, milk, egg, juice, bread, butter, cheese, salad), and at 18.00 hours the subjects received a hot meal. Between these meals, and in the evening the subjects were offered coffee, tea, beer, or mineral water.

Regional intestinal transit times

When the capsule had left the stomach, the location was determined by X-ray examinations (fluoroscopy) immediately after each determination of pH. An average of 10-s exposure time was needed to determine the location of the capsule. The median number of determinations was 26 (range 10–64), which equals a maximal exposure time of 640 s (estimated surface exposure = 250 mSv). The capsule was regarded to be in the proximal part of the small intestine, when, after leaving the stomach it entered the left upper abdominal quadrant. When it entered the right lower quadrant it was regarded to be in the distal part of the small intestine. Between these two positions the capsule was considered to be in the mid-part of the small intestine.[15] The localization of the capsule in the colon relied on the identification of bony landmarks and gaseous outlines.[16] Three intervals were determined: gastric residence time, small intestinal transit time, and colonic transit time. The number of observations within each segment of the small intestine (i.e. proximal, mid, and distal part) and colon (i.e. caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum) was determined, and used to estimate the segmental residence times of the capsule within these intervals.

Statistical methods

The Wilcoxon rank test for paired data was used to test differences in pH between different segments of the gut. The Mann–Whitney test, and the chi-squared test were used to test differences in transit times between groups. Significance was considered at the 5 % level.

RESULTS

In one of the 52 studies a drift of > 1.0 pH unit was observed at recalibration, due to a defective reference cap. The pH results of this study were disregarded. In the remaining 51 studies satisfactory results were obtained. The maximal drift observed in these studies was 0.9 pH units. The median drift was 0.15 pH units.

pH profile of the gut (*Figure* 1)

In all subjects pH values below 3 were found in the stomach. When the capsule entered the duodenum a sharp rise occurred, and the pH reached a median value of

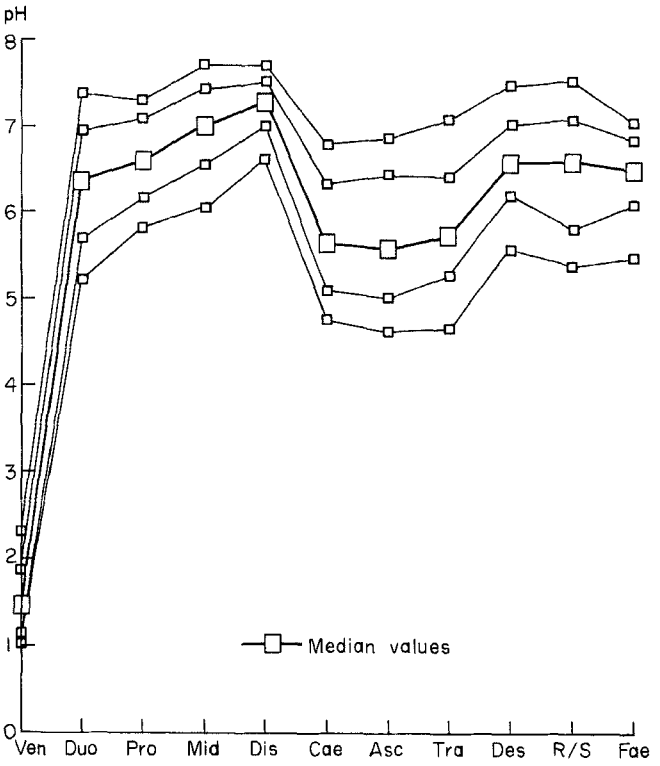


Figure 1. Percentiles (90, 75, 50, 25, and 10) of all pH determinations in relation to the intraluminal location of the capsule. (Ven = stomach, Duo = duodenum, Pro = proximal small intestine, Mid = mid small intestine, Dis = distal small intestine, Cae = caecum, Asc = ascending colon, Tra = transverse colon, Des = descending colon, R/S = sigmoid colon or rectum, Fae = faeces.)

6.4. The pH level gradually increased down the small bowel. The median values were: 6.6 in the proximal part, 7.0 in the mid part, and 7.3 in the distal part of the small intestine. The difference in pH between the duodenum and the distal part of the small intestine was statistically significant ($P < 0.02$). In 17 subjects pH decreased gradually by 0.1–0.8 pH units during the last hours the capsules stayed in the distal part of the small intestine, but the pH did not fall below 6.3. When the capsule reached the caecum the pH dropped from 0.5 to 2.5 pH units to a median value of 5.7 (distal small intestinal pH *vs* caecal pH: $P < 0.01$). The pH levels of the ascending colon and the transverse colon were almost identical to that of the caecum (5.6 in the ascending and 5.7 in the transverse colon), but the pH rose in the descending colon (6.6), and in the sigmoid colon and rectum (6.6). The median faecal pH was 6.5. The difference in pH between the caecum and the sigmoid colon and rectum was also statistically significant ($P < 0.02$).

At 7 of the 10 segments of the gut, and in faeces, day-to-day variations could be determined in more than half of the 13 persons who were studied twice. The variation-coefficients were: stomach 0.31; duodenum 0.12; proximal small intestine

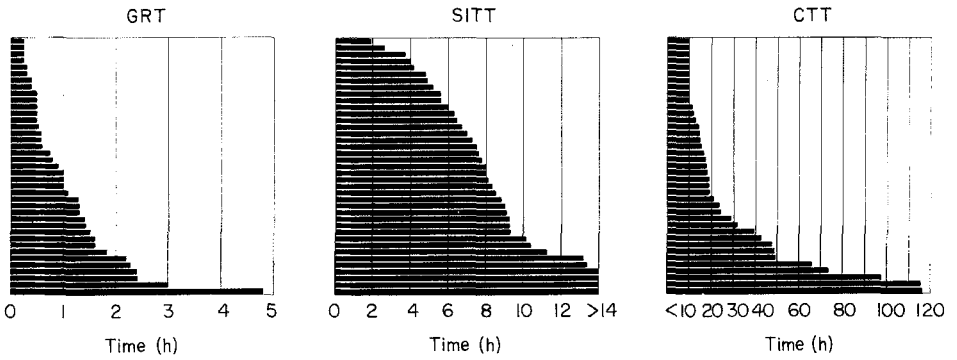


Figure 2. Regional intestinal transit times of the capsule in the 39 subjects. (GRT = gastric residence time, SITT = small intestinal transit time, CTT = colonic transit time.) Note: different time intervals on the *x*-axis.

0.08; mid 0.07; distal small intestine 0.04; caecum 0.13; sigmoid colon/rectum 0.13; faeces 0.11.

Regional intestinal transit times (Figure 2)

The capsule did not travel with a constant velocity through the different segments of the gut. In one subject the capsule stayed in the duodenum for 14 h, but was passed into the stools 11 h later. In two other subjects the capsules were situated in the caecum for 107 and 102 h, respectively, but were passed within 24 h after leaving the caecum. In some subjects the capsules were observed to travel in a retrograde direction in the colon between two determinations (from ascending colon to caecum, from transverse to ascending colon, or from descending to transverse colon).

Total intestinal transit ranged from 9.2 to 129 h, median 26.5 h.

Gastric residence time. The capsule stayed in the stomach for 0–4.8 h (median 0.9 h). No difference was found between males and females (males 1.2 h, females 0.7 h). The day-to-day variation (variation-coefficient) was 1.08.

Small intestinal transit time. The median small intestinal transit time was 8.0 h. The transit time tended to be shorter in males than in females, but the difference was not statistically significant (males 7.5 h, females 9.3 h; $P > 0.4$). The day-to-day variation (variation-coefficient) was 0.40. Based on the number of determinations in each segment of the small intestine, the capsule stayed in the duodenum for 10%, in the proximal part of the small intestine for 6%, in the mid part for 19%, and in the distal part for 65% of the small intestinal transit time.

Colonic transit time. Median colonic transit time was 17.5 h. No significant difference was found between males and females (males 16.6 h, females 19.0 h), but the variation was larger in females than in males, and more females then males had colonic transit times which exceeded the median value with more than 100% (> 35 h): females 9 of 21, males 2 of 18 ($\chi^2 = 4.82$, $P < 0.03$). The day-to-day variation (variation-coefficient) was 0.94.

Judged from the number of observations in each segment of the colon the capsule stayed in the caecum for 51%, the ascending colon for 18%, the transverse colon for 12%, the descending colon for 8%, and in the sigmoid colon or rectum for 11% of the colonic transit time.

DISCUSSION

In order to measure the pH of the gut using a pH capsule, it is imperative to determine the exact location of the capsule at the time of each pH measurement. In previous studies the localization of the capsule primarily has been based on determination of the location where the maximal signal strength was received.[17,18] In our experience this is not a reliable method. The maximal signal strength is obtained when the radiated magnetic flux from the capsule passes through the pickup field of the aerial at a right angle,[19] this means that the position of maximal signal strength not only depends on the location, but also on the orientation of the capsule.

To our knowledge, the present study is the first in which the location of the capsule has been established together with each determination of pH. This allows us to determine the pH of the different segments of the gut. We found that the pH increased from a median value of 6.4 in the duodenum to 7.3 in the distal part of the small intestine. These results differ from the results of earlier studies using a different type of capsule. In these studies the pH values of 2.7–3.4 were found in the duodenum,[20] and a mean pH of 5.2 was found in the proximal small intestine.[21] However, later studies[17,18] have found pH levels which are in agreement with the results of the present study. One of the reasons for the differences between the earlier results and our results probably is that the stability of the capsules and batteries has been improved, which have increased the lifespan of a capsule from 3–6 h to 2000 h. The rise in pH down the small intestine is most likely to be caused by an excretion of bicarbonate into the lumen of the gut,[22] and an absorption of organic acids from the intestinal contents.

The sharp drop in pH in the caecum has been previously described,[23] and it is thought to be caused by bacterial fermentation of non-absorbed carbohydrates. It has been discussed whether this drop occurs in the distal part of the small intestine or in the caecum.[23] In the present study we found that a sharp drop in pH occurred when the capsule had entered the caecum, but in 17 of the subjects pH decreased by 0.1–0.8 pH units while the capsules were still located in the distal part of the small intestine. Studies on normal ileal contents in healthy subjects have shown high counts of many faecal bacteria,[24] and the degradation of non-absorbed sugars may start in the distal ileum in some subjects. The trend towards neutral pH in the left colon and rectum is probably also due to an excretion of bicarbonate by the intestinal epithelium into the lumen of the gut. The day-to-day variation in pH at the distal part of the small intestine was very small, which indicates that pH in this part of the gut is under close control by regulatory mechanisms.

The gastric residence time of a capsule is influenced by the dietary state of the subject. Mojaverian *et al.*[25] have studied the effect of food ingestion on the gastric residence time of a pH capsule, and found that the interval increased from a mean of 1.2 h after fasting, over 2.6 h after a liquid meal to more than 14.5 h during frequent feeding. The gastric residence time in the present study was obtained during a fasting state, and it is almost identical to the value found by Mojaverian *et al.*[25]

In our study, small intestinal transit time ranged from 2.8 to more than 14 h with a median value of 8 h. This result differs from the results of other studies where median values of 3–4 h have been reported.[10, 11, 14] This does not seem to be explained by the size of the capsule, as Davis *et al.*[26] found that the small intestinal transit time of large particles is not different from that of granules. However, Davis *et al.* did not measure colonic transit and therefore could end their experiments when they assumed that the ileocaecal valve had been reached. Our study indicates a slow distal small intestinal transit for large-sized particles as the capsule was located here for 65 % of the small intestinal transit time. We cannot rule out that in some subjects we might have misjudged the location of the capsule in relation to the ileocaecal valve, but in our opinion fluoroscopy is the best available method for determining the location of the capsule in the gut. Using scintigraphic methods[10] the exact location of a capsule located in the lower right abdominal quadrant might be misenterpreted. The H_2 breath test[11] measures the time elapsed from the ingestion of a non-absorbable carbohydrate (lactulose) until the first part of it reaches the caecum. The carbohydrate itself may decrease the transit time,[14] and the mean transit time must be greater than the measured minimal transit time. Both these factors will lead to a low estimate of the small intestinal transit time. In the study of Evans *et al.*[18] a mean small intestinal transit of 5.7 h was found. The determination of small intestinal transit in that study was based on the identification of the rise in pH in the duodenum and the drop in pH in the caecum. In 17 persons in our study the pH decreased during the last hours that the capsules stayed in the distal part of the small intestine. In some of these persons this could have been misinterpreted as the capsule having entered the caecum, had the position not been determined by X-ray.

Colonic transit time in the present study was shorter than found by others.[12, 13] This was mainly due to a shorter residence time of the capsule in the rectum. This part of the gut is under the influence of the will, and the short rectal residence time was almost certainly caused by an interest of the study persons to end the study.

The results of the present study provide a firmer basis for prediction of the level, and the rate of release of active substance from pH-dependent sustained-release oral preparations. It must, however, be emphasized, that the study was performed on healthy subjects, and certain diseases,[27] and drugs may influence intestinal pH and intestinal transit times.

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