Accurate localization of a fall in pH within the ileocecal region: validation using a dual-scintigraphic technique

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Zarate N, Mohammed SD, O’Shaughnessy E, Newell M, Yazaki E, Williams NS, Lunniss PJ, Semler JR, Scott SM. Accurate localization of a fall in pH within the ileocecal region: validation using a dual-scintigraphic technique. Am J Physiol Gastrointest Liver Physiol 299: G1276–G1286, 2010. First published September 16, 2010; doi:10.1152/ajpgi.00127.2010.—Stereotypical changes in pH occur along the gastrointestinal (GI) tract. Classically, there is an abrupt increase in pH on exit from the stomach, followed later by a sharp fall in pH, attributed to passage through the ileocecal region. However, the precise location of this latter pH change has never been conclusively substantiated. We aimed to determine the site of fall in pH using a dual-scintigraphic technique. On day 1, 13 healthy subjects underwent nasal intubation with a 3-m-long catheter, which was allowed to progress to the distal ileum. On day 2, subjects ingested a pH-sensitive wireless motility capsule labeled with 4 MBq 51Chromium [EDTA]. The course of this, as it travelled through the GI tract, was monitored continuously, and position of the capsule relative to pH was established. A sharp fall in pH was recorded in all subjects; position of the capsule relative to this was accurately determined anatomically in 9/13 subjects. In these nine subjects, a pH drop of 1.5 ± 0.2 U, from 7.6 ± 0.05 to 6.1 ± 0.1 occurred a median of 7.5 min (1–16) after passage through the ileocecal valve; location was either in the cecum (n = 5), ascending colon (n = 2), or coincident with a move from the cecum to ascending colon (n = 2). This study provides conclusive evidence that the fall in pH seen within the ileocolonic region actually occurs in the proximal colon. This phenomenon can be used as a biomarker of transition between the small and large bowel and validates assessment of regional GI motility using capsule technology that incorporates pH measurement.

pH profile; wireless (telemetric) capsule

Benign disorders of lower gut function (i.e., motility disorders, characterized by symptoms of constipation, diarrhea, alternating bowel habit, incontinence, and abdominal pain) are prevalent in the general population and constitute a huge healthcare burden, as well as individual suffering (7, 14). Epidemiological studies indicate a prevalence of chronic constipation alone in the general population of up to 28% (43), and the condition is a frequent cause for referral to both the general practitioner and medical and surgical gastroenterologists (13). In 2004 in the United States, for example, a primary presenting symptom of constipation was responsible for 6.3 million patient visits to medical centers with a total (direct and indirect) cost to society of $1.7 billion (20). Patients refractory to simple conservative and medical therapies, and in whom organic causes have been excluded, may be considered for referral for further investigation (13).

At present, on the basis of tests that assess the speed of colonic transit and the efficacy of rectal evacuation, patients with intractable constipation can be broadly subclassified into those with delayed colonic transit (slow transit constipation), a rectal evacuatory disorder, or both (2, 13). Such classification is justified, as it has the potential to direct medical (29), behavioral (9, 10, 37), and surgical therapies (26, 35). Altered motor activity of the colon can underlie abnormal bowel frequency (17) and also evacuatory ability (16) in a significant proportion of chronically constipated patients, and it is now accepted that measurement of colonic transit time (CTT) should be the initial test of choice (13, 29). This is presently achieved in clinical practice by two radiological techniques, radioopaque markers and colonic scintigraphy (17). These methods, however, have limitations; both involve irradiation; there is a lack of standardization (17), meaning that results are difficult to compare between centers; and normative data are lacking. Nevertheless, such studies have shown that approximately half of constipated patients will have delayed colonic transit (range 13–80%) (17, 38). Furthermore, a proportion of these patients have upper gastrointestinal (GI) symptoms, and evidence of a panenteric motor disorder may be found in 18–72% (42, 47). This is of clinical significance, as such patients may have poorer outcome to intervention compared with those patients with an isolated colonic disorder (40).

Until recently, only the technique of whole gut scintigraphy has allowed assessment of regional gut transit in clinical practice (3). However, this test is only available in a handful of specialist centers worldwide. It is expensive, technically challenging, and, because of the necessity of repeated imaging over long periods of time, is limited by geographical and time constraints for some patients (17). GI transit can also be assessed through the use of ingestible telemetric capsules, which can record biological properties such as pH from within the lumen of the gut (6, 39). Although such technology has existed for over 50 years (12), it is only recently that commercially produced devices have become available and have been promoted for clinical use (6). For pH-sensitive devices, fundamental to the validity of such a technique is the knowledge of the precise anatomical location of any pH change. Accordingly, identification of position of the ingested capsule has been based on stereotypical changes in the pH profile along the GI tract (19, 22), including an immediate fall in pH as the capsule enters the acidic environment of the stomach, a sharp rise on exiting the stomach, and a further fall in pH some hours...
later as the capsule is believed to pass from the ileum into the colon (Fig. 1). This latter pH change has subsequently been exploited by the pharmaceutical industry for targeted drug delivery using pH-dependent release formulations (1, 11, 23). Furthermore, such pH landmarks may theoretically be used to determine transit within specific regions of the gut (6, 19, 22).

The exact location of this fall in pH around the ileocecal junction (ICJ) has, however, never been conclusively substantiated. Previous attempts at validating position of the capsule relative to the pH profile of the gut all had fundamental limitations, commonly the fact that intraluminal site was derived indirectly through extracorporeal localization (4, 19, 21, 22, 24, 41, 45). Indeed, doubts about the site specificity of the drop in pH have already been raised in the literature (11, 23, 34), and the exact regional locus of this pH change (ileum, cecum, or colon) remains uncertain (4, 22). If ingestible capsules are to be used as a diagnostic tool to accurately measure regional transit times, then this information is mandatory.

Using a dual-scintigraphic technique, utilizing a novel wireless motility capsule (WMC) (SmartPill; SmartPill, Buffalo, NY), we aimed to accurately determine the anatomical site of pH change and thus whether this pH change can be used as a biomarker of transition from small to large bowel.

MATERIALS AND METHODS

Ethical Approval

This study was approved by the East London and The City Research Ethics Committee (reference no. 07/H0703/77) and also received certification from the Administration of Radioactive Substances Advisory Committee (ARSAC no. RPC 564-935). Use of the WMC device was approved by the Medicines and Healthcare Products Regulatory Agency. All participants in this study gave written, informed consent.

Subjects

Thirteen healthy volunteers (7 women; median age 29 yr; range 26–53) participated in the study. All subjects had a normal bowel habit, defined as between three bowel movements a day and one bowel movement every three days, with no symptoms of rectal evacuatory difficulty. No subject had any GI symptoms or history of metabolic, neurogenic, or endocrine disorder known to influence GI motor activity. In addition, no subject had undergone GI surgery other than appendectomy, and none were taking either laxatives or medications known to influence gastrointestinal motility. Pregnancy was excluded in all subjects before enrolment.

Overall Study Design

pH change relative to anatomical location was determined using a dual-scintigraphic technique. The WMC was labeled with $^{51}$Chromium [EDTA] ($^{51}$Cr[EDTA]), and its position was assessed relative to a background of $^{111}$Indium [diethylenetriamine penta-acetic acid] ($^{111}$In[DTPA]), which outlined gut anatomy around the ileocecal junction. Controlled delivery of the $^{111}$In[DTPA] to the ileum was achieved via a long nasoileal catheter. For each study, subjects remained on their normal diets up to 12 h before study commencement.

Materials

WMC. The WMC (SmartPill, Fig. 2) measures pH, pressure, and temperature synchronously. The capsule is cylindrical, measuring 26.8 × 11.7 mm, and contains a solid-state pressure sensor, an ion-sensing field-effect transducer, pH sensor, a solid-state temperature sensor, electronic subassemblies supporting the pressure and pH sensors, a radio frequency transmitter, and an antenna. The electronic

![Fig. 1. Typical wireless motility capsule (WMC) recording. Phasic pressure activity is shown in red (mmHg, y-axis to left), pH profile in green (pH U, y-axis to right), and temperature in blue. Regional gastrointestinal (GI) transit can be determined on the basis of 2 characteristic changes in pH recorded by the WMC, namely a rise in pH when it exits the stomach, and a fall in pH where it is believed to pass through the ileocecal junction (ICJ). This allows calculation of gastric emptying time (GET), small-bowel transit time (SBTT), and colonic transit time (CTT). Whole gut transit time (WGTT) is the time between ingestion and excretion.](http://ajpgi.physiology.org/)}
assembly is isolated from the external environment by a rigid polyurethane shell. Two 1.5-V silver oxide batteries, connected in series, power the capsule. The capsule employs a “smart-power control system” to maximize the battery life and provides a minimum of 5 days of operational use.

pH is measured in the range of 0.5–9.0 with an accuracy of ± 0.5 pH U. The pressure sensor has a pressure range of 0–350 mmHg with an accuracy of ±5 mmHg below 100 mmHg, and ±10% at or above 100 mmHg. The temperature sensor has a range of 25–49°C, with an accuracy of ±1°C. Data are transmitted in a serial-burst format with each transmission consisting of the sensed pressure value, pH value, temperature, battery voltage, capsule electronic serial number, and a data packet identification number. Each transmission burst contains sensor data acquired during the preceding 20 s for the first 24 h of capsule use and, subsequently, every 40 s for the duration of capsule use. Measurements are transmitted from the capsule within the GI tract at 434 MHz to a patient-worn data receiver. The data receiver uses a single integrated antenna and captures the capsule’s transmitted data. The sensitivity of that data receiver allows the unit to be worn on a belt, a harness, or placed near the subject. All received data are stored within the data receiver. Upon completion of the study, data are downloaded to a personal computer for analysis.

Radionuclide labeling of the WMC. To localize the progression of the WMC along the GI tract, each capsule was labeled with $^{51}$Cr[EDTA] (GE Healthcare, Buckinghamshire, UK), which has a half-life of 27.7 days, suitable for prolonged evaluation of colonic transit. Four megabecquerels of $^{51}$Cr[EDTA] contained within 1.5 ml were injected into a modified outer sleeve that covered approximately two-thirds of the body of the WMC (Fig. 2). This was achieved with the aid of a precision pump (Ultra 2400 series; EFD, East Providence, RI). The outer sleeve was then sealed using a heat sealer (model no. 70; Clamco, Cleveland, OH). Care was taken to check for leaks; the filled WMC was placed in a 50-ml Falcon tube (BD Biosciences, Oxford, UK) containing water on a stirring plate overnight, and a sample of the water was removed and the balloon inflated with 8 ml of air to simulate intestinal peristalsis. Once the tip was seen to be beyond the ligament of Trietz, the subject was provided with a standardized 750-Kcal meal. Following this, the subject was instructed to feed extra catheter length slowly into the stomach at a rate of ~10 cm every 30 min. Position of the tip was determined by fluoroscopy every 2–3 h. When ~1.4 m of the catheter was within the lumen of the gut, the subject was allowed to go home. They were instructed to introduce the catheter further, to a depth of 1.8 m, before retiring to bed; at this point they were told to extract air from the balloon to leave a residual volume of 3 ml (to avoid retraction). A 750-Kcal evening meal was provided for the subjects to eat at 2000, and they were instructed to refrain from eating after 2100. Water was allowed ad libitum.

The subject returned fasted the following morning (day 2), and the catheter tip position was again checked fluoroscopically. The desired location was when the tip approached the right iliac fossa. If required, further introduction of the catheter was performed until the tip was clearly in the terminal ileum. Position in relation to the ileocecal valve (ideally 20–40 cm proximal to this) was also confirmed fluoroscopically by administering 20 ml of Gastrografin (Bayer, Berkshire, UK) through the additional lumen. Administration of the capsule. Once the catheter was satisfactorily positioned, usually around midmorning of day 2, it was secured to the patient’s face with tape, and the balloon was fully deflated to prevent further progression. The WMC was activated and calibrated for pH using buffers of pH 1.0 and 6.0. The subject then swallowed the WMC with around 100 ml of water. pH data were displayed in real time on the portable recorder and monitored continuously. Once the capsule was recognized as exiting the stomach (this occurred after around 1 h in the majority of subjects), indicated by a rise in pH of around 4 U, from pH 1–2 (gastric) to pH 5–6 (duodenal), the subject was allowed to consume a 750-Kcal standardized meal, which they were encouraged to eat within 10 min. After completion of the meal, a first aliquot of 2 MBq $^{111}$In[DTPA], contained in 0.5 ml of water, was administered through the nasoileal catheter. A further 5 ml of water was then instilled to flush the catheter lumen. The subject was then transferred to a couch under a single-headed γ-camera (NuclixX-Ring/R camera; Mediso, Budapest, Hungary), fitted with medium-energy collimator, where an initial static scan was taken.

Tracking of the capsule through the ICJ. Anterior static images were initially acquired every 30 min. To aid anatomical identification, and also allow for movement correction during post hoc data analysis, a $^{57}$Co skin marker was taped in place over the xiphoid process. The diffuse spread of the $^{111}$In[DTPA] enabled clear delineation of the terminal ileum, cecum, and colon so that a background subtraction of these anatomical regions was obtained. The $^{51}$Cr[EDTA] within the WMC was tracked relative to this. When the capsule was seen to cross the midline and progress toward the lower right quadrant, coincident with a stabilization of pH at ≥7.0, indicating location within the ileum, a first dynamic scan was started. This usually occurred around 4 h after the WMC had exited the stomach. During dynamic scanning, the subject was made comfortable and allowed to listen to music via a personal player; the data receiver was placed next to the subject on the couch, and he or she was instructed to move as little as possible. Once the dynamic scan had commenced, a second aliquot of 2 MBq $^{111}$In[DTPA] was administered to supplement identification of the ileocecal region. Online pH continued to be monitored very closely. The dynamic scan was continued for as long as the subject could tolerate, or 4 h maximum. They were then allowed a 15-min rest period, where they were encouraged to stretch.
their legs. Once the subject was back under the γ-camera, dynamic scanning recommenced.

The primary outcomes measures were 1) visual confirmation that the capsule had passed from the terminal ileum into the cecum and 2) a fall in pH of around 1 pH U from the stable ileal level of \( \pm 7.0 \) to approximately pH 6.0. Dynamic scans progressed ideally until the capsule was seen to be at the hepatic flexure.

**Image display and acquisition.** With subjects in the supine position, both static and dynamic images were acquired on a workstation (XRingR Console; Bartec Technologies, Surrey, UK) using a 128 × 128 matrix and three energy windows (Software Version 6.02c; Bartec Technologies). These windows were set for 1) \(^{51}\)Cr peak at 322 kV, with a 20% window, 2) the higher energy \(^{111}\)In peak at 245 kV, with a 20% window, and 3) another centered at 150 kV with a 50% window to include the lower \(^{57}\)Co peak and the \(^{57}\)Co marker. Static images were acquired for 2 min each. Dynamic scans were acquired with the time frame set depending on the subject body habitus at either 45 or 60 s, to a maximum of 240 frames. Of great importance, the clocks of the display software and pH monitor were synchronized.

**Exubation and capsule excretion.** Once the final dynamic scan had been concluded, extubation was performed by gentle traction with prior application of nasal topical anesthesia; this took \( \sim 15-30 \) min. Subjects were then allowed to go home with the data receiver. They returned the next day (day 3) after they had opened their bowels to check that the WMC had been expelled. Capsule expulsion was confirmed by loss of interpretable data from the pH sensor, a sustained drop in temperature recorded by the temperature sensor, and absence of the \(^{51}\)Cr[EDTA] signal on static imaging. If the capsule had not been expelled, the subject was instructed to return each subsequent morning until excretion had been confirmed. Data were then downloaded from the receiver.

**Subject Irradiation**

Whole body effective dose was \( \sim 1.8 \) mSv in total (1.24 mSv for 4 MBq \(^{111}\)In[DTPA]; 0.2 mSv for 4 MBq \(^{51}\)Cr[EDTA]; \( <0.1 \) mSv for the \(^{57}\)Co skin marker; and 0.3 mSv for maximum of 12 freeze frames of fluoroscopy). By way of comparison, the average annual background radiation dose in the UK is 2.2 mSv (25).

**Data Analyses**

**Capsule location relative to the pH drop.** Review of the pH data was performed through dedicated display software (MotiliGI, Smart-Pill). In addition, raw data were exported as an ASCII file to a spreadsheet (Microsoft Office Excel; Microsoft, Mountain View, CA), from which the mean pH value was calculated in 45 or 60 epochs, corresponding to the time-locked acquisition period for each frame of the dynamic scintigraphic scan.

Three independent observers then reviewed the dynamic scans frame by frame on a Linkmed Sun workstation (using MicasXplus Manual Processing Software, Version 5.2; Bartec Technologies) to assess the precise time of passage of the capsule from the terminal ileum through to the cecum and beyond (Fig. 3). Each anatomical region was assigned a numerical value (terminal ileum = 4, ICJ = 5, cecum = 6, ascending colon = 7, hepatic flexure = 8), and the position of the pill during each frame was agreed upon and plotted side by side with the corresponding pH value to accurately determine location of the capsule at the time of onset of pH drop.

**Further data processing.** To corroborate results of frame-by-frame analysis, time-lapse video loops were created to show movement-corrected passage of the capsule through the ICU (Fig. 4). Data processing of dynamic scans was performed on a separate Linkmed Sun workstation with Maps (Link Medical, Hampshire, UK). The sum of all energy windows was movement corrected using the \(^{57}\)Co marker as a reference point. This movement correction was then applied to the associated \(^{51}\)Cr peak image. A composite image was generated from the summed frames, which gave excellent delineation of anatomy, and regions of interest (ROIs) were drawn around relevant parts of the bowel. These ROIs were copied onto the \(^{51}\)Cr movement-corrected image so that activity corresponding to the \(^{51}\)Cr[EDTA] contained in the WMC was clearly visualized, relative to anatomical location (Fig. 4). Movement through the ICJ, relative to synchronously recorded pH, could again be plotted frame by frame or as a movie sequence (Fig. 5).

**Secondary analyses. Magnitude of pH drop around the ICJ.** This was defined as the fall in pH from the stable ileal peak to its nadir value. The duration of this fall was also noted.

**Precise site of pH drop.** The position of the capsule relative to the ICJ at the start of the pH drop was measured. Approximate spatial resolution was calibrated by positioning a capsule containing \(^{51}\)Cr[EDTA] under the γ-camera at the usual imaging distance at two sites separated by 10 cm. This allowed calculation of a correction factor for subsequent analysis.

**GI transit times.** Ingestion of the WMC was considered \( t = 0 \). The time from ingestion to a sustained rise in pH, corresponding to exit of the capsule from the stomach, was considered to represent gastric emptying time (GET). Small-bowel transit time (SBTT) was calculated by subtracting GET from the time of arrival of the capsule in the cecum, as visualized on scintigraphy. CTT was considered the time from arrival at the cecum (as determined scintigraphically) until excretion of the capsule. Whole gut transit time (WGTT) was considered the time from ingestion to the time of excretion. SBTT and CTT were also calculated solely on the basis of pH change.

**Bench Studies**

To determine how rapidly the capsule pH sensor responded to changes in intraluminal pH, a bench simulation study was performed. On 10 successive occasions, the time necessary for the system to record a pH change during transition between fluids of pH equivalent to those around the ICJ was determined. In brief, a WMC calibrated at pH 6 was submerged in 25 ml of simulated intestinal fluid (without pancreatin) (cat. no. 7109.75; Ricca Chemical, Arlington, TX) at pH 7.54 for 2 min until pH output settled at room temperature. The WMC was then transferred to a second container of 25 ml of simulated intestinal fluid (without pancreatin) adjusted to pH 6.36 with approx 3 ml of simulated gastric fluid (cat. no. 7108; Ricca Chemical). The elapsed time for the capsule to come to a stable reading at 6.36 ± 0.1 pH U was recorded as the response time.

**Data Presentation**

All data are expressed as means ± SE for pH and median and range for time.

**RESULTS**

**Procedure Complications**

Catheter intubation to the terminal ileum was successful in 11 of 13 subjects. In one subject, the tip did not progress beyond the pylorus (this subject had a GET of the capsule of \( \sim 7 \) h), and the catheter was removed. In two other subjects, the balloon that facilitated progression inadvertently developed a leak. In one of these the catheter was extubated, but in the other the tip had reached the midjejunum and the catheter was left in situ. In the two subjects in whom the catheter was removed, \(^{111}\)In[DTPA] was given orally in 20 ml water; the first aliquot was given before capsule ingestion, and the second aliquot was administered \( \sim 30 \) min after the capsule had exited the stomach. In two other subjects, the presence of the catheter appeared to impede capsule progression. In one subject, the WMC was immobile within the duodenum and the catheter was removed. In this subject, the second aliquot of \(^{111}\)In[DTPA] was given orally immediately after
extubation. In the other subject, the capsule did not move within the ileum for a period of 2 h. The catheter was withdrawn 50 cm, and the WMC immediately progressed.

Capsule progression through the ileocecal region was accurately assessed in 9/13 subjects. In one subject, the anatomy was impossible to interpret, as ileal loops were overlying the ICJ region. In three other subjects, passage of the capsule through the ICJ unfortunately coincided with the rest/exercise period between dynamic scans.

All subjects expelled the capsule within 30 h after oral ingestion. No adverse events occurred except for minor nasopharyngeal discomfort during intubation and extubation.

**Capsule Location Relative to the pH Drop**

In all nine subjects, a typical pH profile was registered by the WMC pH sensor as the capsule traversed the upper GI tract. Of note, in one of the three subjects in whom ICJ passage was
missed, the pH profile was unusual, in that an acute drop of 1.2 pH U was observed during progress through the jejunum, 80 min after the WMC exited the stomach. In those subjects included for analysis, however, once the WMC was in the terminal ileum, the pH was maintained at a stable value of 7.6 ± 0.05. In 100% of cases (9/9), a drop in pH was observed to occur after the capsule passed through the ICJ and was located in the large bowel (Fig. 6). Review of dynamic scans revealed episodic bolus flow of 111In[DTPA] through the ICJ, and that capsule progression into the cecum invariably occurred with one of these bolus movements. In five subjects, the onset of fall in pH occurred after arrival of the capsule in the cecum; in two subjects, onset was coincident with a move from the cecum to ascending colon; in the remaining two subjects, onset of pH fall was when the WMC was located in the ascending colon. At no time were capsules seen to pass back from the cecum into the terminal ileum. However, a transient increase in pH back toward neutral was seen in two subjects following passage into the large bowel; these events occurred at 15 min and 74 min, respectively, after the pH drop associated with small to large bowel transition, and lasted 33 min and 14 min, respectively. In the first case, the WMC was still located in the cecum when this pH rise occurred, and, in the other instance, the capsule was at the hepatic flexure.

**Magnitude of pH drop around the ICJ.** Overall the magnitude of the pH drop was 1.45 ± 0.20 to a pH value of 6.1 ± 0.1. In those subjects in whom change in pH was noted in the cecum, the fall in pH was 1.35 ± 0.20, compared with those in whom the pH fall occurred in the ascending colon, where the drop was 1.7 ± 0.1. The onset of fall in pH occurred at a median of 7 min 30 s (range 1 min to 15 min 45 s) after passage through the ICJ into the cecum. Nadir in pH was reached at 25 min (3–62 min) after arrival into the large bowel. The fall in pH from stable level to nadir was more rapid (median 4 min) in those in whom the drop occurred in the ascending colon.
compared with those where the drop occurred in the cecum (median 21 min).

**Precise site of pH drop.** The position of the capsule at the time of onset of pH fall was calculated to be 3 cm (range 1–9 cm) distal to the ICJ (though it is acknowledged that this is a 2-D measurement in a 3-D system).

**GI transit times.** GET was 61 min (12–337 min). On the basis of scintigraphic confirmation of passage of the WMC into the cecum, SBTT was 342 min (162–669 min). CTT, from scintigraphically confirmed arrival in the cecum to excretion, was 723 min (310–1,047 min). WGTT was 1,218 min (537–1,706 min).

If pH change alone was used as a surrogate marker, SBTT was 350 min (169–676 min), and CTT was 715 min (288–1,045 min).

**Bench Studies**

Median time to record a drop after transition to pH 6.3 from pH 7.54 was 14 s (range 9–17 s).

**DISCUSSION**

The determination of regional transit times within the GI tract, an important measure to aid clinical management of patients with motility disorders (3, 8), requires accurate surrogates of anatomical location if imaging is not incorporated. The long-documented pH changes along the GI tract (19, 46), and the present ability to measure it in a minimally invasive manner, make this biological phenomenon attractive for application to GI physiological investigation (6). The present study, using an intensive dual-scintigraphic technique, has finally...
provided confirmation that, in healthy subjects, the previously reported fall in pH occurring within the ileocecal region invariably takes place in the first part of the large bowel. However, the specific site of pH drop varied; in the majority it occurred in the cecum, but in a proportion the fall in pH was localized to the ascending colon.

A change in pH around the ileocecal region was first demonstrated almost four decades ago by workers at St. Bartholomew’s Hospital, London (46). Others have reproduced this finding, again using ingestible pH-sensitive radiotelemetry capsules (4, 19, 21, 22, 36). In 1988, Evans et al. (19) measured GI pH in normal subjects and showed that the mean pH in the terminal ileum was 7.5 ± 0.4, and in all subjects studied (n = 64) there was a sharp fall in pH to a mean of 6.4 ± 0.4 as the capsule presumably passed into the cecum. Likewise, Fallingborg et al. (22) reported that pH gradually increased in the small intestine from pH 6 to about pH 7.4 in the terminal ileum. The pH then dropped to 5.7 after transition into the large bowel. More recent studies using the WMC have shown that this decrease in pH is observed in ~85% of healthy subjects and patients with constipation (39). However, attribution of the site of pH drop to be passage through the ICJ is fundamentally flawed by the methods used to previously validate localization. All have important technical limitations. Methods employed include position of maximum signal strength emitted from the ingested capsule (4, 19, 44), fluoroscopic imaging (22), changes in pressure waveform as recorded by the capsule (24, 41, 44, 45), or extracorporeal detection of either a metal sphere (21) or radionuclide attached to the capsule (24, 41, 45).

In the seminal study of GI tract pH profile (19), capsule location was derived by dividing a drawing of the subject’s abdomen into nine sections and mapping position of the capsule relative to anatomy at given time points on the basis of where maximum signal strength was recorded from the ingested capsule (4, 19, 44), fluoroscopic imaging (22), changes in pressure waveform as recorded by the capsule (24, 41, 44, 45), or extracorporeal detection of either a metal sphere (21) or radionuclide attached to the capsule (24, 41, 45).

Fig. 6. Localization of the pH drop. Synchronous position and pH have been plotted for each individual subject. Time is on the x-axis, and anatomical location is on the y-axis (4 = terminal ileum; 5 = ICJ; 6 = cecum; 7 = ascending colon; 8 = hepatic flexure). The solid arrow shows the onset of pH drop. The dashed arrow shows time of passage into the large bowel. In all instances, the pH drop occurred after passage through the ICJ.
time (and up to 64%), meaning that the pH drop itself may not have been captured. Likewise, those studies in which a metal sphere (21) or radionuclide bound to a capsule (24, 41, 45) were tracked extracorporeally were similarly flawed in that true anatomical location could not be ascertained, only that the pH drop occurred within the right iliaca fossa. Fluoroscopy has been utilized (22) to provide a direct appreciation of anatomy, but, in this study, imaging was again only performed intermittently (every 30 min), and thus the zone of pH drop could be confirmed in but a proportion of subjects. Indeed, the authors commented that [we] “cannot rule out that in some subjects we might have misjudged the location of the capsule in relation to the ileocecal valve” (22). The methodology also employed a maximum fluoroscopy time of 640 s, which would be considered unethical by today’s standards. Finally, Thorburn et al. (44) used changes in contractile activity (as recorded by a pressure sensor within the capsule) to determine location, but concluded that “exact entry into the large bowel was difficult to determine as changes in waveform through the ileocecal valve are gradual rather than abrupt” (44).

The methodology employed in the present study has the advantage over previous techniques that anatomy was accurately delineated through the use of a background marker ($^{111}$In[DTTPA]), and that localization was performed relative to this. Furthermore, delivery of the isotopes was controlled, with release of the indium to near the desired location. In addition, synchronous assessment of capsule location and pH change was performed in real time, and not intermittently as performed previously (19, 22). Nevertheless, this complex method was technically challenging and not without its own limitations. To contextualize the difficulty of acquiring the desired primary endpoint (localization of the capsule at the precise time of pH drop), we were looking to capture an event taking only a few min in a study lasting the greater part of two days. In some subjects, indium had to be delivered orally; however, in those subjects we were still able to observe the regions of interest with sufficient clarity. In addition, although the drop in pH around the ICJ region was observed in all cases, the exact location of the capsule at this point was unfortunately missed in three subjects because it coincided with a resting period between dynamic scans. It appeared that a few minutes of exercise in these subjects was sufficient stimulus to promote capsule progression through the ICJ. In all three subjects, the capsule had sat at the ICJ for up to 2 h without significant movement. Finally, anatomy was not clear enough in one subject to allow a confident determination of the location of the capsule. In all other subjects, however, capsule localization was consistently agreed upon by the three independent observers.

It could be argued that recorded timing of the fall in pH was delayed because of ileal chyme being maintained around the pH sensor after passage into the cecum. This was addressed in a bench test wherein pH fall occurred within a few seconds of being transferred between viscous liquids (buffers) of pH equivalence (without agitation), suggesting that the lag to pH change in vivo is a real phenomenon. The recording frequency used also makes it likely that the variation in site of pH drop (cecum or right colon) is real. The varying times recorded in onset of pH change and reaching the lowest pH value likely reflect a pH gradient within the right colon relative to capsule progression (15, 18, 31), and buffering from terminal ileal contents.

The mechanism underlying more acidic pH in the right colon has been attributed to production of short-chain fatty acids (SCFA) by bacterial anaerobic fermentation of nondigestible fiber (4, 15, 31). SCFA production seems to be maximal in the cecum and ascending colon and then decreases progressively along the distal regions of the large bowel (15, 31); nevertheless the biology of SCFA metabolism along the length of the colon remains unclear. As previously mentioned (39), up to 15% of subjects do not show a characteristic sharp drop in pH. The reasons for this are unclear but might be related to ileocecal valve competence (28), diet, or individual colonic bacterial populations. Brinkworth et al. (5) have shown that a very low-fiber diet is associated with a significant reduction in fecal concentration of SCFA compared with a very high-fiber diet (5). There also appears to be marked variation in bacterial colonization between subjects, and an individuals’ microbiota appear to be quite stable over time (33). Low SCFA production in certain subjects may reflect this and account for the absence of the pH drop.

The WMC houses a pressure sensor that records intraluminal pressure change as a surrogate of gut contractions. The duration and maximal frequency of human small and large intestinal phasic contractions differ, and these characteristics could theoretically be used as an alternative measure to identify arrival of the WMC in the colon. However, the unpredictable variability in the state of contractility within the terminal ileum and ascending colon has made identification of passage of the WMC through these regions, on the basis of changes in waveform alone, extremely challenging (44). Therefore, development of analysis software is required, capable of analyzing both individual phasic-contraction duration and dominant frequency, which may ultimately supplement identification of small to large bowel transition, particularly in those subjects in whom the pH drop is unclear. Nevertheless, what has to be borne in mind is that passage through the ICJ takes only 1–2 min, and to truly identify an allied temporal change in contractile parameters (in a system where contraction frequency may be only around 3 per minute) may prove unrealistic.

The assessment of transit in patients with motility disorders is obviously fundamental (30). This is true particularly for conditions characterized by suspected slow GI progression (e.g., gastroparesis, constipation, and chronic idiopathic intestinal pseudoobstruction) but also holds for those conditions in which intraluminal movement may be accelerated (e.g., functional diarrhea). The WMC is a novel device for the diagnostic assessment of patients with functional GI disorders (27); such methodology does not involve radiation, is minimally invasive, and is subject friendly. Simple radiopaque marker studies, accepted as the reference standard (17, 38) and used universally, give no information on regional gut transit, which may be of particular importance in patients suspected as having a more generalized panenteric dysmotility. The only other method that allows this is whole gut scintigraphy (3, 8), which is expensive, time consuming, and constrains the subject to the nuclear medicine department (17). Validation provided by the present study means that nonradiological wireless methods that measure pH can now be used to accurately determine both small bowel and colonic transit times. That the pH drop occurs around 10 min after passage into the first part of the colon is clinically irrelevant when considering transit times of many hours. Measurements of gastric residence time and WGTT have been validated previously using the same technology (27, 32, 39).
In summary, this study has conclusively shown that the pH drop around the ileocecal region can be used as a biomarker of transition from small to large bowel. Furthermore, this fall in pH can be used clinically to determine regional GI transit times. Whether the pH drop is consistent in different GI populations.

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GRANTS

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DISCLOSURES

Dr. J. Semler is employed by the SmartPill Corporation.

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