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The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology

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SUMMARY

Background
Wireless pH and pressure motility capsule (wireless motility capsule) technology provides a method to assess regional gastrointestinal transit times.

Aims
To analyse data from a multi-centre study of gastroparetic patients and healthy controls and to compare regional transit times measured by wireless motility capsule in healthy controls and gastroparetics (GP).

Methods
A total of 66 healthy controls and 34 patients with GP (15 diabetic and 19 idiopathic) swallowed wireless motility capsule together with standardized meal (255 kcal). Gastric emptying time (GET), small bowel transit time (SBTT), colon transit time (CTT) and whole gut transit time (WGTT) were calculated using the wireless motility capsule.

Results
Gastric emptying time, CTT and WGTT but not SBTT were significantly longer in GP than in controls. Eighteen percent of gastroparetic patients had delayed WGTT. Both diabetic and idiopathic aetiologies of gastroparetics had significantly slower WGTT ($P < 0.0001$) in addition to significantly slower GET than healthy controls. Diabetic gastroparetics additionally had significantly slower CTT than healthy controls ($P = 0.0054$).

Conclusions
In addition to assessing gastric emptying, regional transit times can be measured using wireless motility capsule. The prolongation of CTT in gastroparetic patients indicates that dysmotility beyond the stomach in GP is present, and it could be contributing to symptom presentation.

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INTRODUCTION

Motility disorders of the alimentary tract pose major challenges in the daily practice of gastroenterology.[1–5] Gastroparesis is a common motility disorder that can be related to neuropathy or myopathy and is associated with such conditions as advanced diabetes, post-vagotomy complications, as well as idiopathic aetiologies.[3, 6–9] In addition to measuring gastric emptying, assessment of intestinal and colon transit may be useful in gastroparetics in that symptoms of intestinal dysmotility may overlap with those of gastroparesis and complaints of lower gastrointestinal tract dysfunction are often present in patients with gastroparesis.

Commonly employed methodologies for assessing regional gut transit (gastric, small bowel, and colon) include scintigraphy, radio-opaque markers and breath tests.[10] Although gastric emptying scintigraphy studies are widely available, the method is not standardized at the community hospital level with regard to meal composition, monitoring times, the endpoints reported and normal values. This lack of standardization limits the sensitivity and specificity of the test and often results in repeat testing upon referral to an academic centre, adding to the overall cost, radiation exposure, and potential for conflicting test results.[11–13] Recently, The American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine established consensus guidelines for gastric emptying scintigraphy. Adoption of the consensus guidelines, however, will require interest and renewed effort by community hospital nuclear medicine physicians to update their techniques, hopefully with encouragement by their local gastroenterologist.[14] How effectively the guidelines will be adopted remains uncertain.

Whole gut scintigraphy assesses small bowel and colonic transit in addition to providing gastric emptying time. However, the test is available in only a handful of specialized motility centres and requires patients to return for scintigraphic scans on at least two sequential days after the start of the test.[11–13]

Assessing gastrointestinal transit with radio opaque markers (ROM) requires exposure to radiation during follow-up abdominal X-rays. The ROM transit studies used in clinical practice lack standardization of the test protocol including: number of markers, dietary intake and diagnostic endpoints, and measure whole gut transit rather than colonic transit.[15] Breath tests address caecal arrival time of lactulose, but are not accurate tools for determining motility abnormalities within the small bowel.[16–21] Furthermore, small bowel bacterial overgrowth may interfere with the interpretation of the test. Therefore, the search for a more standardized, safe and accessible diagnostic test to detect upper and the lower alimentary tract motility disorders continues.[22–24] In addition, a standardized, convenient test that avoids radiation exposure provides an ideal tool for safe evaluation of pharmacological agents to treat GI motility disorders and to assess the effects of any pharmacological agents on the GI tract as part of standard drug safety profiling.

The assessment of regional gut transit times using a motility capsule and requiring no exposure to radiation is an attractive and practical approach. A wireless motility capsule system (SmartPill GI Monitoring System, The SmartPill Corporation, Buffalo, NY) was approved by the Food and Drug Administration in 2006 for the assessment of gastric emptying and whole gut transit time. In this article, we report a secondary analysis of regional and whole gut transit times from data collected in a previous study, which compared gastric emptying of the capsule with that of a standard radio-labelled low fat eggbeater meal measured by gastric emptying scintigraphy (GES) in gastroparetic patients and healthy controls.[25] The aims of the current analysis were to compare regional transit times as measured by the capsule in healthy controls and patients with gastroparesis (GP).

METHODS

In a study described by Kuo *et al.*[25] gastric emptying time as assessed by a non-digestible solid (wireless motility capsule) and gastric emptying as measured by standard scintigraphy (GES) were found to exhibit comparable sensitivity and specificity for detection of gastroparesis. Healthy controls and patients with previously confirmed gastroparesis (diabetic and idiopathic) were enrolled at seven academic medical centres and this study on gastric emptying is the source database for the analyses for regional and whole gut transit times.[25] The study was approved by the Institutional Review Board of each participating centre and each subject gave informed consent before entering the study. The Clinical Trial is registered with: clinicaltrials.gov, registry number: NCT001282884

This investigation assessed gastric, small bowel, colonic and whole gut transit times. Eligibility was limited to subject data containing the four physiologi-

cal landmarks necessary to assess regional transit (ingestion, gastric emptying, ileocaecal arrival and body exit). The physiological landmarks used are discernable by changes in the pH or temperature profiles and are described later in this section.

Study subjects

General exclusion criteria – all subjects. Subjects with previous GI abdominal surgery were excluded except those with uncomplicated appendectomy and/or laparoscopic cholecystectomy. Prescription medications such as lipid lowering agents, antidepressants, or birth control pills were permitted if the condition and the dose were stable for 6 months prior to enrolment in the study. NSAIDs and narcotic drugs were stopped 1 week prior to the study and other over the counter drugs were stopped 3 days before.

Healthy controls. Men and women between ages 18 and 65 years with no gastrointestinal disease as screened by the Mayo GI Disease Screening Questionnaire[26] and no cardiovascular, endocrine, renal or chronic disease were recruited as healthy volunteers. Additional criteria included average bowel movement frequency of at least one per 48 h, no pregnancy, no surgery within the past 3 months, no clinical evidence of diverticulitis demonstrated by the absence of chronic or acute abdominal pain, no medications or over-the-counter agents that could influence GI motility, no tobacco use within 8 h before and after capsule ingestion, no alcohol use 24 h before capsule ingestion and during the monitoring period and a BMI < 35.

Gastroparesis patients. Men and women between ages 18 and 66 years with history of nausea and vomiting, early satiety, epigastric pain or discomfort for at least 6 months and documented abnormal scintigraphy as defined by local medical centre standards within 2 years were enrolled as gastroparetic subjects. Gastroparetics with excessively delayed gastric emptying time (>90% of a standard egg meal retained after 2 h), average bowel movement intervals exceeding 72 h, evidence of gastric bezoar within the last 3 years, stricture, peptic ulcer, severe dysphagia to solid food and pills, severe vomiting, severe abdominal pain, severe weight loss (>10 lbs in last 2 months), or diabetes with a haemoglobin A1C greater than 10 were excluded. Proton pump inhibitors were stopped for 1 week, histamine$_2$ receptor blockers for 2 days and antacids for 1 day. Medications that affect gastric motility were stopped 48 h before the start of the study unless the subject was on the medication during the previous scintigraphy test.

Experimental procedure

Following adequate screening and on the day of the study, a urine pregnancy test for females of childbearing age and glucose level test for all diabetic subjects were obtained. After an overnight fast, all subjects swallowed the wireless motility capsule, which is equipped with three sensors for continuous measurement of luminal pH, pressure and temperature. Immediately after ingestion of the capsule with 50cc of water, subjects ate a standardized meal of 120 g Eggbeaters (60 kcal) radio-labelled with Technetium-99 m-sulphur colloid, 2 pieces of bread (120 kcal) with jam (74 kcal) and an additional 120cc of water.[11, 12] Total caloric content of the meal was 255 kcal (72% carbohydrate, 24% protein, 2% fibre, and 2% fat). Subjects completed the meal within 10 min of capsule ingestion and underwent a 6 h gastric emptying scintigraphy study as previous reported.[25]

Six hours after ingestion of the capsule and scintigraphy test meal, subjects were provided a second meal of 237 ml (8 fl oz) of Ensure (Abbott Laboratories, Abbott Park, IL, USA). This second meal was given because, apart from the radio-labelled 255 kcal test meal, diabetic patients would have been fasting since midnight and the prolonged fast risked hypoglycaemia. Provision of the Ensure meal, however, imposed a 6-h upper limit cap for the evaluation of the gastric emptying of the test meal.[25] Two hours after the Ensure meal, subjects were allowed to go home and resume normal daily activities and diet. Restrictions included no strenuous exercise (sit-ups, abdominal crunches, prolonged aerobic activity), alcohol use, and use of gastrointestinal medications (bowel cathartics, anti-diarrhoea remedies and prescription medications previously described) that could affect motility.

During and after completing the scintigraphic gastric emptying test, subjects had pH, pressure and temperature continuously measured by the capsule and recorded by a portable receiver worn on the waist or suspended on a lanyard placed around the neck. Subjects maintained an activity diary to record times of bowel movements and meals, gastrointestinal symp-

toms (pain/discomfort, nausea, vomiting), and supine/sleeping times. Subjects used the receiver event button to mark these events in the electronic record.

At 2–3 days post capsule ingestion, subjects returned to the study centre with the diary and the receiver. If no signal was detected from the capsule, an abdominal radiograph was taken to confirm capsule exit from the body. If a signal was detected, the subject was asked to return on day 3–5 post ingestion for additional follow-up. Capsule exit was confirmed in all subjects either by the return of the excreted capsule or abdominal radiograph.

pH, pressure and temperature monitoring

Measures of luminal pH, pressure and temperature were made using the SmartPill GI Monitoring System (The SmartPill Corporation, Buffalo, NY, USA). The capsule contains three sensors (pressure, pH, and temperature) and after ingestion, wirelessly transmits sensed data at 434 MHz to a data receiver worn by the subject. pH is measured from 0.5 to 9.0 pH units and has an accuracy of ±0.5 pH units; pressure is accurate to ±5 mmHg up to 100 mmHg and ±10% between 100 and 350 mmHg and temperature is accurate within ±1.0 °C. The capsule measures 15 × 35 mm and is nearly identical in size to the Given Imaging Ltd (Yoqneam, Israel) capsule used for endoscopy. Data were downloaded from the receiver using a docking station/battery charger via USB connection to a Windows PC compatible computer (Dell Corporation, Round Rock, TX, USA).

Determination of regional transit times. The locations of regional GI physiological landmarks (gastric emptying, caecal arrival and body exit) within the electronic data record were determined by two independent investigators. All discrepancies in landmark times were resolved by further review. If a landmark was absent or discrepancy could not be resolved by the review, the subject data were ineligible for inclusion in the analysis. Figure 1 shows the capsule data tracing from a gastroparetic patient graph with physi-

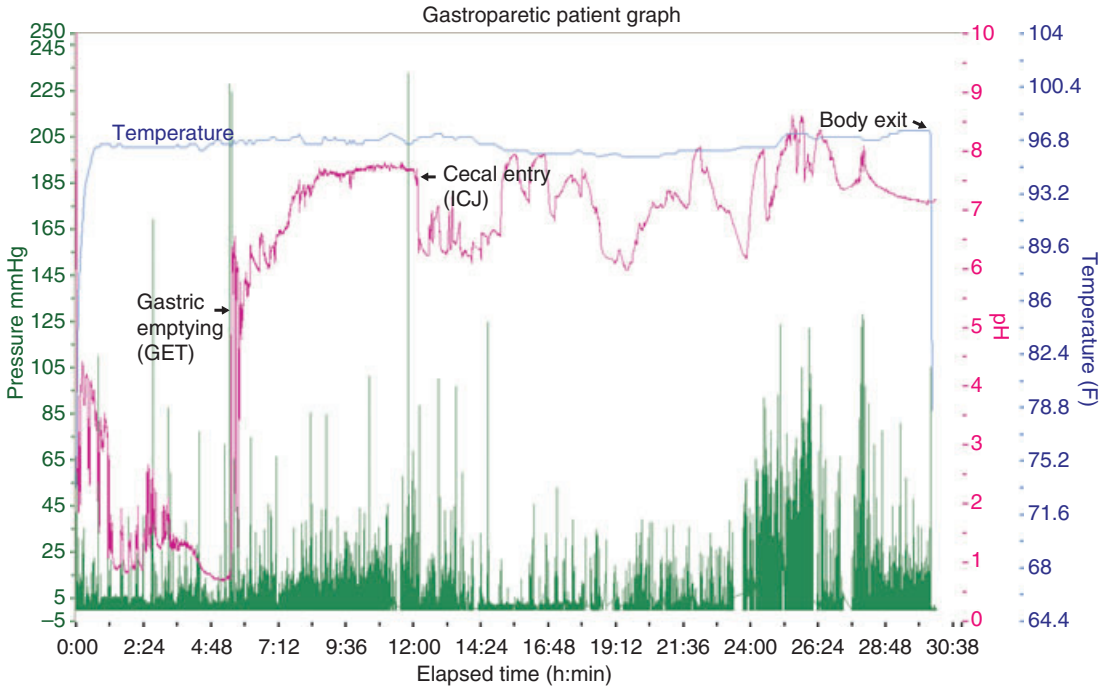

Figure 1. Wireless motility capsule graph from a patient with gastroparesis. pH (magenta), pressure (green), and temperature (blue) profile showing Gastric Emptying signified by a >4 unit sharp pH rise at 5 h, caecal arrival indicated by a 1 unit drop in pH at approximately 12 h into the test and capsule body exit at 30 h after the test started accompanied by a temperature drop.

ological landmarks at gastric emptying, caecal entry and body exit indicated. The regional transit times (elapsed time between physiological pH landmarks) derived from the electronic data are defined as follows:

Gastric emptying time (Figure 1). Gastric emptying time (GET) (or gastric transit time) is defined as the elapsed time between the ingestion of capsule and an abrupt, sustained rise in pH (greater than 2 pH units) as the capsule enters the more alkaline duodenum from the acidic stomach.

Small bowel transit time (Figure 1). Small bowel transit time (SBTT) is defined as the elapsed time from GET until the capsule's arrival at the caecum as determined by a sudden drop of approximately 1 pH unit after a gradual, sustained rise in pH as the capsule passes through the small bowel. The pH drop, indicative of the capsule's arrival at the ileocaecal region, was reported by Evans *et al*., in a study of 72 healthy volunteers who ingested a radiotelemetry capsule.[27]

Colonic transit time (Figure 1). Colonic transit time (CTT) is defined as the elapsed time from the capsule's arrival at the ileocaecal junction until the capsule's exit from the body. The exit of the capsule from the body is determined in one of two ways: (1) Cessation of capsule data coinciding with a bowel movement entry in the subject's activity diary or (2) Presence of a distinct pressure pattern caused by the pressure sensor's intrinsic sensitivity to temperature change as the capsule exits the body.

Whole gut transit time (Figure 1). Whole gut transit time (WGTT) is defined as the elapsed time from ingestion to body exit of the capsule.

Statistical analysis

Small bowel transit time, CTT, and WGTT endpoints are expressed as medians and 25th and 75th percentiles. To assess differences between groups statistically, the Wilcoxon rank sum test was used. Reported *P*-values were obtained from the permutation distributions of the test statistics based on 10,000 Monte Carlo simulations. Associations were characterized using Spearman correlation. With the given sample sizes in our two groups, we have 80% power in detecting differences of 0.6 standard deviations.

For reasons of the Ensure meal administered at 6 h, subjects with GET values greater than 6 h were capped at 6 h. Reported estimates of median GET, therefore, are based on inversion of the Kaplan–Meier curve. To accommodate the capping of GET, the rank based procedure proposed by Gehan[28] was utilized in the statistical comparison of groups.

A nominal significance level of 0.05 was used in all testing. All analyses were performed using SAS (version 9.1, Cary, NC, USA).

RESULTS

Of the 125 subjects included in the analyses of the core study, 106 had confirmed body exit of the capsule. Body exit was missing in 19 subjects because of data loss resulting primarily from the subjects' failure to keep the receiver attached to their body throughout the test. Each of the 106 subjects with a confirmed body exit had a pH increase indicative of gastric emptying. Six subjects had no discernible pH decrease landmark in the ileocaecal region and were excluded from the analysis dataset. Confirmation of pH drop at caecal entry was required for four of the remaining subjects by expert observers. The median value (interquartile range) of the pH drop associated with caecal entry was 1.3 (1.1–1.6). Thus, data from 100 subjects [66 healthy controls (26 females); and 34 gastroparetic patients (25 females)] were included in the subset analysis. Subject demographics are summarized in Table 1.

Regional transit times in healthy controls

Regional transit times in healthy controls are summarized in Table 2 and Figure 2. The median value for WGTT was 27.7 h with 3.6 h for GET, 4.6 h for SBTT, and 18.1 h for CTT.

Table 1. Age and gender breakdown for healthy and gastroparetic groups

Demographic	Healthy controls	Gastroparetic patients
n	66	34
Gender F/M	26/40	25/9
Age mean (Range)	31 (19–57)	43 (20–66)

Transit parameter (h)	Healthy controls	Gastroparesis patients	*P*
N	66	34	
GET median (percentiles)	3.6 (3.0, 4.2)	5.4 (4.1, –*)	$P < 0.0001$
SBTT median (percentiles)	4.6 (4.0, 5.9)	4.5 (3.6, 5.5)	$P = 0.615$
CTT median (percentiles)	18.1 (12.8, 26.8)	24.3 (18.4, 45.7)	$P = 0.004$
WGTT median (percentiles)	27.7 (22.9, 34.3)	45.9 (30.0, 59.0)	$P \leq 0.0001$

* 75% percentile was not observed in gastroparetic patients because of capping at 6 h.

Table 2. Median (25th and 75th percentiles) transit values in hours for GET, SBTT, CTT and WGTT for healthy controls and gastroparetic subjects

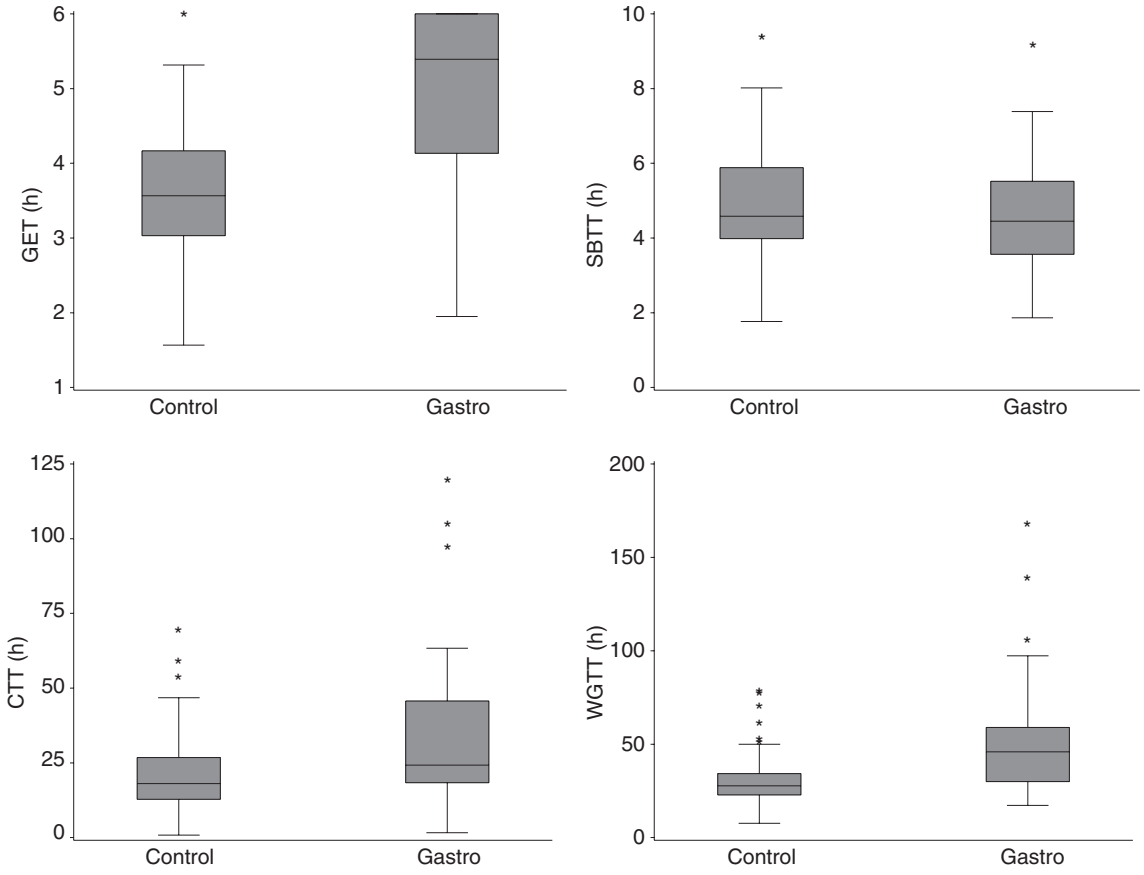

Figure 2. Box and Whisker plots of healthy controls and gastroparesis patients. Gastric emptying time (a), Colonic transit time (c) and Whole gut transit time (d) are significantly prolonged in gastroparetics. Small bowel transit time was not significantly different. Medians are shown as the lines within the box, the box boundaries are the 25th and 75th percentiles. Outliers are depicted by asterisks. The *Y*-axes are transit times in hours.

Regional transit times in gastroparetic patients compared with healthy controls

Transit times in gastroparetic patients were significantly longer in the stomach, colon, and whole gut when compared with those in healthy controls. Small bowel transit (SBTT) in both groups was similar. Idiopathic and diabetic gastroparetic subgroups had significantly slower WGTT ($P = 0.02$ and $P < 0.0001$) along with significantly slower GET than the healthy control group; diabetics had significantly slower CTT. Regional transit time data and comparisons are summarized in Table 2 and in Figure 2.

Relationship of regional transit times

The relationships between transit parameters of the different regions were analysed using Spearman correlation. Strong, significant correlations were found for WGTT to CTT in all subjects ($r = 0.92$, $P < 0.0001$) in healthy controls ($r = 0.90$, $P < 0.0001$) and in gastroparetic patients ($r = 0.93$, $P < 0.0001$). A strong, significant correlation ($r = 0.53$, $P = 0.001$) between GET and WGTT was found in gastroparetic patients.[29]

DISCUSSION

In this report, we explore the use of wireless motility capsule for assessing regional and whole gut transit times as indicators of GI tract motility in healthy controls and patients with diabetic (DGP) and idiopathic (IGP) gastroparesis. Current approaches for assessing transit in both the upper gut and lower gut are poorly standardized leading to difficulty in interpretation of results and often to the need for repeat testing. The wireless motility capsule provides regional transit measures throughout the entire GI tract in a single test. Small bowel and colonic transit times in addition to gastric emptying times measured by the wireless motility capsule are reported here including the prevalence of slow colonic transit in gastroparetic subjects.

In addition to delayed gastric emptying, colonic and whole gut transits were significantly delayed in patients with gastroparesis. Both idiopathic and diabetic gastroparetic subgroups had significantly slower WGTT along with delayed GET, a finding consistent with reports from Sadik *et al.*[30] using radio-opaque markers (ROM), and Bonapace *et al.*[31] using whole gut scintigraphy methods to assess whole gut transit in subjects with upper GI symptoms. Eighteen percent of the gastroparetics in our study had delayed whole gut transit. Sadik *et al.* reported that 17% of his subjects with the primary upper GI symptom of nausea had whole gut transit delay, and Bonapace *et al.* reported that 31% of his subjects with upper GI symptoms (abdominal discomfort, early satiety, nausea and bloating) were delayed. Within our diabetic population, delayed gastric emptying and significantly prolonged CTT were identified, consistent with the broad neuropathy changes reported in diabetes.[22] Iida *et al.*[32] also reported significant delays in colonic and whole gut transit in type II diabetics without symptoms of neuropathy using ROM to characterize whole gut transit. The significantly prolonged CTT and WGTT detected confirm the importance of evaluating regional and whole gut transit in gastroparesis.

Few studies using either scintigraphy or radio-opaque markers for determining small bowel transit have been reported. As in the Degen and Phillips study,[33] we saw no significant difference in SBTT in males and females. Graff *et al.*[34] and Sadik *et al.*[30] reported differences and suggested that the conflicting results reported in the literature could be attributed to differences in methods used to measure SBTT, most of which rely on short duration scintigraphic estimates of isotope in the stomach. Furthermore, gender differences observed in gastric emptying[30, 34] could influence the calculation of small bowel transit time. Our method, relying on pH landmarks within the gastrointestinal lumen to determine SBTT, is not influenced by gastric emptying and has the potential to yield a more exact measure.

For reasons of concerns regarding hypoglycaemia in our diabetic subjects, a second meal was given 6 h after the scintigraphy egg meal & capsule ingestion. The second meal returns the subject to the gastric fed state, delaying capsule exit until the second meal exits. Therefore, the GET values greater than 6 h were capped at 6 h since the values greater than 6 h no longer reflected the emptying of the initially administrated standard test meal. The core study determined that GET values in excess of 5 h are considered prolonged.[25] The introduction of the second meal at 6 h does limit the understanding of the duration and hence, severity of gastric emptying delay.

The start of colonic transit was determined by the observation of a rapid drop of approximately 1.3 pH units after a gradual, sustained rise in pH as the wireless motility capsule transits the small bowel. This physiological pH landmark corresponds to the start of the caecum as reported by Evans *et al.*[27] using a radio-telemetry pH capsule. Fallingborg *et al.* reported the same pH drop observation in a study using a radiotelemetry pH capsule and reported a gradual rise in pH through the duodenum and mid small bowel terminating in a pH of 7.4 at the ileum before dropping to pH 5.9 in the cecum.[35, 36] The significant increase in microflora population in the cecum is suspected to cause the observed pH drop. In ninety-four percent of eligible core study subjects, a discernible drop in pH at the caecum was observed. In the absence of the pH drop, colonic transit cannot be determined and is a potential limitation of the procedure. WGTT can be

used as a surrogate measure, given the high degree of correlation between the WGTT and CTT parameters. Changes in pressure patterns between the ileum and caecum associated with this pH drop have also been reported.[37]

We confirmed body exit by corroboration of a temperature drop with a bowel movement diary entry in 80 subjects. In 26 subjects lacking a diary entry, wireless motility capsule body exit was confirmed by the presence of a distinct pressure pattern that results from the intrinsic sensitivity of the pressure sensor to a temperature change as the capsule exits the body. Thus, body exit was confirmed in 106 of the 125 subjects (85%) analysed in the core study. As the core study focused on upper gut function (gastric emptying) and contained a safety requirement that all capsule body exits had to be confirmed by either retrieval of the capsule from stool or abdominal X-ray, we were not overly concerned about subject compliance with diary entries or diligence in keeping the receiver near the body beyond the initial 2 days of study. Product refinements have been implemented to enhance confirmation of capsule exit based on the electronic data record.

The relevance of transit times obtained with the wireless motility capsule to transit times of physiological food may be questioned because of the artificial nature of wireless motility capsule, and because food and wireless motility capsule are propelled through the stomach by different mechanisms. For instance, digestible food undergoes mixing and breakdown followed by a slow continuous propulsion into the duodenum during the post-prandial state. Wireless motility capsule empties in the fasted state following near complete emptying of the meal with short bursts of either migrating motor complexes or isolated high amplitude antral contractions, as reported by Cassilly *et al.*[38] The strong correlation between the gastric emptying of the radiolabelled meal and the wireless motility capsule reported by Kuo *et al.*[25] and the dependence of the wireless motility capsule emptying on the near complete emptying of the meal suggest that the two different mechanistic events are related. Characteristics of wireless motility capsule movement in the small bowel and colon are not precisely understood. Rao *et al.*[29] reported a strong correlation in colonic transit times measure by wireless motility capsule to those measured using ROM. Recently, Maqbool *et al.*[39] reported a strong correlation between geometric mean values of whole gut scintigraphy and wireless motility capsule, which suggests that wireless motility capsule has whole gut and colonic transit patterns similar to a meal. Further studies are needed to understand and characterize more fully the wireless motility capsule movement. However, the correlations observed with ROM and scintigraphy and the mechanistic studies of Cassilly suggest that transit times derived using wireless motility capsule are at least as clinically relevant as times derived using other clinically accepted methodologies.

In conclusion, we report that regional gut transit times (GET, CTT and WGTT) in patients with gastroparesis are significantly longer than in healthy controls. Numerous authors[40–42] have reported the prevalence of transit delays distal to the main symptom focus in functional motility disorders and this is borne out by our data indicating a significant prevalence of delay in the colon in subjects with gastroparesis. The ability to characterize discreet transit times for each region of the GI tract suggests the potential for this technique to assess drug efficacy and drug effects on the different regions of the GI tract in a single test without exposure to radiation providing a methodology for investigating new gut pharmacology. As there are limited methods available for evaluation of regional transit, the efficiency, convenience, safety and precision of results make wireless motility capsule an attractive choice for assessing regional gut transit and motility.

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