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TITLE

Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol

SHORT TITLE

Gastrointestinal transit and pH using the wireless motility capsule

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ABSTRACT

BACKGROUND: The wireless motility capsule (WMC) offers the ability to investigate luminal gastrointestinal (GI) physiology in a minimally invasive manner.

AIMS: To investigate the effect of testing protocol, gender, age and study country on regional GI transit times and associated pH values using the WMC.

METHODS: Regional GI transit times and pH values were determined in 215 healthy volunteers from USA and Sweden studied using the WMC over a 6.5-year period. The effects of test protocol, gender, age and study country were examined.

RESULTS: For GI transit times, testing protocol was associated with differences in gastric emptying time (shorter with protocol 2: median difference: 52 min, p=0.0063) and colonic transit time (longer with protocol 2: median 140 min, p=0.0189), but had no overall effect on whole gut transit time. Females had longer gastric emptying time (by median 17 min, p=0.0307), and also longer colonic transit time (104 min, p=0.0285) and whole gut transit time (263 min, p=0.0077). Increasing age was associated with shorter small bowel transit time (p=0.002), and study country also influenced small bowel and colonic transit times. Whole gut and colonic transit times showed clustering of data at values separated by 24 hours, suggesting that describing these measures as continuous variables is invalid. Testing protocol, gender and study country also significantly influenced pH values.

CONCLUSIONS: Regional GI transit times and pH values, delineated using the WMC, vary based on testing protocol, gender, age and country. Standardisation of testing is crucial for cross-referencing in clinical practice and future research.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are prevalent and constitute a considerable socioeconomic and healthcare burden [1, 2]. In patients refractory to standard therapeutic interventions, the diagnostic approach may involve using specialised tests of gastrointestinal (GI) function [3]. The assessment of GI transit is widely employed, and abnormalities of regional (i.e. stomach, small bowel, large bowel) transit are frequently identified [3, 4]. As FGIDs of the upper and lower GI tract commonly co-exist, and symptoms originating from one part of the gut may overlap with those from another, localisation of the transit abnormality is now recognised as a critical facet in deciding clinical management of complicated FGIDs [5]. Until recently,

the investigations available for the evaluation of GI transit have primarily been radiological, with measures generally limited to a single GI region. Given that some patients with FGIDs are suspected to have a pan-enteric dysmotility [6], a complete, and also regional GI profile is therefore desirable in delineating pathophysiology and guiding subsequent management. As a 'stand-alone' test, only scintigraphy has been available for the assessment of regional GI transit, but its access is generally limited to specialist centers and entails prolonged periods of imaging and multiple visits to the investigation facility [7]. As an alternative, an ingestible, telemetric device (the wireless motility capsule: WMC) is now commercially available, enabling the measurement of both regional and total GI transit times [8] in a minimally-invasive manner without recourse to the use of radiation.

For a clinical investigation to be considered useful, its endpoint, by necessity, must be able to distinguish abnormality from normality. Thus, robust and reproducible normal ranges need to be defined but also need to be finessed by an appreciation of the factors that may influence such ranges. Unfortunately, for the majority of contemporaneous GI transit tests, normal ranges are largely derived from relatively small cohorts with little or no adjustment for specific testing protocol, age or gender distribution, *see Table 1*. For example, the largest published data set of normal values of small bowel transit, as defined by radionuclide scintigraphy, is derived from only 66 individuals [9]. While gastric emptying time (GET) has recently been studied in a much larger cohort of 319 healthy subjects, the method published involved the use of a non-ambulatory, nuclear medicine technique[10], requiring the patient to be present within a hospital radiology facility throughout the investigation. Moreover, in most cases, methods are not standardised. For instance, for radio-opaque marker (ROM) studies (the most accepted test of whole gut or colonic transit), in excess of 10 different testing protocols have been published [11].

The WMC allows the delineation of regional transit from stereotypical, physiologic pH 'landmarks' recorded as it traverses the GI tract. Our primary aim was to evaluate the effect of testing protocol, gender, age and study country on gastric, small bowel, colonic and whole gut transit times in a large cohort of healthy volunteers. With

regard to the measurement of pan-GI pH, its absolute utility, beyond landmark definition, remains unclear. Differences related to transit and perturbations of the microbiota are, to date, hypothetical. Accordingly, our secondary aim was to establish normative data for regional GI pH values.

Type of Investigation	Sample Size	Region of investigation	Reference
Radio-opaque markers	192	WGTT, CTT	[12]
Radio-opaque markers	43	WGTT	[13]
Radio-opaque markers	148	CTT	[14]
Radio-opaque markers	82	CTT	[15]
Radio-opaque markers	51	CTT	[16]
Radionuclide scintigraphy	319	GET	[10]
Radionuclide scintigraphy	123	GET	[17]
Radionuclide scintigraphy	66	GET, SBTT	[9]
Radionuclide scintigraphy	90	GET	[18]
Radionuclide scintigraphy	9	GET, SBTT, CTT, WGTT	[19]
Combined radio-opaque markers and fluoroscopy	83	GET, SBTT, CTT, WGTT	[20]
Paracetamol absorption test	9	GET	[21]
^{13}C octanoic acid Breath Test	129	GET	[22]
^{13}C octanoic acid Breath Test	21	WGTT	[23]
Real-time ultrasonography	19	GET	[24]

Table 1 – Summary of the major studies describing gastrointestinal regional transit times. GET: gastric emptying time; SBTT: small bowel transit time; CTT: colonic transit time; WGTT: whole gut transit time.

MATERIALS & METHODS

STUDY POPULATION

The study population comprised of healthy volunteers who underwent a WMC test during the period March 2005 to November 2011. Data from studies performed in the USA were supplied by the SmartPill Corporation (JRS), and from studies carried out in Sweden by the principal investigator (PMH). In total, data from 231 studies were available: 191 performed in the USA, and 40 in Sweden. The data acquired in the USA were primarily derived from 2 multi-center clinical trials [25, 26]; further information on subjects acting as controls for a study of gastric emptying in gastroparetic patients [25], and volunteers involved in a trial studying colonic and whole gut transit in constipated patients [26] have been published, in part, elsewhere. The respective Institutional Review Boards or Ethics Committees at the participating sites approved all studies contained herein.

Subjects from the USA were screened with the Mayo GI disease questionnaire [27] and subjects from Sweden were screened with the Rome III questionnaire for detection of FGIDs (translated to Swedish) [28] and the Gastrointestinal Symptom Rating Scale (GSRS) [29] to exclude those with significant symptoms or a history of previous GI surgery, except uncomplicated appendectomy and/or laparoscopic cholecystectomy. Other general inclusion criteria were: aged >18 or <80 years; absence of cardiovascular, endocrine, renal or chronic disease; average bowel movement frequency of at least once per 48 hours; no pregnancy (specifically excluded on testing if the pregnancy status was equivocal); no other surgery within the past 3 months; no clinical evidence of diverticulitis, as evidenced by the absence of chronic or acute abdominal pain; no medications that could influence GI motility; no tobacco use within 8 hours before and after capsule ingestion; no alcohol use 24 hours before capsule ingestion and during the monitoring period; body mass index (BMI) <35 kg/m^2. All volunteers gave written informed consent prior to enrolment.

WIRELESS MOTILITY CAPSULE

The wireless motility capsule (previously SmartPill Corporation, Buffalo, USA; now Medtronic, Minneapolis, MN, USA) has been described in detail elsewhere [25, 26, 30]. In brief, the WMC is a single-use cylindrical capsule, measuring 26.8 x 11.7 mm housing

a solid-state pressure sensor (range 0 – 350 mmHg), a pH-sensing ion selective field effect transistor (range 0.5 – 9 pH units), a solid-state temperature sensor (range 25 – 49°C), and two silver oxide batteries, which provide a minimum of 5 days operational use. Following ingestion, the WMC monitors pressure activity, intra-luminal pH, and temperature change synchronously as it traverses the GI tract. Measurements are transmitted from the capsule at 434 MHz to a data receiver, which can be worn on a belt, a harness, or placed near to the subject under study. All received data are stored within the data receiver, which has a minimum battery life of 7 days. The pH is accurate to within +/- 0.5 units and pressure measurements are accurate to +/- 5 mmHg below 100 mmHg. After completion of the study, data can be downloaded from the receiver to a compatible computer, via a USB docking station, for subsequent display and analysis using proprietary software (MotiliGI; Medtronic).

STUDY PROTOCOL

Subjects attended following an overnight fast. Before ingestion, the WMC was activated and calibrated. Two different study protocols were used: in meal protocol 1, subjects ingested the WMC with 50 ml of water followed by an "egg beater" meal, which consisted of a scrambled egg substitute mixed with 1 mCi ^{99m}Tc sulphur-colloid marker (120 g egg beater, 60 kcal), two slices of bread (120 kcal), strawberry jam (30 g, 74 kcal), and water (120 mL); total caloric value of 255 kcal (72% carbohydrate, 24% protein, 2% fat and 2% fibre) [25]; in meal protocol 2, subjects first ingested a 262-kcal nutrient bar (SmartBar; Medtronic), modeled on the eggbeater meal, composed of 66% carbohydrate, 17% protein, 2% fat, and 3% fiber with 50 mL of water, followed by the WMC [26]. The rationale for reversing the order of meal and capsule ingestion was to preclude the possibility of very rapid emptying of the capsule from the stomach that was observed in a small minority of clinical studies using protocol 1; in these cases, the WMC was likely ejected from the stomach during 'fasted' motor activity (characterized by the migrating motor complex: MMC), prior to conversion to a 'fed' motility state following meal ingestion. All subjects were then

observed for at least 6 hours, during which they were not allowed to eat or sleep. At 6 hours post-ingestion, they were fed a second standardized meal (250 ml Ensure; Abbott Laboratories, Abbott Park, USA). Throughout each study, radiofrequency signals emitted by the capsule were recorded on a receiver that was worn continuously for 5 days, or until the capsule had been expelled by defecation [25, 26].

WIRELESS MOTILITY CAPSULE DATA ANALYSIS

WMC data for each subject were uploaded to a dedicated computer (Dell, Bracknell, UK), and analyzed manually by at least 2 of 3 investigators (YTW, SDM or NZ), with discrepancies resolved by consensus (involving SMS).

REGIONAL TRANSIT TIMES

Regional transit times were based on clear identification of the following stereotypical landmarks, *see Figure 1*:

a) time of capsule ingestion (CI) was identified by an abrupt rise in the recorded temperature and drop in pH (reflecting passage into the acidic environment of the stomach);
b) exit from the stomach (passage through the pylorus: PY) was identified by an abrupt rise in pH of usually more than 3 pH units [25];
c) passage through the ileocecal junction (ICJ) was determined by a drop in pH usually of more than 1 pH unit, sustained for at least 10 minutes, occurring at least 30 minutes after the capsule had exited the stomach [26];
d) time of WMC expulsion (CE) was determined by an abrupt drop in temperature following by loss in recorded signal after the subject had defaecated and expelled the WMC.

Based on these landmarks, the following transit times were determined:

a) GET, defined as the duration between the CI and PY;
b) small bowel transit time (SBTT), defined as the duration between the PY and ICJ;
c) colonic transit time (CTT), defined as the duration between ICJ and CE;
d) whole gut transit time (WGTT), defined as the duration between CI and CE;

e) combined small bowel transit time and colonic transit time (SBTT+CTT)- defined as the duration between PY and CE.

GET, SBTT, CTT and WGTT were also obtained from the automated analysis software (MotiliGI), and compared with the corresponding manually obtained data, to evaluate the agreement between the 2 methods.

INSERT FIGURE 1 HERE

Figure 1 – Determination of landmarks and regional transit times on plot data obtained from a WMC recording. Blue line: temperature; white line: pH; red line: pressure; white arrows: indicate respective points of capsule location; CI: capsule Ingestion; PY: pylorus transit; ICJ: ileocecal junction transit; CE: capsule expulsion; GET: gastric emptying time; SBTT: small bowel transit time; CTT: colonic transit time.

REGIONAL PH VALUES

Regional pH values were measured by the following methods:

a) stomach pH was defined as median pH during GET;
b) small bowel pH was defined as median pH during SBTT;
c) colonic pH was defined as median pH during CTT;
d) pre-expulsion pH was defined as median pH in the final 15 minutes before CE;
e) delta pylorus was defined as the difference between duodenal (defined as median pH in the first 15 minutes after PY) and antral pH (defined as median pH during the final 15 minutes prior to expulsion from the stomach);
f) delta ICJ was defined as the difference between ileal (defined as median pH in the final 15 minutes before passage through the ICJ) and cecal pH (defined as median pH in the first 15 minutes after ICJ).

Recordings where pH values were registered as less than 0 at any point were considered equipment failures and omitted from further analysis.

STUDY ENDPOINTS

The primary study endpoints were GET, SBTT, CTT, WGTT and SBTT+CTT. The secondary endpoints were the regional pH values and changes in pH around the

pylorus and the ileocecal junction. Effects of meal protocol, gender, age, and study country on the transit and pH parameters obtained were examined as exploratory endpoints. Agreement between the automated software analysis and manual readings of the primary parameters was also evaluated.

STATISTICAL ANALYSIS

The primary and secondary parameters were summarised using number of observations, mean and standard deviation. To assess the impact of meal protocol, gender, age and study country on the study endpoints, a multiple linear regression model was employed. Reference ranges for the primary and secondary parameters were estimated directly from the 5th and 95th percentiles of the measurements. Reference ranges were estimated for the combined sample as well as for each subgroup according to factors that had a significant effect on the parameters derived from multiple linear regression modelling. To compare the agreement between automated software analysis and manual reading of primary parameters, a mixed model was used to estimate the intra-class correlation coefficient (ICC). The mixed model included age, gender and meal protocol as fixed effects, and subject as a random effect and interpreted as per Yen *et al.* [31]. An ICC of >0.7 suggests good agreement between the two types of readings, whereas a value <0.4 indicates poor agreement. All statistical analyses were performed using propriety software (SAS, version 9.2, SAS Institute Inc., Cary, North Carolina, USA). Two-tailed tests were used throughout. $P<0.05$ was adopted as the statistical criterion.

RESULTS

PARTICIPANT CHARACTERISTICS

A total of 231 data files were available. Of these, 16 had major signal loss, meaning no regional transit times could be delineated, and were excluded from analysis; most of these recordings came from early studies where prototype equipment was used. Of the 215 remaining data files, 175 came from studies performed in the USA, and

40 came from studies performed in Sweden. Overall, demographic data were missing in 20 subjects. CI and PY were identified in all 215 subjects. ICJ could not be identified in 16 subjects (7.4%), so SBTT and CTT could not be determined in this group. In a further 13 subjects (6.5%), identification of ICJ had to be resolved through consensus. In 21 subjects, CE could not be identified due to either a) battery failure, or b) expulsion time could not be defined due to signal loss. Summary of subject demographics are shown in *Table 2*.

	Overall		Country				*p* value
			USA *		Sweden		
Meal protocol	**1**	**2**	**1**	**2**	**1**	**2**	
(n)	84	128	84	88	0	40	**<0.0001**
Gender (female : male)	87:110 †		66:91		21:19		NS
Median age (interquartile range) ‡	33 (23-49)		37 (25-53)		23 (22-28)		**<0.001**

*Table 2 – Subject demographics. * 3 values missing, † 18 values missing, ‡ 20 values missing.*

GASTROINTESTINAL TRANSIT TIMES

Regional GI transit times are presented as the whole group, and as subgroups classified by the 2 most significant factors identified from the linear regression analysis, i.e. meal protocol and gender, *see Table 3*. For evaluation of GET relative to the test meal, ingestion of a second meal at 6 hours set a 'ceiling' at 360 min (accordingly, subjects with a GET >6 hours were excluded from GET analysis, but included in analysis of other parameters). Overall, 96% of male subjects had expelled the capsule before consumption of the second meal, compared to 89% of female subjects (although 94% of females using meal protocol 2 had expelled the capsule by 6 hours).

Parameter	Meal protocol	Gender	N	Mean	SD	5th percentile	95th percentile
Gastric	All	All	199 †	3:25	1:01	1:49	5:10

emptying time *	1	F	27	3:53	0:54	2:34	5:25
		M	48	3:45	0:50	2:39	5:18
	2	F	49	3:20	0:57	1:52	4:58
		M	58	2:54	0:58	1:42	4:53
Small bowel transit time	All	All	199	4:27	1:41	2:17	7:36
	1	F	32	4:30	1:35	2:04	7:32
		M	46	4:38	1:43	2:30	7:36
	2	F	50	4:55	2:15	2:16	8:42
		M	54	4:07	1:02	2:26	5:45
Colonic transit time	All	All	182	23:08	15:45	3:26	50:32
	1	F	30	24:20	17:13	2:26	59:09
		M	43	17:50	11:46	2:20	36:26
	2	F	45	25:20	14:13	7:28	49:37
		M	50	22:44	16:02	4:19	50:32
Small bowel transit time + Colonic transit time	All	All	194	27:48	16:06	6:45	62:59
	1	F	30	28:56	17:19	6:27	64:22
		M	45	22:04	12:02	5:26	41:41
	2	F	49	30:33	14:51	10:13	65:29
		M	55	27:23	16:32	6:46	62:59
Whole gut transit time	All	All	194	32:12	16:37	9:44	67:51
	1	F	30	33:57	16:42	8:50	70:41
		M	45	26:54	12:46	9:12	46:42
	2	F	49	35:23	16:33	13:32	72:40
		M	55	30:40	16:46	10:26	65:28

*Table 3 – Normative data for whole and regional GI transit times (hours : minutes). * values are relative to the initial test meal. ᵗ all values >6 hours excluded (n = 16), as second meal given at this time. M = male, F = female.*

WGTT and also CTT showed an interesting clustering of data at values separated by 24 hours, *see Figure 2*, rather than being distributed normally, as has been presented previously [13]. As shown in *Figure 2*, nearly 50% of CE occurred around 24 hours after capsule ingestion, with a second peak (comprising another 17%) occurring at 48

hours.

INSERT FIGURE 2 HERE

Figure 2 – Frequency polygon of whole gut transit time (WGTT) in hours. WGTT: whole gut transit time. Frequency: percentage of WMCs expelled.

EFFECT OF TESTING PROTOCOL, GENDER, AGE AND STUDY COUNTRY ON TRANSIT TIMES

Linear regression analyses demonstrated that meal protocol 2 (WMC ingested after the meal) was associated with a shorter GET (p=0.0063), but longer CTT and also SBTT+CTT (p=0.0189 and p=0.0307, respectively). There was no overall effect of meal protocol on WGTT (p=0.06). Female gender did not influence SBTT, but was associated with significantly longer GET (p=0.0307), CTT (p=0.0285), SBTT+CTT (p=0.0195) and WGTT (p=0.0077). Increasing age was associated with shorter SBTT (p=0.002). Studies performed in Sweden were associated with longer SBTT (p=0.0019), but shorter CTT (p=0.0263).

AGREEMENT BETWEEN MANUAL AND AUTOMATED RESULTS

The agreement between regional GI transit times determined manually and those obtained by the automated software, as expressed as intra-class correlation coefficients, were 0.98 for GET, 0.54 for SBTT, 0.93 for CTT and 0.91 for WGTT.

GASTROINTESTINAL pH; EFFECT OF MEAL PROTOCOL, GENDER AND AGE

Normative values for regional GI pH measurements are presented in *Table 4*. Meal protocol was statistically significantly associated with a difference in pH in the stomach (higher with protocol 2: p<0.0001), and with changes in pH recorded across the pylorus and also the ICJ (smaller magnitude of change for both delta pylorus and delta ICJ with protocol 2: p=0.0055 and p=0.009, respectively). Gender differences

significantly influenced pH (female higher in both cases) in the small bowel (p=0.0177) and 15 minutes prior to capsule expulsion (p=0.0117). Age had no effect on pH. Studies performed in Sweden were associated with an overall lower pH in the stomach (p<0.0001), small bowel (p=0.0104) and colon (p=0.0004), and also a smaller magnitude of change for delta ICJ (p=0.0125).

Parameter	Meal protocol	Gender	N	Mean	SD	5th percentile	95th percentile
Gastric pH	All	All	205	1.9	1.3	0.7	4.6
	1	F	30	1.5	0.5	0.7	2.7
		M	45	1.2	0.8	0.7	1.7
	2	F	54	2.1	1.5	0.7	4.9
		M	58	2.2	1.4	0.5	5.1
Small bowel pH	All	All	198	7.2	0.5	6.3	7.8
	1	F	30	7.3	0.5	6.3	8.0
		M	41	7.2	0.4	6.4	7.8
	2	F	54	7.2	0.4	6.5	7.9
		M	56	7.0	0.6	6.2	7.7
Colonic pH	All	All	182	7.0	0.8	5.7	8.1
	1	F	27	7.2	0.8	5.8	8.7
		M	38	7.1	0.8	6.0	9.0
	2	F	51	6.9	0.8	5.5	8.1
		M	53	6.8	0.7	5.3	7.6
Delta pylorus	All	All	201	5.1	0.7	4.1	5.8
	1	F	29	5.2	0.5	4.1	6.0
		M	44	5.2	0.8	4.0	6.0
	2	F	54	5.0	0.6	4.0	5.7
		M	57	5.0	0.5	4.2	5.7
Delta ICJ	All	All	186	1.2	0.5	0.3	2.1
	1	F	28	1.4	0.4	0.8	2.1
		M	42	1.5	0.5	0.7	2.2
	2	F	50	1.2	0.5	0.4	2.0

		M	51	1.1	0.6	0.2	1.9
15 minutes pre expulsion	All	All	176	7.3	0.9	6.0	8.7
	1	F	24	7.7	1.0	5.8	9.5
		M	37	7.4	1.0	6.2	10.0
	2	F	49	7.3	1.1	6.1	9.0
		M	53	7.0	0.7	5.8	8.0

Table 4 - Normative WMC data for regional GI pH values. M = male, F = female.

DISCUSSION

To date, this is the largest reported data set that explores pan-gastrointestinal and regional GI transit times in healthy humans. GI transit times measured by the WMC have previously been shown to correlate strongly with those of other established methods of investigation [17, 25, 26, 32, 33]. The current study presents robust evidence that the testing protocol, gender, age and study country influence regional GI transit times (and also intraluminal pH), and therefore should be taken into consideration when interpreting data in a clinical context. However, as a broad benchmark, the data presented herein demonstrates that if the WMC is not expelled by the 3rd morning after ingestion (i.e. 72 hours), transit through the whole gut (and at least 1 region of the GI tract) is pathologically delayed.

As the WMC is an indigestible solid, its expulsion from the stomach is facilitated by distally propagating high amplitude antral contractions from phase III of the migrating motor complex [34]. This pattern occurs in the fasting state, so expulsion of WMC from the stomach is dependent on cessation of "fed state" stomach contractions, associated with the initial test meal [30]. The study protocol employed included resetting the fed state by feeding subjects a second meal at 6 hours, which would impede the expulsion of capsules retained in the stomach at this time. This is supported by the observation that of the 15 subjects (6.9% overall: 11 females) with a GET >6 hours, 11/15 (73%) did not expel the WMC from the stomach for in excess of 3 hours after their second meal (which reset the "fed state"), while the remaining

4 subjects all emptied within the first 20 minutes of the second meal (before initiation of the "fed state"). Therefore, only a GET of less than 6 hours is clinically relevant, and indeed, previous studies have 'capped' the upper limit of GET at 6 hours [25, 26]. For meal protocol 2 (test meal consumed prior to swallowing the capsule, which is now the recommended standard protocol in clinical use [5]), male subjects had a measurable upper limit for GET of approximately 5 hours. For females following meal protocol 2, 87% had expelled the capsule from their stomach by 5 hours, in agreement with the boundary proposed from the original study [25], and 94% had done so by 6 hours.

The data presented in the current study agrees with previous studies that have shown a shorter GET when subjects consumed the meal before capsule ingestion (meal protocol 1) [25, 32]. In such subjects, recording of GET began approximately 15 minutes before conversion into the fed state by the test meal. Conversely, in subjects who ingested the meal first (protocol 2), gastric contractility would have already been converted into the fed state prior to the start of the WMC recording. This is the cause of the statistically significant difference in overall median GET between the study protocols of 52 minutes. Indeed, from early clinical studies employing meal protocol 1, it was observed that gastric expulsion of the WMC was extremely rapid in a small number of subjects (within 5 minutes of capsule ingestion: data supplied by SmartPill Corporation); for this reason, adoption of meal protocol 2 (consuming the standard test meal (SmartBar) prior to ingesting the WMC), as well as restriction from a second meal for at least 6 hours after the study commences, is now recommended. These results further highlight the need for a standardised protocol to enable valid cross-referencing of data.

Overall, regional transit times were generally longer in females, mirroring previous observations [26, 35-38]. For example, Sadik *et al*. demonstrated in a study of 83 healthy controls, using a combination technique of ROM and fluoroscopy, that gastric emptying, small-bowel transit and colonic transit were significantly slower in females [20]. The menstrual cycle *per* se may also influence GI transit, for example, Wald *et al.* reported that GI transit time was prolonged in the luteal phase of the menstrual

cycle in comparison to the follicular phase, thereby implying an effect of rising progesterone on retarding transit [39]. Nevertheless, these data and ours highlight the importance of refining reference ranges particularly by gender, but there is a similar argument also to do so by BMI, stage of the menstrual cycle and menopausal status. Indeed, a limitation of our study is that we did not collect data on menstrual cycle and status, although we did exclude subjects with a BMI in excess of 35 kg/m^2. Variations in small bowel and colonic transit times were also seen between countries, though these results should be interpreted with caution as only 18.6% of recordings (40 of 215) were from Sweden. Nevertheless we postulate that host, environmental, and particularly dietary differences between Sweden and the USA, which are known to influence gut microbiota [40], metabolites [41] and consequently motility [42], may account for some of these differences. This is supported by differences in regional luminal pH seen between study countries (gut pH more acidic in the Swedish population).

One striking finding of this study was that WGTT (and CTT) showed an interesting clustering of data at values separated by 24 hours (see *Figure 2*). These frequency peaks appeared to be the result of capsule expulsion with the first bowel movement of the day. It is known that both morning waking and meal consumption result in an increase in colonic contractile activity [43], with the combined effect of both of these physiological stimuli thereby producing strong colonic contractions which precede defecation; accordingly, CE is most likely to occur in this period. This finding is of major importance with regard to the performance of current ROM techniques. Given that the data presented in this study show that whole gut (and also colonic) transit cannot be described as a continuous variable (as promoted by several existing methods) [35, 44], we propose that a more physiological way to report whole gut (and colonic) transit time(s) is as increments of 24 hours. Our data demonstrated that 36% of subjects expelled the capsule by 24 hours, 85% by 48 hours, and 96% by 72 hours. Such an approach requires subjects to commence the investigation at the same time of the day, which is now the recommended protocol, *see Table 5*. It would also be desirable, though clearly impractical, to standardise meal composition throughout the study period (and perhaps for a couple of days prior to the start of

the test also). Lack of standardisation remains a major limitation with almost all other contemporary tests of GI function, especially those involving radiology, where scheduling conflicts presents a logistical challenge to establishing a common ingestion time. The lack of use of standardized meals and scan times also continues to be problematic. In contrast to other motility testing, with the exception of high-resolution esophageal manometry [45], the WMC offers uniformity of test administration and interpretation. Despite these advantages, the intra-individual reproducibility of the WMC remains to be fully determined.

Standardized Wireless Motility Testing Protocol	
1	Overnight fast
2	Record subject details
	a. age b. gender c. BMI
3	Discontinue use of medications
	a. proton pump inhibitors for 7 days prior to, and throughout study period b. histamine-2 receptor antagonists for 3 days prior to, and throughout study period c. antacids stopped for 1 day prior to, and throughout study period d. prokinetics for 3 days prior to, and throughout study period e. laxatives for 2 days prior to, and throughout study period
4	Commence test in the morning
	a. consume SmartBar®, or “eggbeater” meal b. ingest WMC as soon as meal is completed
5	Standardised meal 6 hours after WMC ingestion
6	No standardisation of meals thereafter, with subjects instructed to follow their ‘normal eating habits’
7	Record eating habits (including meal constituents), symptoms, periods of sleep, and bowel movements in a patient diary
8	Download recorded data to PC for analysis

Table 5 – Proposed standardized test protocol.

The United States Food and Drug Administration have approved the WMC for the measurement of GET in those patients in whom gastroparesis is suspected, the evaluation of CTT in patients with suspected slow transit constipation, and the measurement of pH, pressure and temperature throughout the GI tract. The American and the European Neurogastroenterology and Motility Societies have endorsed these indications in a recently published position paper [46]. Within these endorsed indications, the current upper limit of normal for GET is 5 hours [47]. We agree with the original investigators who optimized the cut-off for clinical utility in these populations, and thus we would advocate not redefining this value.

With regard to regional pH values, *in vivo* data on the pH profile throughout the gut were first described in 1972 [48]. The use of pH changes to determine transition from stomach to small bowel (transit across the pylorus) and from small bowel to large bowel (movement across the ileocecal junction) has since been validated [49-52]. In the current study, PY was identified in all subjects, but determination of ICJ was not possible in 16 subjects, as there were no clear pH drop. It is possible that excluding these data introduced a degree of bias, although we would argue that, if indeed present, it would be small given that these 16 subjects made up only 7.4% of the cohort. Although the method of identifying ICJ transition has recently been verified [52], it was recognised that the drop in pH occurred a median of 7 minutes after passage through the ICJ and that there is variability in the magnitude and morphology of this drop. Such variations have been attributed to ileocecal valve incompetence or variation in acidity in the right colon created by metabolite production (e.g. short-chain fatty acids) through bacterial fermentation [53-55]. In the event that the ICJ cannot be identified, SBTT+CTT can be used as a surrogate to diagnose delayed transit [33]. Abnormalities in intraluminal pH may feasibly represent alterations in gut microbiota [56]. A recent paper by Farmer *et al.* reported differences in both cecal pH and delta ICJ pH in IBS patients compared to healthy controls [55]. The authors concluded that these measures, as recorded by the WMC, may represent quantifiable surrogate biomarkers of fermentation, potentially identifying those

patients that may preferentially benefit from antibiotic or dietary interventions [55]. Furthermore, this metric may potentially provide further insight into the mechanism of action of probiotics in the treatment of IBS [56]. A further interesting potential of this technology is in evaluating both the changes in motility and surrogate changes in fermentation in response to the nascent therapeutic area of faecal microbiota transplantation [57].

When testing agreement between manual and automated analysis, the former was taken as the 'gold standard'. Stereotypical pH changes around the pylorus and ICJ are readily appreciated qualitatively (100% and 93% respectively), but subtle (and morphologically variable) pH changes across the ICJ are poorly identified by the automated software analysis, which resulted in SBTT being significantly different from that identified manually (ICC = 0.54). While this also affected CTT, the longer time period of CTT meant that the difference was of a much smaller magnitude. In contrast, the large (and morphologically less variable) pH change across the pylorus was reliably identified by the automated software, which is reflected by a high degree of agreement (0.98) with the manually obtained value. At the present time, we would advocate manual verification of the fall in pH around the ICJ (which is indeed prescribed by the device software), as the automatic algorithm is sub-optimal and warrants refinement. Notably, the pH drop was <1.0 pH unit in 52 subjects (26%), which is in contrast to the defining criterion of "usually of more than 1 pH unit" [26,48]; this needs to be allowed for.

As with regional transit times, testing protocol significantly influenced pH values in the stomach and also the magnitude of pH change across the pylorus and ICJ, again supporting the need for a standardised protocol to be adopted. Female gender also significantly influenced both small bowel pH, and pH in the distal large bowel, which may be allied to sex differences in gut microbiota. The clinical importance of this finding is unclear.

In conclusion, the WMC is an ambulatory, minimally invasive, and non-radiological method for determining whole and regional GI transit times and pH. We have

demonstrated that in healthy subjects, both transit and pH are influenced by gender, age, testing protocol and country where the study is performed. Normative values for regional transit times and delta ICJ are presented for reference in clinical practice, *see Table 6.*

	Accelerated Transit (hours:min)	Delayed Transit (hours:min)
GET	<1:45	>5:00 *
SBTT	<2:15	>8:00
	US <2:15	>6:00
	Sweden <3:30	>8:45
CTT	<5:00	>50:30
	US <4:30	>58:45
	Sweden <5:00	>39:30
SBTT+CTT	<8:15	>65:15
WGTT	<10:45	>68:45 †
	Decreased (ΔpH)	**Increased (ΔpH)**
Delta ICJ	<0.4	>2.0

Table 6 – Simplified table of normative cut-offs for both accelerated and delayed GI transit and pH change across the ICJ for use in clinical practice.

For ease of clinical use, transit time values rounded-up to the nearest 15 min

* proposed cut-off based on 87th percentile

† cut-off alternatively described as **>3 days** after ingestion; data show WGTT is a non-continuous variable

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CONFLICT OF INTEREST/STUDY SUPPORT

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Adam D Farmer: drafting of the manuscript; statistical analysis; critical revision of the manuscript for important intellectual content.
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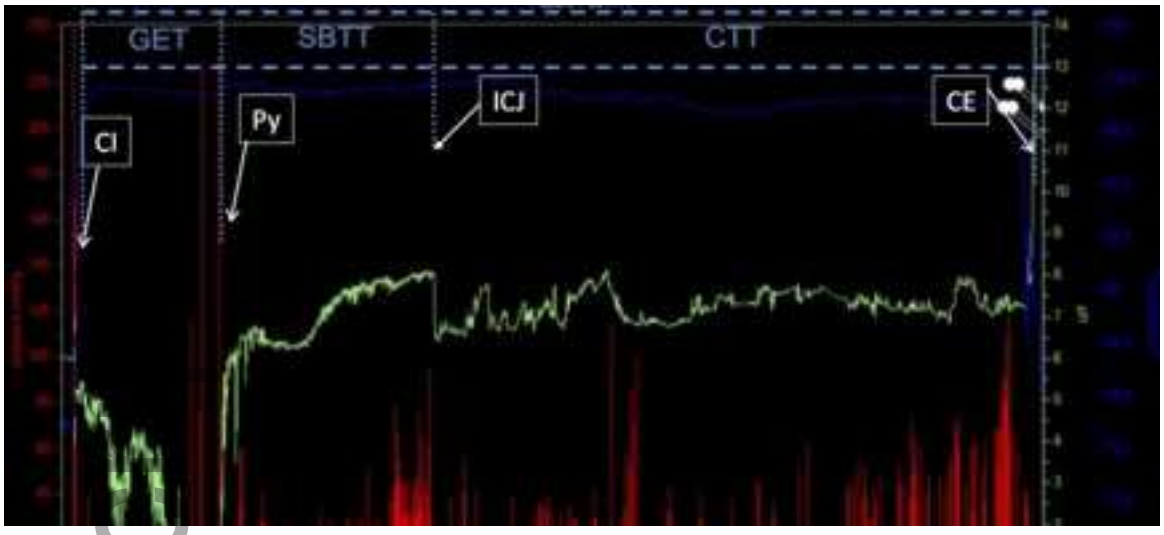

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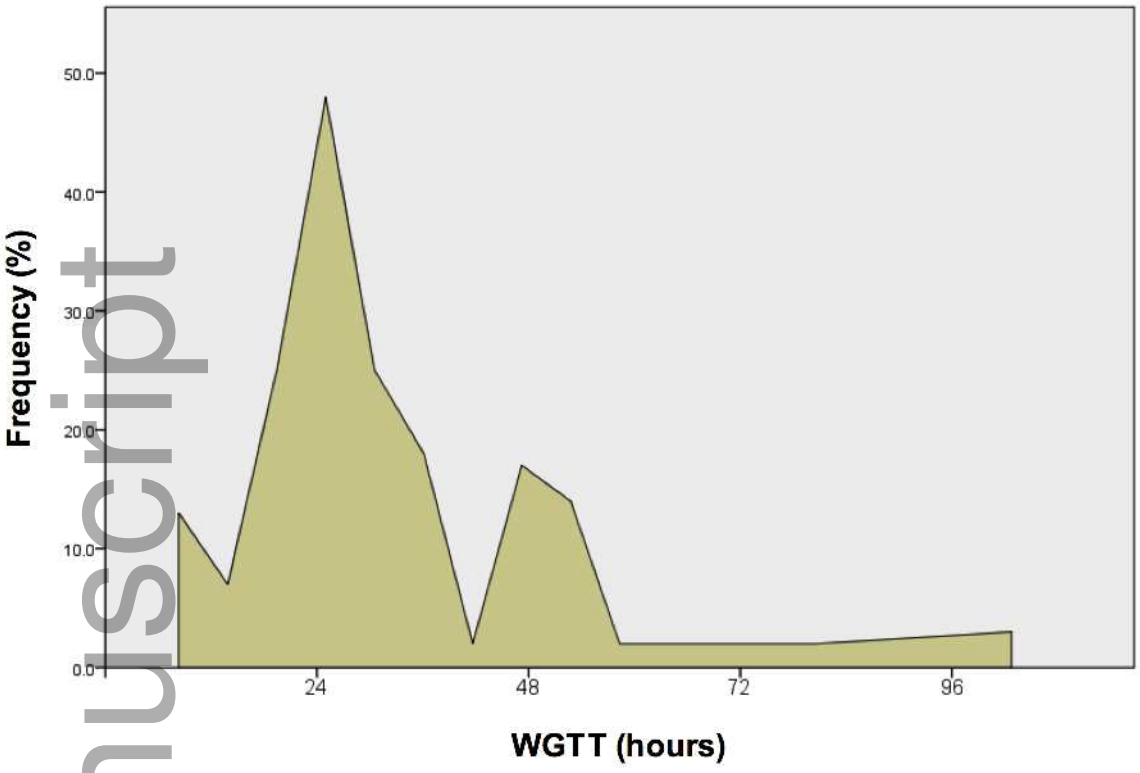

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