Evaluation of small-bowel transit for solid and liquid test meal in healthy men and women

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Abstract. Evaluation of severe functional gastrointestinal motility disorders requires an investigation of the entire gastrointestinal tract. This should be possible with a single radionuclide imaging study. The purpose of this study was (1) to define normal values of small-bowel transit in men and women and (2) to assess a possible difference between gender or test meal, since it has been shown that women have slower gastric emptying than men, and gastric emptying of solids is slower than liquids. A standard gastric-emptying test for a solid (technetium-99m sulphur colloid, 230 Kcal) and liquid (indium-111 DTPA water) test meal was performed in 12 healthy male and 12 healthy female volunteers. After 135 min, the volunteer was placed in the supine position for static imaging of the abdomen every 15 min for 6 h. Decay and crossover-corrected geometric mean gastric-emptying data were fit to a modified power exponential function to determine the 10% stomach emptying time for solids and liquids separately. An ROI was drawn around the caecum and ascending colon to determine the arrival time of at least 10% of the solid and liquid test meal. Ten percent small-bowel transit time (10%SBTT) and orocaecal transit time (OCTT) were calculated. The OCTT for males and females, respectively for solids and liquids, are 294.6±18.8; 301.3±24.5; 294.6±18.8 and 301.3±24.5 min. The 10%SBTT for males and females, respectively for solids and liquids, are 280.3±18.4; 280.6±24.0; 288.2±18.9 and 297.4±24.4 (mean±SEM) min. We observed a simultaneous transfer of solids and liquids from the terminal ileum to caecum (correlation coefficient 0.90). There is no statistically significant difference in SBTT between gender or solids and liquids. In contrast to the gastric-emptying time, the SBTT of solids and liquids were not significantly different nor was a gender difference found. Determination of the OCTT seems to be the simplest and most accurate approach to measure SBTT. Since ileocaecal transfer occurs as a bolus phenomenon, a ^{111}In-labelled test meal can also be used for the determination of colon transit in a single imaging study protocol.

Key words: Gastric emptying – Small-bowel transit – Gender-related differences

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Introduction

Symptoms of functional gastrointestinal disorders occur to some degree in about 25% of apparently healthy people [1, 2]. Most of them, however, do not seek medical help. Subjective interpretation of symptoms, in addition to psychological and socio-cultural factors, determine whether medical help is sought [2]. Gastrointestinal dysmotility symptoms are a major problem in the routine clinical practice. If after careful history-taking, thorough physical examination, appropriate biochemical and haematological screening and the conducting of examinations like radiology or endoscopy, with or without biopsy, no structural, infectious or biochemical cause can be found, the diagnosis of functional gastrointestinal transit disorder can be made [3]. Irritable bowel syndrome is an example of one of the most frequent functional disorders of the digestive tract, presenting with possible motor disorders in all parts of the intestine [4]. Constipation can also be the result of gastrointestinal transit disorders at different levels in the gut [5].

Evaluation of severe functional gastrointestinal motility disorders therefore requires an investigation of the entire gastrointestinal tract. To determine the correct therapeutic option, it is important to differentiate between a diffuse gastrointestinal motor disorder and dysfunction of an isolated gastrointestinal segment. If conservative management fails and finally partial resection

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is considered, it is useful to investigate the preoperative function of the remaining intestine [6].

Radionuclide gastric-emptying studies are routine investigations in most nuclear medicine departments. Without increasing radiation exposure, it is possible to extend a radionuclide gastric-emptying study to assess small intestine, ileocaecal and colon motility and create a non-invasive tool for documenting dysmotility of any segment of the gastrointestinal tract [6].

Recently, we confirmed a significant difference in gastric emptying of a solid test meal between healthy male and female volunteers [7]. It has been demonstrated that gastric emptying is slower in healthy premenopausal women, where both half emptying time and lag phase are significantly more prolonged than in men [7]. When evaluating small-bowel transit as part of an entire bowel-transit protocol, determination of the 10% small-bowel transit time (10%SBTT) for a solid test meal could be different for male and female patients. The purpose of this study was to define normal values of small-bowel transit in men and women, and to assess if there is a gender difference or a difference between solids and liquids.

Materials and methods

Subjects

We studied 12 healthy female volunteers (mean age 22.8± 0.5 years) and compared the scintigraphic results with 12 healthy male volunteers (mean age 22.6±0.9 years). All volunteers had a body mass index within 20–25 kg/m^2. Exclusion criteria were a history of chronic or recent gastrointestinal disease or complaints, abdominal surgery and the use of drugs with known interference on gastrointestinal motility [8, 9]. Female volunteers were studied in the first 10 days of the menstrual cycle to exclude pregnancy and minimise progesterone effect [10]. The ethics committee of the university hospital approved the study, and informed consent was obtained from each subject.

Scintigraphic test procedure

All volunteers were studied after an overnight fast of at least 8 h. Gastric emptying was evaluated after ingestion of a standardised test meal consisting of 50 g scrambled egg labelled with 74 MBq of technetium-99m-sulfur colloid, two slices of regular white bread and 150 ml water labelled with 3.5 MBq of indium-111-DTPA. The solid test meal contained approximately 230 kcal with 35% fat, 47% carboxyhydrate and 18% protein. The liquid test meal was non-caloric to standardise the methodology of gastric-emptying scintigraphy with previous trials conducted at our centre [7, 11, 12]. Simultaneous 1-min anterior and posterior static images (128×128 pixels) of the stomach were acquired on the 140-KeV ^{99m}Tc and 247-KeV ^{111}In peaks, with the subjects sitting between the two detectors of a dual-head gamma camera. Images were taken every 10 min for 1 h and every 15 min for the 2nd h. After the 2nd h, the volunteer was placed in the supine position. A static image of 2 min of the abdomen was made every 15 min for 6 h. An additional 1-min image with anatomical ^{99m}Tc-point source reference on the right upper anterior iliac spine was acquired after every frame. Finally, an additional 24-h 5-min image of the abdomen was obtained.

The volunteer received a standardised (non-labelled) meal consisting of one ham or cheese sandwich, and 20 cc mineral water 4 h after the start of the study to imitate as closely as possible the physiological situation of meal intervals (breakfast – lunch). After 8 h, the volunteer was free to eat and drink.

Data analysis

Gastric-emptying images. Regions of interest (ROIs) were drawn around the total stomach for both solids and liquids at each time interval on anterior and posterior images. After correction for technetium decay and indium down-scatter, geometric mean counts were determined. Because of interval scanning, total stomach data for solids were analysed using the power exponential function $y(t)=1-(1-e^{-\kappa}k^{t})^{\beta}$, which permits determination of the lag phase ($t$lag), emptying rate (ER), 10% gastric emptying time and half-emptying time ($t_{1/2}$) [13]. This function permits the separate identification of the two phases of the emptying process: the initial delay portion of the curve characterised by the lag phase, and the second phase, characterised by a constant emptying rate. The parameters κ and β were determined by a non-linear least-squares algorithm, where κ represents the emptying rate in min^{-1} and β the Y-intercept extrapolated from the terminal portion of the curve. The lag phase can be defined as the time in min when the second derivative of the function becomes zero and is numerical equal to $\ln \beta/\kappa$ ($t$lag). Total stomach liquid emptying data were fit to a single exponential function to determine the emptying rate, 10% gastric emptying time and half-emptying time.

Abdominal small-intestine and colon-filling images. The small-bowel transit images were corrected for decay and crossover. A geometric mean was calculated. The terminal ileum, caecum and colon were located on the images, comparing all frames and referring to the anatomical marker on the right upper anterior iliac spine. An ROI was drawn around the caecum and ascending colon to observe the phenomenon of ileocaecal transfer (i.e., ileal emptying and colon filling) and to determine the moment of at least 10% arrival of the solid and liquid test meal. The 10% small-bowel transit time (10%SBTT) was calculated by subtracting the 10% gastric-emptying time of the 10% colon arrival time. The orocaecal transit time (OCTT) was also determined as the time interval between the start of the study and in the arrival of the tracer colon. The correlation between colon filling of solids and liquids was determined at the moment of at least 10% arrival of tracer in the caecum. Therefore, the percentage of total activity of solids and liquids in the ROI (caecum – ascending colon) was calculated separately. The relationship was observed between the standard lunch administered 4 h after the start of the test and the time of colon filling. Finally, the percentage of total activity in the colon for solids and liquids was calculated after 8 and 24 h, respectively.

Dosimetry

Using 74 MBq of ^{99m}Tc-sulphur colloid and 3.5 MBq of ^{111}In-DTPA administered orally, the effective whole-body dose equivalent was 3.9 mSv in female and 3.0 mSv in male volunteers per study, with the largest single organ dose to the large bowel wall [14].

Statistical analysis

Data were tested for normal distribution by means of normal probability plots and Shapiro-Wilk statistics. All data showed a normal distribution, except the 10% gastric-emptying time for liquids in female volunteers. All results are expressed in minutes as mean±SEM (normal distribution) or median and interquartile range (non-normal distribution). Emptying rate results are reported in % per minute. Student's *t*-test for comparison of two samples was used in cases of normal distribution. The Mann-Whitney U-test for non-paired samples was used for comparison of non-normal distributed data. All statistical tests were two-tailed, and differences were evaluated at the 5% level of significance. A Bonferroni correction was applied for multiple comparison testing ($n=28$), and differences were considered significant when $P<0.002$. The correlation between filling of the colon for of solids and liquids was determined with a non-parametric rank correlation test.

Results

Gastric emptying

The determined mean and median 10% gastric-emptying time, half-emptying time and lag time values are shown separately for male and female volunteers in Table 1. There is a significant difference between gender in the half-emptying time and emptying rate of solids ($P<0.002$). The difference between gender in lag time for solids is significant before ($P<0.05$), but not after Bonferroni correction. The differences between gender in 10% gastric-emptying time for solids and liquids and in half-emptying time for liquids are not significant. As expected, there was a significant difference between solids and liquids in half-emptying time in both male and female volunteers (Table 2). The 10% gastric-emptying time of solids and liquids was significantly different in female volunteers. In male volunteers, the 10% gastric-emptying time was significantly different before ($P<0.01$), but not after Bonferroni correction. The same occurred for the emptying rate of solids and liquids in both male and female volunteers.

Current trial gastric emptying data were compared with the gastric-emptying data of another trial in normal volunteers acquired under identical circumstances and recently published [7]. There was no significant difference between the current and previous data for the different gastric-emptying parameters. Combination of data of both trials for male and female gastric-emptying of solids showed a significant difference ($P<0.002$) in lag time (TLAG) between males and females (Table 3).

Small-bowel transit

Small-bowel transit was observed on the sequential plain images of the abdomen, both for solid and liquid test meals. After leaving the stomach, the tracer migrated in

Table 1. Current trial: male vs female gastric-emptying data. Results are expressed as mean±SEM, SD, median and interquartile range. Parameters are reported separately for solids ($_S$) and liquids ($_L$)

	Male					Female					
	n	Mean	SD	Med	IQR	*n*	Mean	SD	Med	IQR	*P*
$T10_{(S)}$	12	14.3±2.1	7.1	11.3	12.3	12	20.7±2.3	8.1	21.1	11.1	NS
$T10_{(L)}$	12	6.4±0.9	3.3	4.9	10.0	12	(3.9±0.5)	(1.8)	3.3	5.3	NS
$T50_{(S)}$	12	50.5±3.9	13.6	46.6	25.6	12	84.0±7.1	24.7	75.3	25.3	<0.002
$T50_{(L)}$	12	35.4±3.5	12.0	34.3	38.4	12	29.8±2.8	9.6	29.5	15.5	NS
$TLAG_{(S)}$	12	23.3±4.3	14.8	19.2	27.5	12	37.0±3.8	12.7	41.5	20.3	NS (*****)
$ER_{(S)}$	12	2.28±0.17	0.60	2.15	0.75	12	1.42±0.17	0.60	1.46	0.58	<0.002
$ER_{(L)}$	12	2.34±0.29	1.00	2.20	1.55	12	2.33±0.35	1.22	2.10	1.90	NS

Table 2. Current trial: solid vs liquid gastric-emptying data. Results are expressed as mean±SEM, SD, median and interquartile range. Parameters are reported separately for male ($_M$) and female ($_F$) volunteers

	Solid					Liquid					
	n	Mean	SD	Med	IQR	*n*	Mean	SD	Med	IQR	*P*
$T10_{(M)}$	12	14.3±2.1	7.1	11.3	12.3	12	6.4±0.9	3.3	4.9	10.0	NS (*****)
$T10_{(F)}$	12	20.7±2.3	8.1	21.1	11.1	12	(3.9±0.5)	(1.8)	3.3	5.3	<0.002
$T50_{(M)}$	12	50.5±3.9	13.6	46.6	25.6	12	35.4±3.5	12.0	34.3	38.4	<0.002
$T50_{(F)}$	12	84.0±7.1	24.7	75.3	25.3	12	29.8±2.8	9.6	29.5	15.5	<0.002
$ER_{(M)}$	12	2.28±0.17	0.60	2.15	0.75	12	2.34±0.29	1.00	2.20	1.55	NS (*****)
$ER_{(F)}$	12	1.42±0.17	0.60	1.46	0.58	12	2.33±0.35	1.22	2.10	1.90	NS (*****)

Table 3. Combination current trial and historic data: male vs female. Results are expressed as mean±SEM, SD, median and interquartile range. Parameters are reported separately for solids ($_S$) alone

	Male					Female					
	n	Mean	SD	Med	IQR	*n*	Mean	SD	Med	IQR	*P*
$\text{TLAG}_{(S)}$	43	24.7±2.0	13.0	23.4	47.3	32	41.3±3.3	18.0	41.9	25.2	<0.002

Table 4. Current trial: male vs. female small-bowel transit data. Results are expressed as mean±SEM, SD, median and interquartile range. Parameters are reported separately for solids ($_S$) and liquids ($_L$)

	Male					Female					
	n	Mean	SD	Med	IQR	*n*	Mean	SD	Med	IQR	*P*
$\text{OCTT}_{(S)}$	12	294.6±18.8	64.9	285	60.0	12	301.3±24.5	84.7	285	101.3	NS
$\text{OCTT}_{(L)}$	12	294.6±18.8	64.9	285	60.0	12	301.3±24.5	84.7	285	101.3	NS
$10\%\text{SBTT}_{(S)}$	12	280.3±18.4	63.7	262.2	65.0	12	280.6±24.0	83.3	67.2	112.4	NS
$10\%\text{SBTT}_{(L)}$	12	288.2±18.9	61.4	280.1	269.0	12	297.4±24.4	84.4	278.9	101.6	NS

all volunteers without signs of obstruction. In every single volunteer a phenomenon of accumulation in the terminal ileum was observed before the occurrence of ileocaecal transfer. In all volunteers ileocaecal transfer occurred within the 6-h period of abdominal scintigraphy.

Colon filling

In all 24 volunteers, quantification of colon activity as a percentage of the total activity for solids and liquids was performed separately at least once just after ileocaecal transfer of a minimum of 10% tracer. In four volunteers, colon activity was measured at two separate time intervals. There was good correlation between colon filling of solids and liquids (r=0.90, P<0.01).

The 10% SBTT and OCTT values are shown in Table 4. Although not identical, there is no statistically significant difference in small-bowel transit time (SBTT) for gender or between solids and liquids. A SBTT, as determined by the OCTT of 297±65 min with a 95% range of 154–440 min, was calculated as a normal value in this investigation.

All female and 8 male volunteers had additional imaging for quantification of total colon activity. Four male volunteers refused additional imaging. Ten of 12 female volunteers had more than 90% and 12/12 had 100% of ileocaecal transfer after 8 and 24 h respectively. Six of 8 male volunteers had more than 90% and 8/8 had 100% of ileocaecal transfer after 8 and 24 h respectively.

Discussion

When evaluating small-bowel transit as part of a scintigraphic entire bowel-transit protocol, there are several possible ways to calculate the SBTT. One possibility is the analysis of gastric-emptying and colon-filling curves, by subtracting them from normalised total abdominal activity to yield a small-bowel transit curve [15]. Another possibility is subtracting the 10% time for gastric-emptying from the time of 10% colon filling to yield the 10%SBTT [16]. As a variant, the 50%SBTT can also be determined [17, 18]. Finally, SBTT can be measured by means of the orocaecal transit time (OCTT), analogous to the principle of breath testing.

In recent years, it has become more and more evident that women have slower gastric-emptying rates for solids [10, 19–21]. We recently confirmed a significant difference in gastric-emptying for gender [7]. In the assessment of small-bowel transit, this might have an important repercussion on the results of calculations where the SBTT is determined on observations depending on gastric-emptying.

When generating a small-bowel transit curve or calculating the 10%SBTT, the starting point of the exercise is dependent on gastric-emptying, in this case the lag phase and post-lag slope. In a previous article, we not only confirmed a significant difference in half-emptying time of solids, but also a significant longer lag phase in women [7]. The results of gastric-emptying obtained in the present study are not significantly different from those previously determined. The 10% gastric-emptying time was not significantly different between solids and liquids, or for gender. The lag time for solids was not significantly different after Bonferroni correction, but was significantly different for gender in our previous study (P<0.001), where a larger number of volunteers were observed [7]. When combining the lag time of all volunteers in the two studies, the difference for gender is highly significant (P<0.002).

A method defining the SBTT, depending on gastric-emptying, will result in a different starting point in men and women. The same consideration can be made for a liquid test meal, which has a shorter gastric half-emptying time and no or a minimal lag phase, depending on the caloric value as compared to a solid test meal.

It has been shown that solids and liquids, once they reach the small-bowel, move at the same speed with a mean transit time of approximately 160 min [22]. Visual interpretation of the 15-min interval dual isotope abdominal images in our population of female and male volunteers gave the same impression of simultaneous transit of the solid and liquid test meal. However, we have to consider the relative lack of resolution, even more pronounced on the ^{111}In-DTPA liquid-phase images. In most cases it is very difficult to distinguish between different small-bowel loops, and interpretation of small-bowel transit is made on the varying shape of the abdominal activity mass, indicating net propulsive movement towards the terminal ileum. Whether liquids reached the terminal ileum earlier than solids could not be visually determined because of the 15-min time-interval acquisition and the inherent difference in the quality of ^{99m}Tc and ^{111}In images.

Another issue is the terminal ileum, which has been described as a region of relative stasis that appears to serve as a reservoir before filling of the colon [15]. It has been proposed that the rate of isotope accumulation in the terminal ileum can be used to calculate an index of small-bowel motility [23]. This technique was not used in our study. However, we did observe the phenomenon of stasis in the terminal ileum in all studies performed.

We observed ileocaecal transfer by placing an ROI over the caecum and ascending colon. The caecal arrival time was defined as the time for accumulation of at least 10% of total abdominal counts in the caecum and ascending colon. It has been described that ileocaecal transfer occurs as a multiple bolus phenomenon [24]. This could not be determined in our study population because of the 15-min interval scintigraphy. Except for a few cases, the first frame with caecal activity consisted of 10% or more of the total abdominal activity. The mean caecal arrival time (i.e. OCTT) in the present study was identical for solids and liquids, both in male and female volunteers. There was no significant difference for gender. We found that there was an excellent correlation between the percentage of solid and liquid test meal detected in the caecal ROI just after ileocaecal transfer of 10% or more. This suggests that liquids, despite the minor advantage of earlier gastric-emptying, are mixed up completely or accumulate longer in the terminal ileum before simultaneous ileocaecal transfer. One could argue that simultaneous administration of solids and liquids increases the likelihood of mixing in the stomach, reducing possible differences in small-bowel transit. However, other authors also report solids leaving the stomach at a slower rate than liquids, but describe separate progression of both phases at similar speeds once the small-bowel is reached [22]. On the other hand, if a minimal difference in transit speed is to be expected, it would be difficult to prove this difference by means of scintigraphy on separate occasions because of the inherent intra-individual daily variability [25].

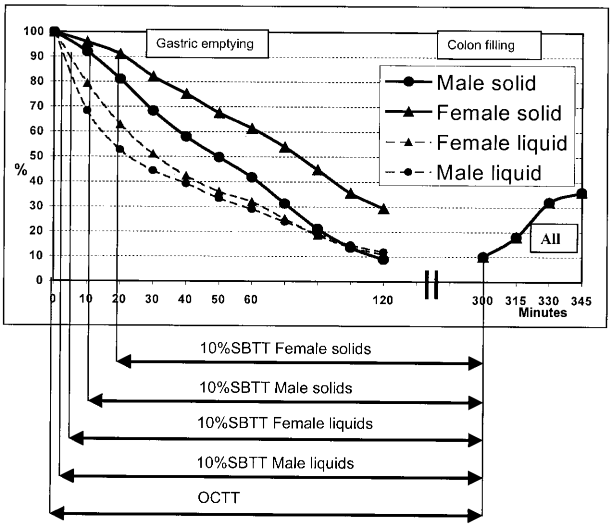

Fig. 1. A schematic illustration of normal time activity curves of gastric-emptying and colon filling in males and females for solids and liquids. The 10% gastric-emptying and colon-filling time points are marked and the different small-bowel transit times are illustrated. These differences are not significant in healthy people

As a consequence, the observations described above might give a false impression of slower small-bowel transit of liquids than solids, or faster small-bowel transit in females than in males when assessing the subject by means of the 10%SBTT. This phenomenon is illustrated in Fig. 1. This effect could be even more pronounced when the 50%SBTT is calculated because the difference in half-emptying time values for solids are more pronounced for gender or between solids and liquids than the 10% gastric-emptying time or lag-time values. However, the 10%SBTT was not statistically significantly different between solids and liquids or for gender. This can partially be explained by the methodological difference in determination of the 10% gastric-emptying time by means of a fitted curve and the caecal arrival time by means of 15-min interval scintigraphy. The latter is also responsible for the identical OCTT values for solids and liquids, both in male and female volunteers. Since ileocaecal transfer of both phases seems to occur at the same time, caecal accumulation of at least 10% of total abdominal activity of tracers will be detected in the same time frame on 15-min interval scintigraphy. Continuous abdominal scintigraphy would provide more accurate information in both cases, but is unfeasible in clinical practice. Fitting caecal activity, on the other hand, does not seem feasible because of the multiple bolus transfer observed by other authors [24].

When addressing the problem of functional gastrointestinal motility disorders, it is known that in the case of gastroparesis, the lag phase can be altered (prolonged) [11, 26]. When ileocaecal transfer is not delayed, a prolonged lag phase would have a more pronounced effect on 10%SBTT values, giving the impression of even faster small-bowel transit than in healthy people. The difference in 10%SBTT values between solids and liquids will also be more pronounced since gastric-emptying of liquids is far less affected or not at all in idiopathic gastroparesis [11]. The OCTT values for solids and liquids might not be affected and are interesting parameters to observe.

The lag phase, emptying rate and the shape of the gastric-emptying curve will have an effect on small-bowel transit as an input function. If the transport of solids and liquids, once the small-bowel is reached, move at the same speed and accumulate and mix up in the terminal ileum, it is not clear whether a prolonged lag phase or delayed gastric-emptying has an immediate effect on ileocaecal transfer time. Although there is a significant difference in gastric-emptying for solids, as determined by half-emptying time and lag-time values, we did not observe a significant difference in mean caecal arrival time for gender. The same reflection can be made for the difference in gastric-emptying of solids and liquids, which does not result in a significant difference in caecal arrival times. This would in fact suggest that accumulation in the terminal ileum compensates for differences in small-bowel input.

When the ileocaecal transfer is unchanged, the OCTT would not be different in cases of delayed gastric-emptying with normal small-bowel transit. This is in contrast to the 10%SBTT, which is influenced by gastric-emptying values as a starting point of measurement. The hypothesis that OCTT measurement is more reliable than determination of 10%SBTT has to be evaluated in a trial comparing patients with gastroparesis to data from normal subjects.

Determination of the OCTT is an easy approach, analogous to the principle of breath testing, with the advantage of visual correlation of quantitative data, where breath testing only gives normal or abnormal values and scintigraphy enables regional abnormal gastrointestinal function to be visualised. An abnormal OCTT can immediately be correlated with detailed regional gastric and small-bowel transit data to determine the location of the delay.

It has been described that there might be a relationship between the phenomenon of ileocaecal transfer and an ingestion of a so-called “push” meal [24]. All our volunteers received a standardised lunch 4 h after the start of the test, which can be regarded as a push meal at a fixed moment. Although 7/24 bolus transfers occurred within 30 min and another 6/24 within 60 min after ingestion of the push meal, it is not possible to determine a relationship for these data without control studies with another timing of the push meal.

We observed almost total ileocaecal transfer at 8 h and total ileocaecal transfer for solids and liquids at 24 h in all volunteers observed. Orally administrated ^{111}In-DTPA has been compared with direct caecal intubation in the assessment of colon motility, without a significant difference [27]. Our observations of ileocaecal transfer support the hypothesis that the ileocaecal transfer bolus phenomenon can be used as a start for colon motility studies without the need for less physiological techniques using capsules, dissolving in the terminal ileum or using techniques of caecal instillation of tracer [28–31]. A study using the liquid ^{111}In-DTPA fraction from entire-gut transit scintigraphy to evaluate colon transit is currently being performed on patients with severe functional gastrointestinal dysmotility.

In contrast to gastric-emptying, the SBTT of solids and liquids was not significantly different, nor was a significant difference for gender found in healthy volunteers. Determination of the OCTT seems to be the simplest and most accurate approach to measure SBTT by means of scintigraphy, because it is less dependent on gastric-emptying even though no significant difference could be demonstrated in healthy controls. Whether or not, defining the 10%SBTT as well will be helpful in differentiating between gastric and small-bowel dysmotility in idiopathic gastroparesis must still be elucidated. Since ileocaecal transfer occurs as a bolus phenomenon, an ^{111}In-labelled test meal can also be used for the determination of colon transit in a single imaging, whole-gut study protocol.

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