Proof of Concept: Design and Initial Evaluation of a New Device to Measure Gastrointestinal Transit Time

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Abstract

Chronic constipation and gastrointestinal motility disorders constitute a large part of a gastroenterology practice and represent a significant impact on patient quality of life and lifestyle. In most cases, medications are prescribed to alleviate symptoms without an objective measurement of response. Commonly used current investigations of gastrointestinal transit times are limited to radiopaque markers or electronic capsules. Repeated use of these techniques is limited due to radiation exposure or the significant cost of the devices. We present the proof of concept of a new device to measure the gastrointestinal transit time using commonly available and inexpensive materials with only a small amount of radiotracer.

Methods: A gelatin capsule containing paraffin and radiolabeled rice was assembled using ^{67}Ga-citrate as the tracer material. This point source transit device (PSTD) was tested for stability in-vitro and subsequently given to 4 normal volunteers and 10 patients with symptoms of constipation or diarrhea. Imaging was performed at regular intervals until the PSTD was excreted.

Results: The PSTD remained intact and visible as a point source in all subjects until excretion. Used in combination with a diary of bowel movement times and dates, the total transit time could be determined. The PSTD could be visualized either alone, in combination with a barium small bowel follow through study, or in conjunction with a gastric emptying study.

Conclusions: The use of a PSTD for the determination of GI transit time is a feasible alternative to other methods. The PSTD is inexpensive, easy to assemble, requires only a small amount of radiotracer and remains inert through the GI tract allowing for accurate determination of gastrointestinal transit time. Further investigation with this device is required to establish optimum imaging parameters and normal values. The use of gastrointestinal transit time measurements may be useful in the management of patients with dysmotility and to help select the appropriate pharmaceutical management.

Key Words: whole gut transit scintigraphy; gastrointestinal scintigraphy; small-bowel transit; colon transit; constipation

Introduction

The investigation of gastrointestinal function and motility can be traced to the very early days of radiology. Shortly after the discovery of X-rays by Roentgen in 1895, stomach motility was explored by Lindeman (1897) and the physiology of swallowing and peristalsis was described by Cannon (1898) (*1,2,3*). Bismuth was used as an early contrast by Rieder in 1904 to explore the stomach and bowel motility and was later replaced by the less toxic barium in 1910 (*4,5*). For decades a variety of barium studies became the standard techniques to investigate the anatomy and physiology of the GI system.

Some previously described methods to determine GI transit time include the use of glass beads (*6*), dyes (*7*), and other non-digestible materials (*8*) and noting the time that they first appear in the stool. Radiopaque markers have also been used successfully, but require serial radiographs repeated radiation exposure (*9*). More recently a wireless capsule has been used to measure transit time (*10*). This technique however is expensive and the capsule is sometimes difficult to swallow due to its size.

Early scintigraphic techniques to evaluate gastric emptying utilized ^{51}Cr (*11*), ^{113m}In-DTPA or ^{99m}Tc-DTPA in saline (*12*). In 1976 Meyer described the use of ^{99m}Tc-labelled chicken liver as a marker of solid food emptying from the stomach (*13*). Today the Society of Nuclear Medicine and Molecular Imaging procedure guideline for adult solid-meal gastric-emptying version 3.0 recommends 4 oz. of cooked liquid egg white, two slices of toasted white bread, 30 gm of jelly or jam and 120 ml. of water as the standard meal (*14*). A technique using ^{111}In in activated charcoal in a capsule coated with pH sensitive methacrylate has also been described to investigate GI transit time (*15*). Once the methacrylate dissolves in the terminal ileum, the contents of the capsule are released and mix with the contents of the large bowel. The geometric center of the activity then needs to be determined. A scintigraphic technique using liquid tracer sealed in plastic tubing has also been described (*16*). More recently, scintigraphy has been recognized as an effective method of measuring gastrointestinal motility and new Current Procedural Terminology codes are available. The description of these studies can be found in a joint practice guideline from the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine (*17*). This is an area of current evolution and the application of these studies in various pathologies has been recently described. (*18*)

Patients with motility disorders represent a significant part of a gastroenterologists practice. Irritable bowel disease has a significant impact on patient lifestyle and quality of life. There is an estimated 2.5 million US visits to the physician annually for constipation (*19*) and over $800 million in laxative use (*20*). This is likely underestimated due to use of other over the counter preparations.

Dysmotility may have several origins or be the result of medications taken by the patient, an underlying allergies, inadequate hydration, organic etiologies or psychogenic origins. The etiologies are often difficult to identify and a variety of attempts are made to correct the symptoms with little objective evidence of results. In current practice, subjective improvement of symptoms often dictates therapy introduction and modification. This "trial and error" approach leads to prolonged exposure to multiple different medications which may not be without consequence. Indeed, even if transit time is normalized, patients may continue to have complaints. An inexpensive, safe and easy to perform procedure with a low radiation burden to objectively measure GI transit time would be beneficial for

this patient group. These results could help identify the effect of the interventional medication, document normalization of transit and perhaps direct the physician to other causes of the symptoms.

Our goal in this project was to develop a point source transit device (PSTD) for the measurement of GI transit time. With the exception of the isotope, the PSTD would ideally be constructed using inexpensive and commonly available materials.

Methods

Capsule Design

When considering the design of a device to be followed through the GI tract, we followed the principles of radiopharmacy (*21*). The device needed to reflect the underlying physiology without the possibility of changing it. The device also had to be biologically inert, non-toxic, not absorbed, and move readily with the GI contents. To evaluate the movement of solids as they pass through the GI tract, it needed to have no appreciable bulk and be easily detected and measurable for many days in patients with slower GI motility.

Our first consideration was to select the ideal isotope to work with. The readily available isotopes that have longer half-lives and are amenable to gamma camera imaging are ^{201}Tl, ^{67}Ga and ^{111}In. Thallium was discounted due to its lower energy. If the PSTD were ever to be used in combination with a ^{99m}Tc gastric emptying study, the ^{201}Tl activity might be difficult to detect. Indium and gallium would both be effective isotopes for long term imaging and could be easily distinguished from background technetium activity. We chose ^{67}Ga-citrate for this investigation primarily due to its lower cost when compared to ^{111}In-chloride.

The next consideration was to identify the vehicle to carry the isotope through the GI tract. For this, a non-digestible material was necessary. Most plastics are biologically inert but empty plastic capsules to contain the tracer were not easily found. Paraffin wax is a non-reactive material that is impervious to both acid and alkali. On further investigation, we also found that paraffin remains solid at physiologic temperatures with a melting point of approximately 58-62° C (*22*). An additional benefit is that paraffin is an established non-toxic material that is FDA approved and widely used in food preparation and storage (*23*). Commonly available and inexpensive, it is an ideal material that would remain unaltered as it passes through the GI tract. Unfortunately the isotope and paraffin are immiscible and could not be easily combined to form a single source. A third component would be needed to contain the isotope within the paraffin.

The majority of any radiopharmaceutical as dispensed from a radiopharmacy is water with relatively few atoms of radioactive material. Evaporation of the liquid phase from the radiopharmaceutical would leave the radioactive atoms behind, but these would be impossible to manipulate. A porous or hygroscopic material could absorb the radiotracer and allow for easier manipulation. While a variety of porous materials were considered, we continued to pursue the use of materials that are commonly available and non-toxic. Grains of food grade rice are hygroscopic, small, and easy to manipulate. We

investigated and developed a technique to evaporate the liquid phase of radiopharmaceutical and concentrate the activity within the grain of rice.

Finally, we required a mechanism to protect the grain of rice with paraffin to prevent digestion as it passes through the GI tract. Simply dipping the grain of rice in melted paraffin was insufficient to create a uniform coating and might not protect the grain sufficiently. A method to easily and uniformly contain the grain of rice within the paraffin was required. We chose to use a standard gelatin capsule as a container. After filling the gelatin capsule with melted paraffin, the grain of rice could be placed into the center and more liquid paraffin added to completely encase the grain of rice. Using this design at least 1-2 mm of paraffin coating would surround the grain of rice (Figure 1). We felt this to be sufficient for protection and proceeded with testing the PSTD.

Laboratory Evaluation

Earliest testing of the device integrity was performed using blue food dye to check for leakage. Subsequently, to investigate in-vitro stability, five PSTD devices were constructed using ^{99m}Tc-pertechnetate as the tracer. The activity of each device ranged between 17.2 MBq (464 µCi) and 22.6 MBq (610 µCi) with an average of 18.8 MBq (509 µCi). These five devices were placed in a 1 liter beaker water bath and warmed to a temperature of 45° C (113° F) for three hours with continuous stirring by a magnetic stir rod. A 3 ml sample of the water was obtained prior to beginning testing and at 1, 2 and 3 hours. These samples were each measured in a well counter for three minutes to evaluate for leakage from the devices.

In a standard ^{67}Ga-citrate study using 185 MBq (5 mCi), approximately 10% (18.5 MBq) of the intravenous administered dose is excreted through the GI tract (*24*). Since the PSTD uses approximately 20% of the above activity expected in the GI tract, dose estimates for the stomach, small intestine, upper large intestine and lower large intestine are 2 mGy, 3.6 mGy, 5.6 mGy and 9 mGy respectively.

In the unlikely event that the PSTD would become lodged in the appendix or a diverticulum and deliver the entire dose of radiation at that location, we estimated the dose at 0.97 Gy. Such a dose is significantly less than a single fraction of radiotherapy and would be delivered over a much longer period of time. Even in this worst case scenario, the dose is unlikely to result in an acute local reaction of the appendix or diverticulum.

Clinical Evaluation

Population

The study populations consisted of 4 normal volunteers and an additional 10 symptomatic patients. All subjects (14/14) were greater than 18 years of age. The normal volunteers had no gastrointestinal complaints. The ten additional symptomatic subjects with GI complaints were referred by a gastroenterologist, and needed to be scheduled for either a nuclear medicine gastric emptying study or small bowel follow through study. GI complaints consisted of constipation (9/10) and diarrhea (1/10). None of the volunteers or symptomatic subjects had prior GI surgery (appendectomy and cholecystectomy were permitted). All volunteers and symptomatic subjects fasted after midnight.

Symptomatic subjects stopped any medication relating to their GI motility for 24 hours prior to the study. All human investigation was approved by the Loyola University Medical Center institutional review board and all subjects signed an informed consent form. The Loyola University Medical Center radiation control committee also approved the investigational use of the device.

Dose
The first of the 4 normal volunteers received the PSTD containing 6.62 MBq (179 µCi) of ^{67}Ga-citrate. Based on the intensity seen on the images, the activity in all subsequent PSTDs was decreased and ranged from 2.39 – 3.55 MBq (64.7 – 96.0 µCi). Normal volunteers swallowed the PSTD with 8 oz. of water and then were allowed to resume their normal diet.

Imaging
For the initial validation phase of the study, 4 normal volunteers underwent periodic imaging after swallowing the PSTD until it was no longer visualized on gamma camera.   No other imaging was performed concurrently on the normal volunteers. For the 10 symptomatic subjects, imaging was performed immediately, at 15, 30, 45 and 60 minutes after swallowing the PSTD. Subsequent images were obtained every hour thereafter until 6 hours at which point subjects could resume their normal diet and GI medications. Symptomatic subjects were asked to return for images on subsequent days to identify excretion of the PSTD. Of the symptomatic subjects 3/10 had a barium small bowel follow through study performed concurrently and took the PSTD with 500 cc of barium. The remaining 7/10 symptomatic subjects had a nuclear medicine gastric emptying study performed concurrently and swallowed the PSTD during the standard radiolabeled meal. In subjects who had the gastric emptying study, a dual isotope acquisition was performed.

Two minute anterior projection images were obtained using a gamma camera (Forte – Philips Medical Systems (Cleveland), Inc.) with a medium energy collimator.   Normal volunteers (4/4) and those symptomatic subjects that had a concurrent barium small bowel follow through study (3/10) were imaged with a ^{57}Co sheet source behind them to help identify the anatomical location of the PSTD. Those symptomatic patients who took the PSTD in conjunction with a gastric emptying study (7/10) did not require a sheet source behind them during imaging to assist in determining anatomical location.

Stability
The PSTD was considered stable if the final image with activity prior to excretion of the device demonstrated a point source on scan. If the PSTD integrity failed, presumably the leaked activity would be seen as a "blush" and be dispersed within the bowel contents.

Total Gastrointestinal Transit Time
All volunteers and symptomatic subjects kept a diary of the dates and times of their bowel movements. The PSTD excretion time was defined as the first bowel movement that occurred between the time of the last image demonstrating device activity and the subsequent image with no activity. Total Gastrointestinal Transit time (TGIT) was calculated as the time difference between swallowing the PSTD and the determined PSTD excretion time point. The PSTD was not recovered as part of this study.

Results

Stability

Initial stability testing in the laboratory found the PSTD to be stable when warmed to 45° C (113° F) for three hours in an agitated water bath. None of the water bath samples demonstrated activity above background. Although the gelatin capsule covering dissolved, the central paraffin-rice combination remained intact. The use of blue food dye in early leak testing was found to be useful in the later construction of the device. The darker color of the grain of rice made for easier visualization and subsequent manipulation when inserting the grain into the melted paraffin. Based on initial stability findings and the non-significant risk nature of the device, the Loyola University Medical Center Investigational Review Board and the Radiation Control Committee approved the use of the PSTD. We report here only on the stability and detectability of the PSTD to measure gastrointestinal transit times.

In all normal and symptomatic subjects (14/14), the PSTD remained visible without apparent leakage (blush) until the patient either withdrew from the study or the imaging was completed.

Total Gastrointestinal Transit Time

All normal volunteer subjects (4/4) excreted the PSTD by 24 hours. Average TGIT for the 4/4 normal volunteers was 15 hours and 57 minutes (15'57"; Std. Dev. 7'18", Range 7'00" – 22'18"). One volunteer (1/4) excreted the PSTD at 7 hours and on questioning was found to have consumed several large cups of coffee subsequent to taking the PSTD. Despite drinking hot coffee, the PSTD remained intact and visible on images obtained at 3 and 5 hours.

One (1/10) symptomatic subject with constipation who received the PSTD in conjunction with the barium small bowel follow through study refused further imaging after 4 hours. Another subject (1/10) with constipation declined to return for imaging after the 24 hour images. The remaining 8/10 continued with imaging until the PSTD was excreted. Average TGIT for the 7/10 symptomatic subjects who had complaints of constipation was 40 hours and 45 minutes (40'45"; Std. Dev. 18:13, Range 9'50" – 67'43"). A summary of TGIT for all patients is summarized it table 1.

Although the symptomatic complaint for patient number 9 was constipation, this subject had three bowel movements between the 6 hour image and the next day delayed image. Excretion may have occurred at any of these times. As per our definition above, the TGIT we determined was based on the first bowel movement that occurred after the 6 hour image resulting in a transit time of 9'50". The two subsequent bowel movements prior to the final image without activity occurred at 22' and 24'30" post administration. It is unknown if excretion occurred at one of these time points instead.

Location Determination

Determination of the location of the PSTD is important if small bowel transit time is to be determined. In the 4 normal subjects and the 3 symptomatic patients who took the PSTD along with barium for a small bowel follow through study, imaging was performed using a sheet source behind the patient (Figure 2). This technique allows a general localization of the device (upper abdomen, mid abdomen, lateral abdomen or pelvis) but doesn't with confidence identify the time that the PSTD enters the

ascending colon. In the 7/10 symptomatic subjects that swallowed the PSTD in combination with a gastric emptying study, digital fusion of the planar images obtained using dual isotope acquisition of ^{99m}Tc and ^{67}Ga windows (Hermes Medical Solutions. London. UK) allowed the greatest confidence in determination of the device location within the stomach, small bowel or large bowel (Figure 3).

Discussion

The current available non-scintigraphic techniques to measure GI transit times are either expensive (wireless capsule) or result in multiple x-rays of the abdomen and greater radiation exposure (radiopaque markers). Barium and other liquids mix with the GI contents and may not reflect the physiologic motility of solids making transit time calculations difficult. Marker methods using indigestible foods or dyes have similar limitations.

The described PSTD is considered by the FDA as a device rather than a radiopharmaceutical *(25)*. The nature of the device is such that it falls into the classification of non-significant risk (*26*). No similar device is currently available on the market so that near term future use and clinical investigations will still require IRB approval. It is inexpensive, easy to make and composed of commonly available and non-toxic food grade materials. The PSTD was visible in-vivo for several days and although the number of subjects in this study is admittedly small, device stability was proven in all subjects.

Using the PSTD, the evaluation of TGIT is simple to perform and only requires a few additional imaging time points and for the patient to record the timing of their bowel movements. In this investigation, the bowel movement diary was only for the duration of the exam. To obtain a more complete clinical picture of the GI motility, a diary of bowel movements for a week prior and a week after the exam may be of use. In addition, any medication the patient was taking for their GI symptoms was only discontinued for a short time prior to entering this study. A better evaluation of the transit times might be derived while the patient is discontinued from medication for a longer period of time. Due to the frequency of bowel movements seen in patients with diarrhea, this protocol is unlikely to capture the true TGIT. Further, the frequency of bowel movements would need to be addressed regardless of the transit time. The PSTD is therefore more likely to be beneficial in patients with constipation.

Used in combination with a gastric emptying study or other scintigraphic techniques, the TGIT time for a solid can be estimated in addition to gastric emptying. There is potential to use the PSTD in combination with a gastric emptying study to estimate the small bowel transit time. The protocol and timing of the images however needs to be optimized to derive these results and further investigation in this technique is ongoing. Fusion of planar images obtained using dual isotope imaging allows for the greatest ability to identify the anatomic location of the PSTD.

Further investigation with this device is required to explore its utility and identify the optimum timing of imaging. The current continuous 6 hours spent in the department can be demanding for the patient. When used in conjunction with a gastric emptying study, the standard imaging every 15 minutes for the first hour and every hour thereafter for four hours would normally be performed. If the PSTD is not seen at the ileocecal junction, additional imaging could be performed at 6 and/or 8 hours. The

scheduling of delayed imaging at 24 or 48 hours or even later can be more flexible for the patient since the image is only used to correlate with bowel movements and estimate the time of excretion.

Objective measurements of bowel transit may be useful to clinicians in evaluating the therapeutic response since some of the medications used to treat chronic constipation can be quite expensive. Documentation of baseline transit time and any change to transit time due to medication can then be objectively used to guide therapy. Should the transit time normalize after intervention and symptoms persists, an alternative cause such as dietary, allergic, or psychogenic etiologies can be considered. A larger study of normal patients is also required to more firmly establish the normal range for this device. We continue to accrue symptomatic subjects into our ongoing study. Finally, the knowledge of normal or abnormal transit times may be reassuring for the patient and allow both patients and physicians to pursue other solutions for symptoms.

Conclusion

We have described the proof of concept for a new device for the measurement of GI transit time. Inexpensive and easy to produce from commonly available materials, it has proved to be stable in-vivo and effective in estimating total gastrointestinal transit times for solids using only a small amount of tracer. Such a device may prove to be useful in combination with other described scintigraphic techniques. Additional investigation is required to establish the optimum dose, imaging times, and techniques as well as normal and pathological values. A larger study is also required to determine if this technique is a useful complement to patient management and to help select the proper pharmaceutical therapy for individuals with chronic constipation.
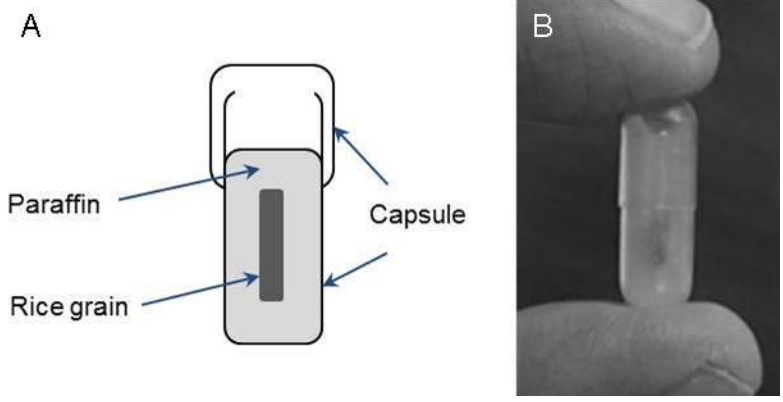
Disclosure

Figure 1

A diagram of the device design (A) illustrates the central core composed of a grain of radiolabeled rice surrounded by paraffin wax. The final assembled device (B) is small and easily swallowed. Note that the grain of rice is stained with blue food dye to assist in construction.
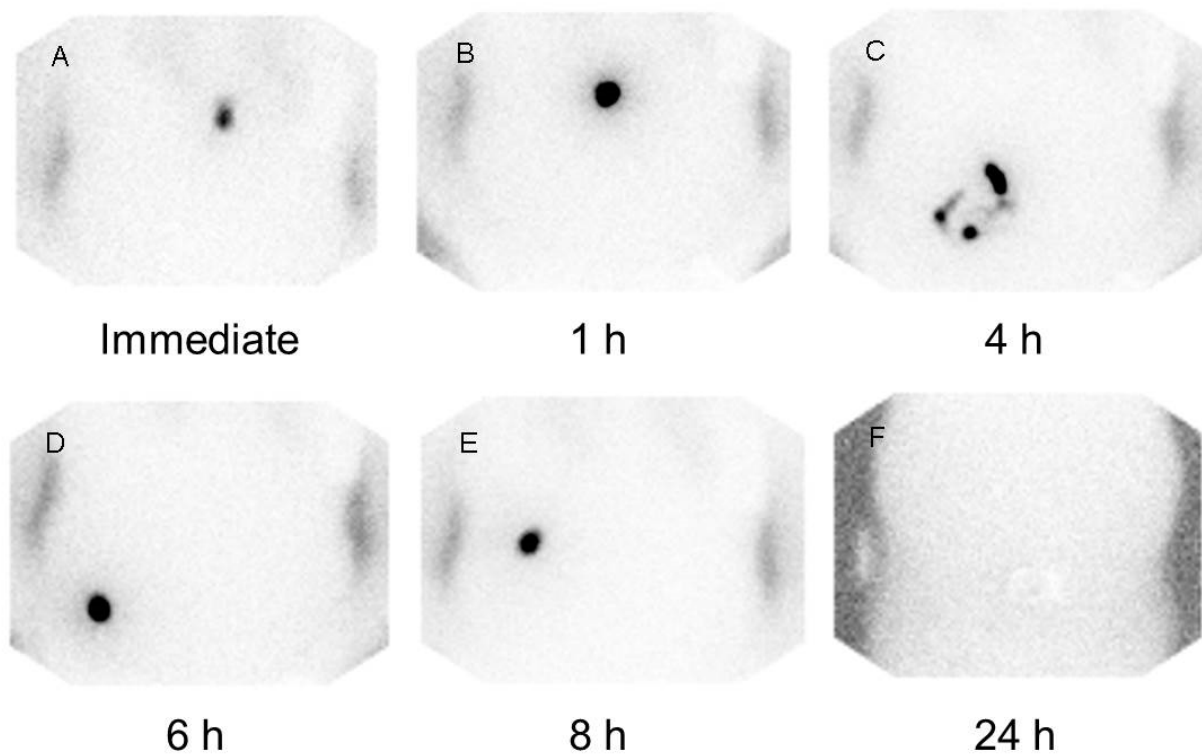
Figure 2

The first image (A) demonstrates the PSTD immediately after swallowing. Images were obtained using a ^{57}Co sheet source behind the subject. When the device is used alone, it is difficult to determine with confidence the time that the device enters into the small bowel. The 4 hour image (C) demonstrates motion of the device within the small bowel during the image acquisition. The device is likely at the ileocecal junction at 6 hours (D) and in the ascending colon at 8 hours (E). The device has been excreted at 24 hours (F).
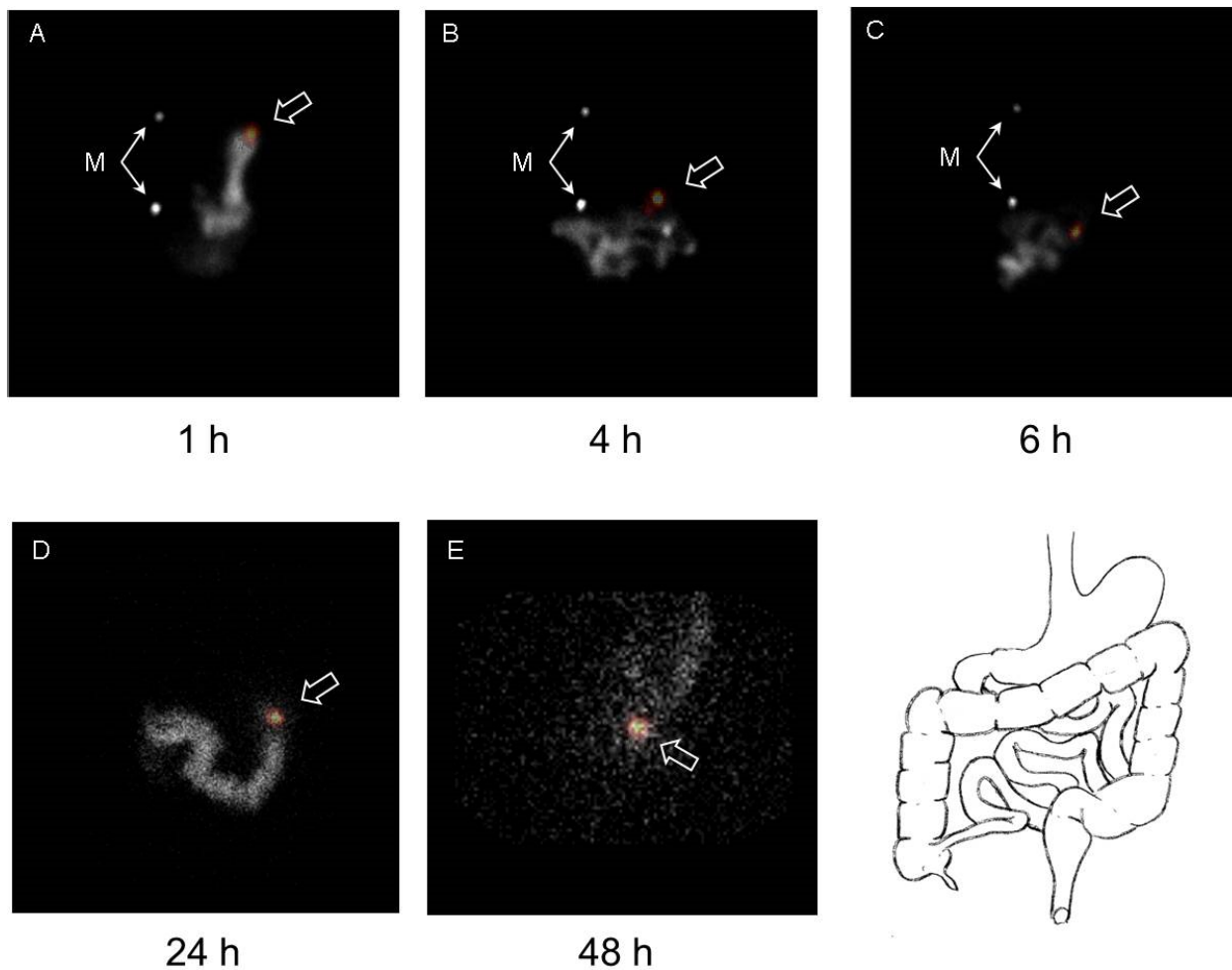
Figure 3

When used in conjunction with a gastric emptying study, the location of the PSTD (open arrow) can be more clearly defined when dual isotope acquisition is used and the images digitally fused. In this patient with a history of constipation, the PSTD is still in the stomach at 4 hours (B) but visible in the small bowel at 6 hours (D). At 24 hours the PSTD is in the transverse colon (D) and at 48 hours in the rectosigmoid region (E). A 72 hour image demonstrated no activity to be present. Point source markers visible on the 1, 4, and 6 hr. images (M) are placed on the surface of the patient to the right of the midline and located approximately at the levels of the nipple and umbilicus to ensure consistent patient positioning between images. A diagram of the normal anatomy is often helpful in identification of the location of the PSTD.

Table 1

Gastrointestinal Transit Times for Subjects

Subject	Symptoms	TGIT Time (hours', minutes")	Results Gastric Emptying Study
Normal 1	None	21'30"	
Normal 2	None	22'18"	
Normal 3	None	13'00"	
Normal 4	None	7'00"	
Patient 1	Constipation	43'33"	
Patient 2	Constipation	Withdrew	
Patient 3	Constipation	46'46"	
Patient 4	Constipation	21'39"	Normal
Patient 5	Diarrhea	21'39"	Normal
Patient 6	Constipation	67'43"	Normal
Patient 7	Constipation	46'21"	Normal
Patient 8	Constipation	26'02"	Accelerated
Patient 9	Constipation	9'50"	Delayed
Patient 10	Constipation	Withdrew	Normal

The total gastrointestinal transit times for all subjects (normal and symptomatic) are listed above. Average TGIT for the normal subjects was 15'57". This may be artificially low since subject 'Normal 4' drank several cups of coffee after taking the device. The average TGIT for symptomatic subjects with a history of constipation was 40'45". It is possible that this value is artificially low since subject 'Patient 9' had three bowel movements between the last image the device was visible and the final image showing the device had been excreted. The results of the gastric emptying study are also listed.

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