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Development of a new method for small bowel transit study

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Background and Purpose: Currently, most studies combine the small bowel transit examination with gastric emptying time examination. There are significant drawbacks to this method. The radiotracer does not enter the small intestine in a bolus and the starting time for transit in the duodenum is difficult to define. This makes the result unreliable. In this study, we used a commercial enteric capsule containing radioactive charcoal to solve these problems. ***Materials and Methods:*** Activated charcoal powder was mixed with Tc-99m pertechnetate and loaded to the enteric capsule which can resist gastric acid and dissolve only in the small intestine. *In-vitro* stability experiment was performed by immersing these capsules in a colorless phosphate buffer of variable pH which mimicked the condition in stomach and small intestine. In addition, ten healthy Chinese volunteers were included for *in-vivo* experiment. Anterior and posterior views of abdomen were obtained at regular 30-minute intervals until the eighth hour after administration of the radioactive enteric capsule. Small bowel transit time was calculated. ***Results:*** The enteric capsule remained intact for at least 480 minutes in the solution mimicking gastric content (pH = 3.0) and disrupted at a mean duration of 227.2 minutes at a pH of 6.8 and at a mean duration of 212.4 minutes at a pH of 7.4 in the solution mimicking pancreaticobiliary secretions. In nine of ten volunteers, the small bowel transit time was between 30 to 270 minutes with a mean transit time of 140 min. In one volunteer, we failed to detect the exact time of small bowel transit because the capsule remained in the stomach throughout the study for up to 8 hours. ***Conclusions:*** We consider activated charcoal labeled with Tc-99m pertechnetate using an enteric capsule as the carrier to be a potential radioactive marker for small bowel transit study.

Key words: Tc-99m pertechnetate, enteric capsule, small bowel transit, activated charcoal

INTRODUCTION

GASTROINTESTINAL DYSMOTILITY SYMPTOMS are a major problem in routine clinical practice.[1–3] It is often clinically helpful to define the motor function to understand the basis for the patient's symptoms and develop appropriate therapeutic strategies. Evaluating motility of the esophagus, stomach and colon has been widely applied in many hospitals.[4–6] However, investigation of the motility of the small bowel is more complex owing to the anatomical arrangement of this organ.

Many methods have been introduced to evaluate small bowel transit. However, all these methods have significant drawbacks. Radiographic barium studies provide anatomical information, but may bear little relationship to the transit time for true nutrients.[7] Orally administered radiopaque pellets can be used for assessment of colonic or total gut transit, but give little information on small bowel transit.[8] Orocecal transit tests, such as the lactulose-hydrogen breath test[9,10] and the plasma sulfapyridine response to oral salicylsulfapyridine,[11] require metabolism of a substrate by colonic bacteria. However, up to 25% of the population cannot metabolize the sugar

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because they lack the proper bacterial strains in the colon.[12,13] On the other hand, bacterial overgrowth in the small intestine may cause early hydrogen peaks which are interpreted as a rapid transit.

Radioisotopes are ideally suited to provide information about transit through the gastrointestinal tract. The ability to image frequently and obtain precise quantitative information provides a measure of the pattern and effectiveness of transport which is difficult to obtain by other means. Scintigraphic methods in the evaluation of esophageal transit time, gastric emptying time and colonic transit time have been well established.[4–6] However, an ideal scintigraphic method in the evaluation of small bowel transit is still not available. Currently, most studies combine the small bowel transit examination with gastric emptying time examination.[14–16] The small bowel transit is evaluated after the radioactive meal is emptied from the stomach, which has the consequence that the input of the radionuclide into the small intestine is variable and depends on the gastric emptying rate.[16] The starting point for transit in the duodenum is therefore difficult to define. Moreover, the radiotracer does not enter the small intestine in a bolus, which is also a shortcoming of this method. Recently, Gryback et al. used Tc-99m HIDA scan to evaluate the small bowel transit.[17] Although the radiotracer reaches the duodenum as the starting point and the problem of variance of gastric emptying has been solved in a Tc-99m HIDA scan, the radiotracer still does not enter the duodenum in a bolus. In addition, the amount and time of Tc-99m HIDA appearing in the duodenum is variable, especially in patients with abnormal liver function. The amount of radiotracer entering the small intestine may be not adequate for imaging in a case with severe liver malfunction. An improved method is thus needed for physiological studies for the small intestine.

In this study, we used a commercially available empty enteric capsule, which is made to resist gastric acid and only dissolves in the small intestine, and to carry Tc-99m labeled with activated charcoal into the small intestine in a bolus. We observed the disruption *in vitro* and dissolution *in vivo* of the capsules to evaluate the potential of this new method for small intestine transit study.

MATERIALS AND METHODS

1. Labeling of activated charcoal with Tc-99m pertechnetate

Activated charcoal is the residue from the destructive distillation of various organic materials; it is treated to increase its adsorptive power. Activated charcoal occurs as a fine, black, odorless, tasteless powder and is free of gritty matter. It is neither adsorbed nor metabolized in the gastrointestinal tract.

Five mg of activated charcoal powder (mixed size, 90% 100 μm, 50% 30 μm; Merck Co., Darmstadt, Germany) was mixed with Tc-99m pertechnetate (37 MBq in 0.5 m*l*) and evaporated to dryness from the aqueous phase of physiological saline on a hot plate for approximately 20 min.

2. Preparation of radioactive enteric capsule for small intestine

The dry Tc-99m pertechnetate activated charcoal was placed in the small intestine enteric capsule (Model A Empty Enteric Capsule, Chaozhou Medicinal Capsule Factory, Guangdong, China). The radioactive activated charcoal must be dry so the enteric capsule does not dissolve. After the charcoal was packed inside the capsule, it was closed with the capsule cap. The capsule was ready for ingestion.

3. In vitro *stability of the capsules*

Each capsule was then immersed in a colorless phosphate buffer of variable pH. The pH values were set at 3.0, 6.8 and 7.4. These pH ranges were selected in view of the known ranges of pH of gastric contents and enteric contents in humans. In the pH = 3.0 group, pepsin was added to mimic the gastric content. 1 mM glycochenodeoxycholate was also added to the solution. Each incubation was performed in a water bath kept at 37°C. Capsule disruption was determined by the visual appearance of colored liquid in the colorless buffer. The whole procedure lasted for 480 minutes (8 hours) if there was no observed disruption of the capsule. The same procedure was repeated in the pH = 6.8 and pH = 7.4 groups by adding lipase and trypsin, 2,000 U/m*l* each, to the solution. These concentrations were selected to mimic the levels of pancreatico-biliary secretions.[18] Five tests were performed in each group.

4. Small bowel transit studies

Ten healthy Chinese volunteers (four were male and six were female, their ages ranged from 25–52 yr, with a mean of = 35.6 yr) were included. None of these volunteers had a history of gastrointestinal (GI) disease or complaint. None of these volunteers took any medication that could affect GI motility. This study was approved by the Ethics Committee at this hospital. All volunteers signed a consent form after the procedure was explained to them. All subjects fasted overnight (at least 8 hours). Then, each subject swallowed one radioactive enteric capsule containing about 37 MBq (1 mCi) of Tc-99m pertechnetate with 200 m*l* of water at 9 o'clock the next morning. Two hours after the capsule was given, the subject was asked to eat a standard meal: breakfast (scrambled egg, whole wheat bread, and skim milk; 35% protein, 52% carbohydrate, and 13% fat; 219 kcal). Then, 4 hours later, the subject ate the standard lunch (chicken, potato, pudding, and water; 18% protein, 47% carbohydrate, and 35% fat; 536 kcal). Anterior views of the abdomen were obtained in 256 × 256 matrix frame size for 10 seconds, using a two-headed gamma camera (Elscint

Table 1 The disruption times of enteric capsule in solutions with different pH values of different enzymes

Tube No.	minutes		
	3.0 + pepsine	6.8 + BA + L & T	7.4 + BA + L & T
1	>480	198	186
2	>480	246	192
3	>480	228	210
4	>480	248	228
5	>480	216	246
Mean ± 1 STD	–	227.2 ± 21.0	212.4 ± 24.6

BA, glycochenodeoxycholate (1 mM); L & T, lipase and trypsin (2,000 U/m*l* each).

Table 2 The disruption of the enteric capsule and the small bowel transit time

No.	Age	Sex	Time of Capsule (minutes)			(minutes)
			Left Stomach	Disruption	Reached Cecum	Small Bowel Transit Time
1	25	M	150	180	270	120
2	44	M	180	240	240	60
3	52	M	60	180	180	120
4	38	F	150	150	180	30
5	40	F	210	240	390	180
6	25	M	90	90	270	180
7	29	F	90	120	360	270
8	27	F	150	180	360	210
9	48	F	90	120	180	90
10	28	F	>480	>480	–	–

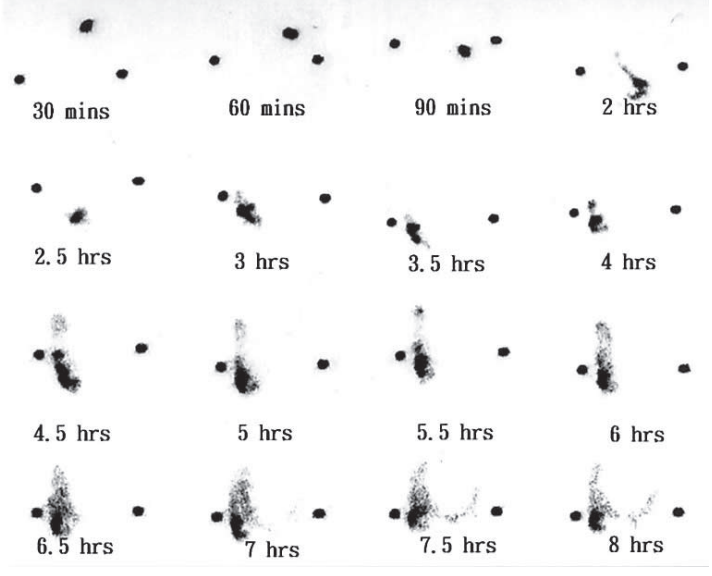

Fig. 1 Sequential anterior view of the abdominal images in a normal volunteer (No. 9) after intake of enteric capsule containing Tc-99m activated charcoal. The capsule left the stomach at 90 min after intake of the capsule and was disrupted at 120 min. The Tc-99m activated charcoal mixes well with bowel content and arrives at the cecum at 180 min. The small bowel transit time is 90 min.

Varicam). Images were obtained 30 minutes after ingestion of the capsule and at regular 30-minute intervals until the eighth hour. All images were obtained with the subjects in the supine position. The subjects were allowed to read or watch TV in a waiting room in between scanning. Radioactive markers were placed for reference on the bilateral anterior iliac crests.

5. Quantitation of small bowel transit

Once the radioactive capsule left the stomach, the time was recorded as the starting point. The time when the radiotracer reached the cecum or ascending colon was recorded as the end point. The time interval between the starting-point and end-point was calculated as the "small bowel transit time."

RESULTS

Table 1 demonstrates that the capsule could resist the acid very well and would disrupt when the pH became higher. The enteric capsule remained intact for at least 480 minutes in the solution mimicking gastric content (pH = 3.0) and disrupted at a mean duration of 3.78 hours at the pH of 6.8 and at a mean duration of 3.54 hours at the pH of 7.4 in the solution mimicking pancreaticobiliary secretions.

The disruption of the enteric capsule and the small bowel transit time are shown in Table 2. The time of the capsules leaving the stomach varied from 60 minutes to >480 minutes. In one volunteer, we failed to detect the exact time of small bowel transit because the capsule remained in the stomach on the 480-minute image. For the other nine volunteers, the small bowel transit time was between 30 min to 270 min with a mean transit time of 140 min (1STD = 76.5 minutes) (Fig. 1). Eight of the capsules dissolved at the small intestine and one at the cecum.

DISCUSSION

The main purpose of this experiment was to establish a new, simple, inexpensive and convenient method for the measurement of small bowel transit. Tc-99m pertechnetate is inexpensive and available in all nuclear medicine departments in the world. The activated charcoal powder used is consistent with the USP standard,[19] is not expensive, and is FDA-approved to be non-toxic. Hayden and Comstock evaluated its effects when ingested, adsorbed by skin contact and inhalation, and found it to be safe.[20] In 2000, we successfully established a new method to measure colonic transit time using Tc-99m labeled with activated charcoal which is carried to the cecum-colon region by a commercial enteric capsule for the colon.[21] The capsule does not dissolve in the stomach or small intestine, only in the terminal ileum and cecum-colon region. The result is encouraging. In this study, we used the same labeling technique but changed the empty enteric capsule for the colon into the capsule for the small intestine, which can resist gastric acid and dissolve only in the small intestine where the pH value becomes higher.

The empty enteric capsule used in this study is a commercial product developed as a carrier to deliver drugs to the small intestine. The capsule does not dissolve in the stomach, only in the small bowel. According to company literature, the quality of these capsules is controlled by the following procedure. Load six capsules with talc powder and put them in a HCl solution (pH < 4) for 2 hours. No disruption or crack on the capsules should be observed. Take out the capsules and wash them with fresh water. Place the six capsules in a phosphate buffer solution with a pH value of 6.8. All six capsules must be disrupted or completely dissolved within one hour. If any one capsule is still intact, these capsules are not qualified for release to the market. There are several advantages to use the enteric capsule. 1) This capsule is a commercial product and therefore available in many countries. 2) The preparation of this marker for small bowel transit study is very simple. 3) The radiotracer enters the small bowel in a bolus, which makes the accurate measurement of the starting point possible. 4) Once the capsule was disrupted, the radioactive tracer could mix with the intestinal content well. This made the measurement of the small bowel transit time more physiologic.

In the *in-vitro* study, the enteric capsule resisted the acid-pepsin solution well. It remained intact for at least 480 minutes in conditions of pH = 3.0. When the pH value was above 6.8 and in the presence of lipase and trypsin, the capsule disrupted at a mean duration of 227.2 minutes at a pH of 6.8 and at a mean duration of 212.4 minutes at a pH of 7.4. In the *in-vivo* study, the capsule could resist the gastric acid very well. In the case who failed to empty the capsule from the stomach, the enteric capsule remained intact in the stomach throughout the study up to 480 minutes. Once the capsule entered the small intestine, the capsules disrupted at a mean duration of 36.7 minutes which was much shorter than that in the *in-vitro* study. One possible explanation for the shorter time of capsule disruption in the human body might be the peristalsis of the intestine, which could apply pressure to the capsules and speed their disruption.

In the study by Gryback et al., Tc-99m HIDA was used to measure the small bowel transit time in 30 healthy subjects.[17] The small bowel transit time of their study was between 21 minutes and 153 minutes by computer analysis and between 23 minutes and 158 minutes by visual measurement. In our study, the small bowel transit time was between 30 minutes and 270 minutes with a mean of 140 minutes. Although the Tc-99m HIDA enters the duodenum directly and solves the problem of defining the starting point, there are still a few disadvantages to Gryback's method including 1) the radiotracer did not enter the duodenum in a bolus and 2) the application to patients with severe liver malfunction may be limited since the amount of Tc-99m HIDA appearing in the duodenum is usually poor and delayed in these patients. Using the enteric capsule method, these problems can be solved easily. However, there were also several limitations to our method. One was the difficulty of the localization of the stomach although the radioactive markers at the bilateral iliac crests could be a very useful landmark for the localization in most cases in our study. Usually,

identifying when the capsule left the stomach was easy when serial images were available for confirmation. Nevertheless, it could be difficult at times to determine the very first image when the capsule left the stomach. We consider that injecting patients with a very small amount of Tc-99m pertechnetate (for example 3.7 MBq) may help to solve the problem, since the Tc-99m pertechnetate can accumulate in the gastric wall and outline the stomach. Further examination is recommended to confirmed this. The second drawback is the variance of gastric emptying of the capsule. In a patient with significantly prolonged gastric emptying time, the calculation of small bowel transit time may fail if the radiotracer did not reach the end point during working hours. Of the 10 healthy subjects in this study, calculation of the small bowel transit time failed in one case because the capsule remained in the stomach throughout the study. The third drawback is the time interval between the images. Since the capsule was suspected to leave the stomach between 60 minutes and 210 minutes, and the small bowel transit was between 30 minutes and 270 minutes, the time interval of 30 minutes between the images may not be sufficient. A shorter time interval may be necessary for a more accurate measurement.

The time of the capsules leaving the stomach ranged from 1 to >8 h in our study. It might be longer than what we would normally expect. However, no standard gastric emptying time for indigestible solids has been documented in the current literature. Gastric emptying is a complex multifactorial phenomenon that results from interactions of various mechanisms. The stomach, in fact, physiologically empties the three components of meals (liquids, digestible solids and indigestible solids) at different rates. The indigestible solids are emptied from the stomach during phase III of the migrating motor complex. The gastric emptying of an indigestible capsule, especially a large capsule (our capsule is 7 × 18 mm in size), is usually unpredictable and takes longer than ingested digestible solids.[22,23] Some indigestible capsules may stay in the stomach for longer than 6 hours without any pathological evidence.[24] The quality of small bowel transit study can be greatly improved by enhancing the emptying of the enteric capsules from the stomach. There are two ways which may shorten the gastric emptying time of the indigestible capsule: 1) to use prokinetic agents such as erythromycin, which may potentially speed up gastric emptying of indigestible solids,[25] 2) to change the consistency of the capsule. Soft particles emptied significantly faster than hard ones.[26]

The subjects in our study consumed a standard meal two hours after the ingestion of the radioactive capsule. There is no consensus in the current literature with regard to the optimal timing of meal ingestion after the subject took the capsule for either small bowel transit or colon transit studies. Various timings, ranging from thirty minutes to 4 hr, have been used in bowel transit studies and some authors even allowed their subjects to have their normal meals freely during the study.[21,25,27–29] The indigestible solids are emptied from the stomach during the interdigestive motor cycle that recurs periodically until being disrupted by food intake. Theoretically, fasting during the whole small bowel transit study may be a better way to initiate the emptying procedure of the indigestible capsule from the stomach. However, the long fasting time is inhuman, not physiological and routinely impractical, especially for ill or elderly patients. In conclusion, we do not yet know the optimal timing to commence feeding in the bowel transit study. Multiple factors, including the use of prokinetic agents, average gastric emptying time of the capsule and the condition of the patients, should be taken into consideration.

In conclusion, activated charcoal labeled with Tc-99m pertechnetate using an enteric capsule as the carrier can be a potential radioactive marker for small bowel transit study.

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