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Calculating colon transit time with radionuclide-filled capsules in constipated patients: a new method for colon transit study

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Abstract

Background: Colon motility disorders require reliable methods for calculating segmental colonic transit time. This study evaluated bowel transit time by means of a safe, easy, cheap, nondigestive, and nondisintegrating radionuclide-filled capsule that provided accurate and clear images.

Methods: Radionuclide-filled minicontainers (MCs) were prepared from infusion sets by an apparatus used for sealing blood bags or plasmapheresis sets. In vitro stability studies were performed by immersing 5% methylene blue dye-filled MCs in buffers of variable pH and enzymes simulating the conditions in the stomach and the small bowel. Colon transit scintigraphy was performed with MCs filled with iodine 131 ($n = 5$) and thallium 201 ($n = 8$) that were placed in a commercially available capsule.

Results: By in vitro acid, base, and intestinal enzyme resistance tests, no methylene blue leakage was determined visually and by spectrophotometric analysis. Accurate and clear images were obtained for colon transit study in constipated patients. After excretion of MCs in the feces, abdominal, myocardial, thyroid, and urinary bladder region counts were found to show the same activity as the background. Radionuclide leakage from MCs was not determined in vivo by gamma camera.

Conclusion: This is a suitable, safe, easy, and cheap method to provide accurate and clear images for colon transit study in constipated patients.

Key words: Colon transit—Constipation—Radionuclide—Scintigraphy

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Bowel transit time can be calculated by many methods. Nuclear medicine methods are mostly preferred because of easy preparation, good tolerance by patients, and results are largely not operator dependent [1–5]. For small bowel and colon transit time measurement, many radiopharmaceuticals have been used in nuclear medicine. Despite attempts to simplify the study, whole-gut transit scintigraphy still requires a significant commitment of time and equipment. As with other gastrointestinal studies, each laboratory must determine which protocol best fits its clinical needs, equipment, and staffing [6].

Constipation encompasses a wide range of physiologic changes and subjective symptoms, including decreased bowel frequency, the need to strain excessively, passage of hard stools, and difficulty with, or a sense of incomplete, rectal evacuation [7]. Chronic constipation is a common problem and affects from 3% of young adults to 20% of the elderly population [8].

The aim of our study was to evaluate bowel transit time by means of a safe, easy, cheap, and nondigestible radionuclide-filled capsule.

Materials and methods

Preparation of the capsule

For preparation of the minicontainer (MC), 2-cm-long pieces were cut from an intravenous infusion set. The set had 75 shore A hardness, 3.0 mm inner diameter, and 4.1 mm outer diameter and also fitted the biological compatibility tests according to ISO 10993 standards. One end of the piece was sealed with a polyvinylchloride (PVC) tube sealing apparatus (Biosealer CR4, Ljungberg & Kögel AB, Sweden) that is used for blood-bag tubes or plasmapheresis sets. The listing number of the apparatus in U.S. Food and Drug Administration is B024145. After the container was filled with 40 μL of solution (5% methylene blue dye or radionuclide), the other end was

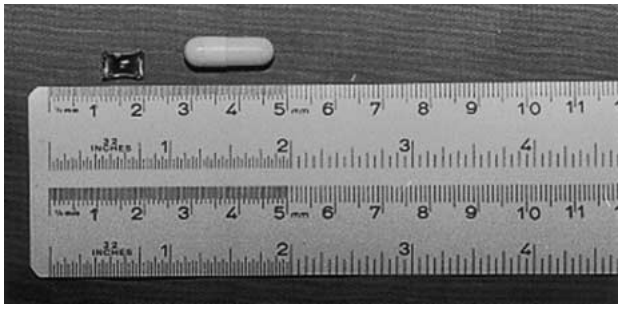

Fig. 1. Minicontainer and capsule are shown to scale.

sealed at the upper level of the solution. MCs that were not sealed at the upper level of solution (for probability of contamination) or visually included more than 20% air were excluded. The MC was inserted into a commercial empty drug capsule for the comfort of the patient during swallowing. The MC and the capsule are shown in Figure 1.

Pressure test of the MC

The MC was initially tested with evident external pressure between the thumb and index finger in a plastic bag. Then the bag was placed under a pressure of 1 kg weight for 30 min. MCs that leaked were excluded.

In vitro acid and base resistance test of the MC

Colorless acid and base media, each containing 5-mL solutions, were prepared with hydrochloric acid and sodium hydroxide at pH values of 2, 4, 6.8, 7.4, and 8.7. These pH values were selected because of the known ranges of pH of gastric and enteric contents in humans. MCs filled with 5% methylene blue dye (Sigma, UK) were prepared and washed with soap and dried. Fifteen methylene blue dye-filled MCs were immersed into each solution. MC disruption was evaluated by spectrophotometric analysis and by visual appearance at 2, 4, 24, 48, and 72 h. Ultraviolet absorbance peak was monitored with a variable-wavelength ultraviolet detector (model 4054 ultraviolet/visible spectrophotometer; LKB Pharmacia, Cambridge, UK) at 665 nm. The entire procedure lasted 72 h. Then, all MCs were taken out, dried, and tested with the same external pressure.

Intestinal enzyme resistance test of the MC

Colorless acid and base media, each containing 5-mL solutions, were prepared with hydrochloric acid and sodium hydroxide at pH values of 2, 6.8, and 7.4. MCs filled with 5% methylene blue dye were prepared and washed with soap and dried. Five milligrams of porcine pepsin (Sigma, UK) was added to solution, pH 2. A mixture of 4250 U of protease and amylase and 340 U of lipase was added to each solution, pH 6.8 and 7.4. Fifteen MCs were immersed into each solution. All solutions were mixed for 3 min and incubated in a water bath kept at 37°C. MC disruption was evaluated by visual appearance in colorless solutions at 2, 4, 24, 48, and 72 h. The entire procedure lasted 72 h. Then all MCs were taken out, dried, and tested with the same external pressure.

Table 1. Patient characteristics

	^{131}I-filled–MC capsule	^{201}TI-filled-MC capsule
No. of patients	5	8
Mean (range) age (years)	47 (36–63)	49.8 (42–64)
Male	2	2
Female	3	6
Activity (mCi)	0.178 ± 0.06	0.255 ± 0.06
Colonic transit time (h)	74 ± 8.4	78 ± 12.2

Evaluation of bowel transit time in constipated patients with capsules containing MCs filled with iodine 131 or thallium 201

Thirteen patients (nine women and four men, mean age 48.7 years, age range 36–64) with chronic constipation were enrolled in this study. Women were required to have a negative pregnancy test within the 24-h period before each of the study days. Written informed consent was obtained from all subjects and carried out according to the guidelines in the Declaration of Helsinki. All patients had a history of fewer than three spontaneous evacuations per week and constipation lasting longer than 5 years. Barium enema and/or endoscopic evaluation and serum biochemical examinations were performed to exclude organic causes for constipation. No patient had undergone previous abdominal surgery and none was taking any medication. Patients' characteristics are presented in Table 1. Five patients (three women and two men, mean age 47 years, age range 36–63, with normal findings in their additional thyroid ultrasonographic examination and known to be euthyroid by the thyroid function tests that were included in routine biochemical evaluation for constipation) were studied with capsules that contained MCs filled with iodine 131 (group A). The remaining eight patients (six women and two men, mean age 49.8 years, age range 42–64 years) were studied with capsules that contained MC filled with thallium 201 (Group B). One capsule that contained an MC filled with iodine 131 (0.178 ± 0.06 mCi) or thallium 201 (0.255 ± 0.06 mCi) was taken with 200 mL of water at 12:00 AM. After 30 min, all patients consumed 100 mL of orange juice and the test meal comprised 220 g of rice pudding. The total meal provided 325 kcal. During the study days, breakfast consisted of a standardized light breakfast consisting of two slices of toast with butter and 150 mL of orange juice at 9 AM, lunch

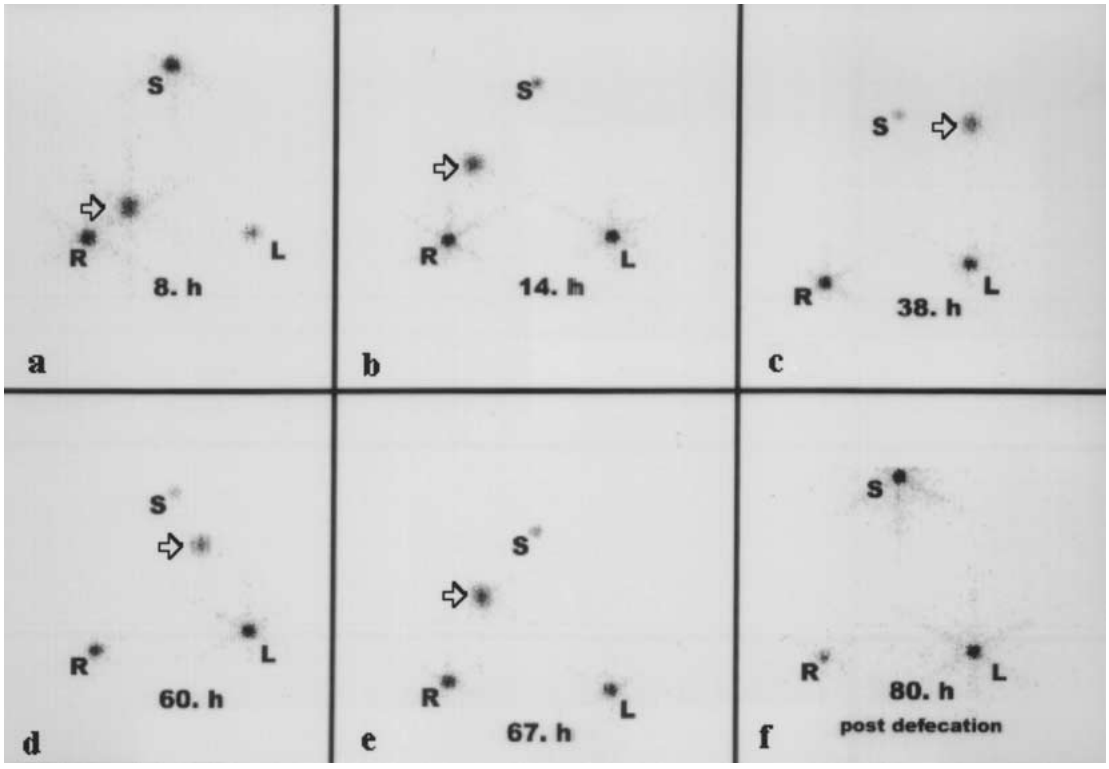

Fig. 2. Anterior abdominal scintigraphic images of iodine 131–filled minicontainers (*arrows*) and capsules at 8, 14, 38, 60, 67, and 80 h in a constipated patient. *L* left anterior iliac crest; *R* right anterior iliac crest; *S* xiphoid process.

consisted of a standard 600-kcal sandwich with 180 mL of water or fruit juice at 1 PM, and supper consisted of a 1000 kcal with 180 mL of water or juice at 6 PM. Patients were asked to maintain their usual activities of daily life.

In group A, anterior thyroid region and abdominal static gamma camera images (Adac Vertex V60, ADAC Inc., Milpitas, CA, USA) were acquired with a medium energy collimator and 20% window centered on the 364 keV iodine 131 photopeak. In group B, abdominal static gamma camera images were acquired with a low energy, general purpose collimator and 20% window centered on the 80 keV thallium 201 photopeak. Radioactive markers were placed on the anterior iliac crests and xiphoid process for reference. In both groups the first images were obtained 8 h after swallowing the capsule and subsequent images were obtained at different intervals depending on the localization of activity until its excretion in the feces.

Results

Excluded MC ratios by two physicians were 2% and 4% with pressure tests and 7% and 13% for sealing problems (sealed at the upper level of solution or visually included more than 20% air).

By in vitro acid and base resistance tests and intestinal enzyme resistance tests, no leakage of methylene blue was determined visually and by spectrophotometric analysis.

No gastrointestinal symptoms (nausea, vomiting, abdominal pain, abdominal cramping, or abdominal bloating) were reported during ingestion of the capsules in all 13 patients. All capsules were well tolerated by patients and clear images were obtained (Fig. 2).

In the first images (at 8 h), all MCs were found in the right lower quadrant, suggesting that they had reached the distal ileum and cecum or entirely in the cecum and proximal ascending colon in all constipated patients.

On early and postdefecation images in group A, thyroid and urinary bladder region counts showed the same activity as the background. On similar images in group B, myocardial and urinary bladder region counts were found to show the same activity as the background.

Discussion

Colon motility disorders require reliable methods to measure segmental colonic transit time. This can be calculated by many methods.

Radiologic methods for colonic transit time are simple and economical, and the time and number of technical devices needed are minimal compared with other procedures [9]. Polyethylene radiopaque markers, radiopaque polyethylene tubes, rings, insoluble barium

(lentils), and radiopaque pellets were generally used as radiopaque markers for measurement of total and segmental colonic transit times [2, 10, 11]. However, these studies did not provide a dynamic picture of colon activity. There is also concern that the markers are not physiologic and therefore do not always represent meal behavior in the colon [12]. Measurement of segmental transit time using these methods in constipated patients may require repeated radiographs [13]. The main advantages of the radiopaque markers are that they are nondigestible and nondisintegrating. Thus, the images obtained during these radiologic studies are clear and interpersonal variation is small. MCs used in this study have the same advantages of these markers. The PVC tube sealing apparatus is widely used in blood banks and hematology laboratories. The cost of the MC is lower than $1 excluding the radiopharmaceutical and the sealing apparatus. It can be prepared in less than 2 min. In addition, an MC can be filled with a radiopaque solution and can be used as a radiologic marker. Even smaller MCs can be prepared for this purpose by scalp vein infusion sets.

Scintigraphic techniques are well-established methods to assess gastrointestinal transit patterns. The main advantage is represented by the ability to evaluate patients in a noninvasive manner [1]. Many radiopharmaceuticals have been used in nuclear medicine and they can be classified as liquid and solid radiopharmaceuticals. Gallium 67 citrate and indium diethylenetriamine penta acetic acid (^{111}In-DTPA) are currently the most popular liquid agents. These radiotracers have been shown to provide an accurate measurement of segmental colonic transit. However, ^{111}In-DTPA, which is a relatively expensive isotope and not always readily available, and gallium 67 citrate require additional computer analysis to calculate colonic transit time [14]. The MCs that we used in our study do not require further analysis and any available radioisotope that has the appropriate physical properties can be used.

Resin pellets; methacrylate polymer-coated capsule, and radioisotope-activated charcoal in enteric capsules with isotopes such as technetium 99m or indium 111 have been used as solid radiolabels. However, the preparation of these markers is very tedious and the coating material (methacrylate) is not approved by the U.S. Food and Drug Administration. The disruption of these capsules depends on the thickness of their coatings. In addition, it would be necessary to use the same technician for coating to reduce the variation in technique [12]. Preparation of the MCs we used in our study was quite easy.

Smart et al. [15] found no significant difference in regional colonic transit time by a liquid (^{111}In-DTPA) or a solid marker (cellulose labeled with iodine 131) in dual isotope studies of nonconstipated controls and constipated subjects. Bartholomeusz et al. [14] found no significant difference in colonic transit time of the liquid (^{111}In-DTPA and gallium 67 citrate) isotope marker or radiopaque marker in controls and constipated subjects.

Although both isotopes have half-lives long enough to evaluate constipated patients, the physical properties of thallium 201 for external imaging are superior to those of iodine 131.

In our study, iodine 131 was used to determine small contamination, leakage, and capsule degradation in vivo. In consideration of radiation safety, instead of iodine 131, we believe that thallium 201, gallium 67, and indium 111 should be preferred.

In conclusion, we studied a safe, easy, and cheap radionuclide-containing capsule to assess bowel transit time in constipated patients by using an infusion set and a PVC tube sealing apparatus. The described method does not require additional cost, equipment, or staffing. The capsule was well tolerated by patients. Further, this technique can be used in any motility disorders of gastrointestinal system.

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