Segmental Colonic Transit After Oral ^{67}Ga-Citrate in Healthy Subjects and Those with Chronic Idiopathic Constipation

Dylan Bartholomeusz, Barry E. Chatterton, Johan C. Bellen, Robert Gaffney and Andrew Hunter

Department of Nuclear Medicine and Colorectal Surgical Unit, Royal Adelaide Hospital, Adelaide, Australia

Measurement of segmental colonic transit is important in the assessment of patients with severe constipation. ^{111}In-diethylenetriamine pentaacetic acid (DTPA) has been established as the tracer of choice for these studies, but it is expensive and not readily available. ^{67}Ga-citrate is an inexpensive tracer and when given orally is not absorbed from the bowel. It was compared with ^{111}In-DTPA in colonic transit studies in nonconstipated control subjects and then in patients with idiopathic constipation. **Methods:** Studies were performed after oral administration of 3 MBq (81 μCi) ^{67}Ga-citrate or 4 MBq (108 μCi) ^{111}In-DTPA in solution. Serial abdominal images were performed up to 96 h postinjection, and computer data were generated from geometric mean images of segmental retention of tracer, mean activity profiles and a colonic tracer half-clearance time. **Results:** There were no differences in segmental retention of either tracer or in mean activity profiles between control subjects and constipated patients. Results in constipated subjects were significantly different from those in controls. The mean half-clearance times of tracer for control subjects were 28.8 h for ^{67}Ga-citrate and 29.9 h for ^{111}In-DTPA in control subjects and 75.0 h for ^{67}Ga-citrate and 70.8 h for ^{111}In-DTPA in constipated patients. **Conclusion:** Oral ^{67}Ga-citrate can be used as a safe alternative to ^{111}In-DTPA for accurate measurement of segmental colonic transit.

Key Words: oral ^{67}Ga-citrate; colonic transit studies; idiopathic constipation; scintigraphy

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Constipation is a relatively common disorder (*1,2*). It may be caused by various endocrine, metabolic, neurological and connective tissue disorders or by drugs. The idiopathic form of constipation is more common in women and may be related to altered bowel motility caused by pelvic floor damage, anal sphincter dysfunction resulting in obstructive defecation, generalized slow bowel transit, abnormal gastrocolic reflex or irritable bowel syndrome (*3–8*). Study of these disorders requires a method of reliably measuring segmental colonic transit. Early transit studies used markers such as dyes, seeds and even ball bearings (*9–11*). They provided only crude data on oral–anal transit. Subsequent studies used radiopaque markers that could be followed by performing serial abdominal radiography (*12,13*). Although more accurate than earlier techniques, measurement of segmental transit using these methods in constipated patients may require repeated radiographs (*13*). More recently, techniques using radionuclide studies have been shown to provide accurate data on segmental colonic transit. Earlier investigations involved invasive instillation of tracer into the cecum (*14,15*) and these were followed by studies using oral tracers such as ^{131}I-labeled cellulose and then ^{111}In-diethylenetriamine pentaacetic acid (DTPA), either adsorbed onto polystyrene pellets or in solution (*16–19*). All of these methods have been shown to provide an accurate measurement of segmental colonic transit. However, indium is a relatively expensive isotope and not always readily available. ^{67}Ga-citrate, with its 78-h $t_{1/2}$, is more readily available and less expensive. Previous studies have shown that ^{67}Ga-citrate given orally is not absorbed from the bowel and 98% or more of the ingested dose is excreted in the feces (*20*). Our aims in this study were to compare the results of colonic transit studies performed using oral ^{67}Ga-citrate as the tracer with those of studies using ^{111}In-DTPA in a group of nonconstipated control subjects. This was followed by studies in a further group of patients with severe idiopathic constipation.

MATERIALS AND METHODS

Subjects and Data Acquisition

Sixteen female volunteers with normal bowel habits and 20 female patients thought to have slow transit idiopathic constipation were studied. The nonconstipated control subjects were divided into two groups. The first group was of 8 control subjects of median age 58 y (range 39–80 y). They underwent colonic transit studies with ^{111}In-DTPA solution according to a previously published method (*19*). The other 8 control subjects of median age 49 y (range 44–70 y) underwent colonic transit studies after ingestion of oral ^{67}Ga-citrate. We also performed ^{111}In-DTPA and ^{67}Ga-citrate colonic transit studies in the 20 patients with slow transit constipation. Ten of these patients (median age 39 y; age range 23–65 y)

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For correspondence or reprints contact: Dylan Bartholomeusz, MD, Department of Nuclear Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000.

underwent ^{67}Ga-citrate studies and 10 patients (median age 43 y; age range 34–68 y) underwent ^{111}In-DTPA studies. All of these subjects had a history of chronic constipation with more than 5 d between stools and associated straining. They were thought to have idiopathic constipation after exclusion of other possible causes on history and physical examination and whenever possible normal anorectal manometry results. We were unable to perform dual-isotope studies in the subjects because of limitations related to radiation exposure.

Radionuclide transit studies were performed according to a similar protocol. After an overnight fast, the subjects ingested 4 MBq (108 μCi) ^{111}In-DTPA or 3 MBq (81 μCi) ^{67}Ga-citrate in solution. Serial images of the abdomen were then obtained at 6, 24, 48, 72 and up to 96 h. Abdominal images were performed (with the patient lying supine on the scanning bed) using a large-field-of-view (LFOV) gamma camera and medium-energy collimator with 20% window centered on the 172- and 247-keV photopeak if indium was the tracer or on the 92-, 185- and 300-keV photopeaks for gallium. At each scanning time, anterior and posterior images of the abdomen were obtained on a digital computer for 10 min using a 64 × 64 matrix. A single 10-min background image was also obtained before administration of tracer for background subtraction. Patients were allowed to maintain their normal diets, but laxatives and other drugs that could affect transit were not ingested during the study. The study was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

Computer Analysis

We used the method previously described by Smart et al. (*19*) in their ^{111}In-DTPA studies (with appropriate correction for the $t_{1/2}$ of ^{67}Ga-citrate if necessary). In this method, a composite image of the colon is obtained by imaging those recorded on multiple days. Regions of interest (ROIs) are drawn and 11 single-pixel ROIs are marked starting at the cecum and ending at the rectum. By joining of consecutive points, a continuous "colon line" from cecum to rectum is obtained. After background image subtraction, a geometric mean is calculated and the aforementioned ROIs are superimposed. The distribution of activity along the colon is graphically displayed as an activity profile. A mean position of activity along the colon is calculated and, after correction for radioactive decay, a colonic half-clearance time is calculated. Analysis in all of these patients was performed by the same operator. For this analysis, retention in arbitrarily defined right colon, left colon and rectosigmoid regions was recorded.

Radiopaque Marker Studies

In all control subjects and patients, scan results were also compared with mean colonic transit time (MCT) measured according to the method described by Metcalf et al. (*21*) using radiopaque markers and a single 4th d radiograph. In this technique, subjects ingest 20 plastic radiopaque markers daily for 3 d. Then the MCT is calculated on the number of markers still present in the colon and rectum shown on an abdominal radiograph performed on the 4th d in which the MCT = 1.2 × the number of markers present in the colon and rectum.

Statistical Analysis

The Wilcoxon rank sum test was used to compare segmental colonic retention profiles within the patient groups.

Radiation Absorbed Dose

Radiation absorbed doses were calculated based on published results of tracer distribution and on mean transit times obtained (*22*).

RESULTS

Control Subjects

Studies were well tolerated in all subjects, and clear images were obtained using either tracer. The colonic half-clearance time of ^{67}Ga-citrate in the control subjects was 28.8 h (±12.5 h). This compared with a mean half-clearance time of 29.9 h (±12.5 h) when indium was used. Comparison of the mean segmental percent retention of gallium or indium in control subjects is shown in Figure 1. No significant difference is seen within the groups. Examples of a normal gallium colonic transit study result, activity profile, half-clearance time and mean activity position are shown in Figure 2.

Constipated Patients

The mean half-clearance time in the patients with idiopathic constipation was longer than that in control subjects at 75 h (±9.7 h) with gallium and 70.8 h (±16.0 h) with indium. The segmental percent retention of gallium and indium for the constipated patients is shown in Figure 3. No

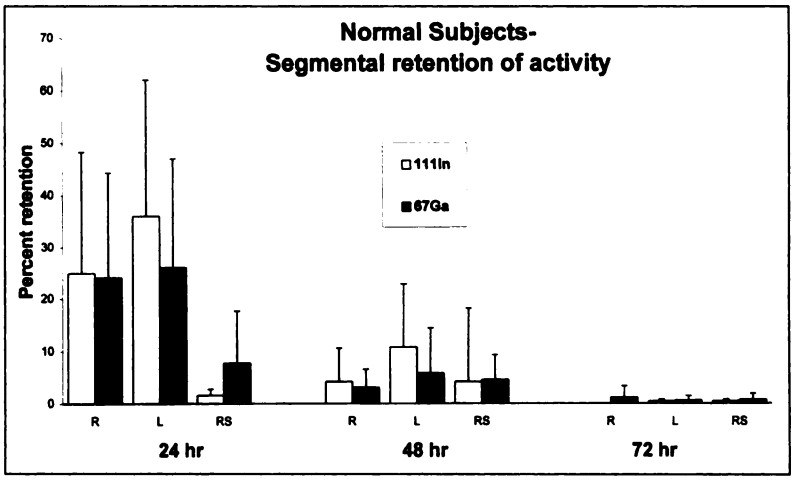

FIGURE 1. Percentage retention of tracer (mean ± SD) in control subjects 24, 48 and 72 h after tracer ingestion. R = right colon (ascending to mid-transverse colon region); L = left colon (distal half-transverse colon and descending colon region); RS = sigmoid colon and rectum.

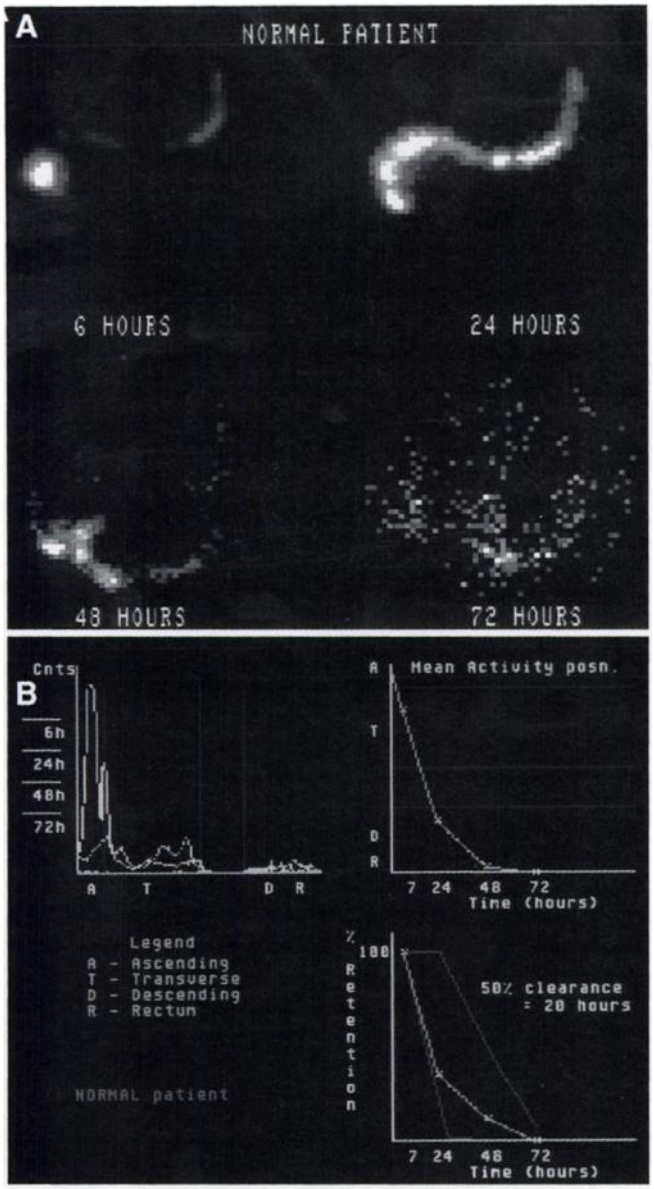

FIGURE 2. (A) ^{67}Ga-citrate colonic transit study in control subject. (B) Mean position of activity profile, half-clearance time of tracer and segmental activity profile.

difference was noted with either tracer, but retention of both tracers in constipated patients was significantly different from that in control subjects. The total mean percents of tracer in the colon at 24, 48 and 72 h in control subjects and constipated patients are shown in Figure 4. Once again, whereas results with ^{67}Ga-citrate and ^{111}In-DTPA are similar in each group, much more activity was retained by the constipated patients. Comparison of the mean positions of activity in control subjects and constipated patients at 24, 48 and 72 h with both tracers is shown in Figure 5. Movement of tracer in each group was similar using either tracer, but there was much more progression of tracer down the colon in control subjects than in constipated patients. An example of a ^{67}Ga study in a patient with slow-transit constipaton is shown in Figure 6.

Comparison with Radiopaque Marker Studies

The half-clearance time of tracer was compared with the MCT measured using radiopaque markers (Fig. 7). No significant difference was seen on the MCT in control subjects or in constipated patients studied with either tracer, but the constipated patients had a much higher mean MCT.

Radiation Dosimetry

The calculated total effective dose equivalent for 3 MBq (81 μCi) ^{67}Ga-citrate is 2.94 mSv. This compares with the effective dose equivalent of 1.2–2.8 mSv for 4 MBq (108 μCi) ^{111}In-DTPA (*19*).

DISCUSSION

This study shows that ^{67}Ga-citrate can be used as an alternative liquid radiotracer to ^{111}In-DTPA for studies of colonic transit. Gallium has many of the properties of an ideal marker for transit studies. It is not absorbed from the bowel when given orally, it appears to follow the normal passage of liquid bowel contents and its $t_{1/2}$ of 78 h compares well with the 67-h $t_{1/2}$ of indium, allowing studies to be performed over many days. This is important because scanning may be necessary for up to 5 d after ingestion of tracer, particularly if delayed emptying of the descending colon or rectum is to be diagnosed correctly. Although ^{111}In is considered to have better imaging properties, the quality of images that we obtained with ^{67}Ga and the quantitation were equally good and allowed correct identification of colonic segments.

The acquisition protocol for these studies and the method of data analysis were based on previously published methods with alteration for the $t_{1/2}$ of gallium. The ideal method of comparing the two tracers would probably have been dual-isotope studies in the same patient. We were unable to do this because of restrictions on radiation exposure to volunteer subjects defined by our Human Ethics Committee. Downscatter from the gallium photopeaks could also have been a further complicating technical factor. The two groups of control subjects we studied were similar. Comparison of the segmental retention of either tracer in these groups of patients showed remarkable similarity with no significant differences over any period of study. Furthermore, the mean half-clearance time, mean activity profiles and segmental retention of tracer data in this study are similar to those reported by Smart et al. (*19*) in their original publication using ^{111}In-DTPA. Patients with idiopathic constipation had quite different clearance times and segmental tracer retention. The study group was confined to patients who were thought to have slow-transit constipation. In these patients, the gallium colonic transit studies were able to provide data on regional and overall colonic transit. Further study of patients with pelvic floor incoordination and anal dysfunction would allow more detailed understanding of regional abnormalities of colonic function in these conditions.

At present, there is a wide choice of tracers that can be used for studies of colonic transit. These include those with

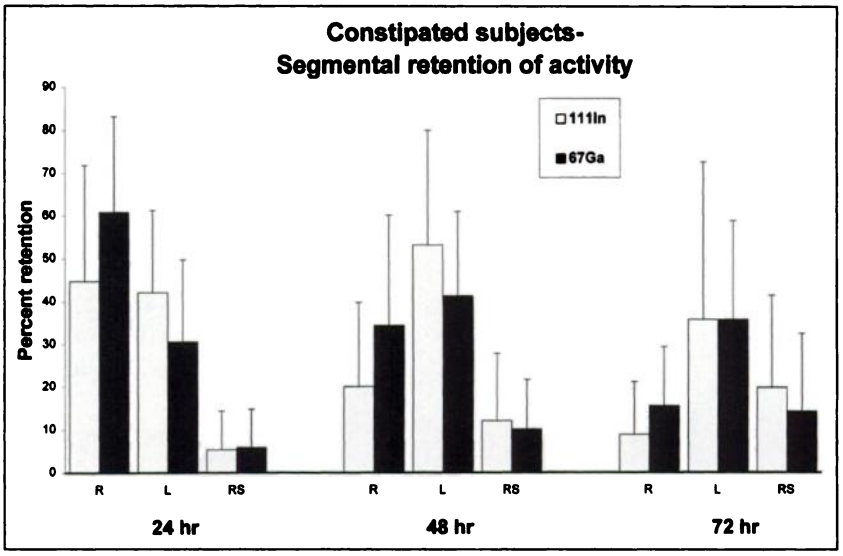

FIGURE 3. Percentage retention of tracer (mean ± SD) in constipated patients at 24, 48 and 72 h. R = right colon (ascending to mid-transverse colon region); L = left colon (distal half-transverse colon and descending colon region); RS = rectum and sigmoid colon.

^{111}In-DTPA bound to resin pellets and then incorporated into a methacrylate-coated capsule designed to dissolve in the distal small bowel (*18*), ^{111}In-DTPA bound to resin pellets alone (*13*), ^{131}I-labeled cellulose (*16*) and ^{111}In-DTPA in solution as a liquid marker (*19*). The reported advantage of methacrylate-coated capsules is their ability to deliver a bolus of tracer into the cecum (*23,24*). This method requires equipment for on-site preparation and administrative support to meet regulatory requirements, resulting in the development of ^{111}In-labeled activated charcoal as a marker (*25*). The iodine-labeled cellulose method has disadvantages related to the complicated labeling technique and the radiation exposure related to the radioisotope. The merits of using a liquid marker had been shown by Krevsky et al. (*14*) in their studies of regional colonic transit using radioisotope instilled into the cecum by peroral tube. In their studies comparing ^{131}I-labeled cellulose with ^{111}In-DTPA solution, Smart et al. (*19*) showed no significant difference in regional colonic transit of either the liquid or solid marker in dual-isotope studies of unconstipated controls and constipated subjects. The ascending colon in particular does not appear to discriminate between solids and liquids (*26*). These results suggest that liquid markers could be used for the study of colonic transit. Oral administration of liquid tracer in these earlier studies and in this study resulted in very good delivery of isotope to the cecum and ascending colon at 6 h. This was seen in all of the control subjects and constipated patients studied. Use of an oral agent simplifies the test, reduces invasiveness of the procedure and reduces the potential effect of peroral or rectal tubes on intestinal motility. Because more studies are performed in patients with constipation, there is likely to be a group of subjects who have generalized abnormalities of gastric and small bowel transit. In these patients, the tracer may take longer to reach the cecum. The study protocol may need modification in these patients but this would be necessary whether a solid or liquid marker were used. Use of ^{67}Ga as the liquid meal in gastric-emptying studies enables the tracer to be followed and used in whole-gut scintigraphy, the measurement of which is important particularly if colonic surgery is considered (*27*).

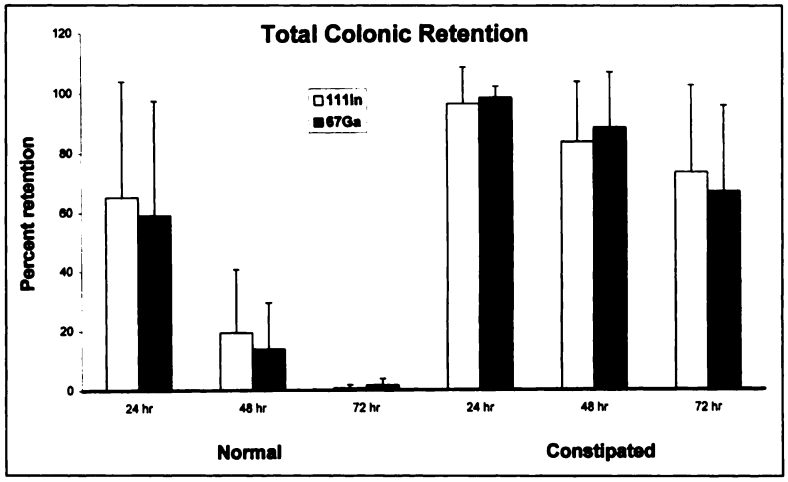

FIGURE 4. Total colonic retention of tracer (mean ± SD) in control subjects and constipated patients at 24, 48 and 72 h.

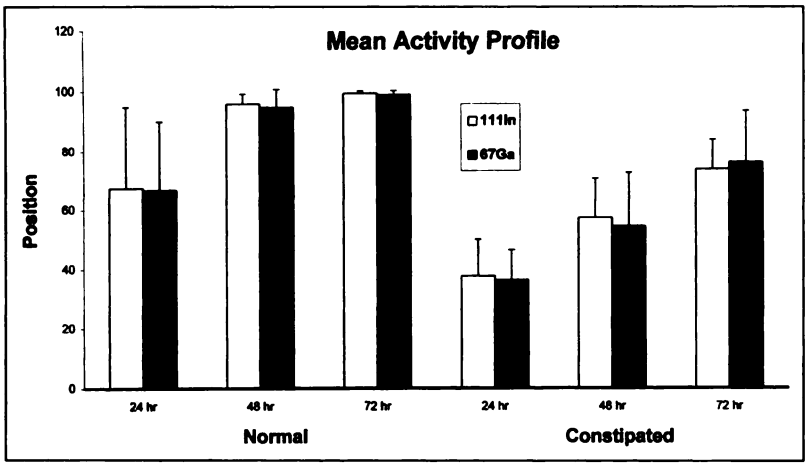

FIGURE 5. Comparison of mean position of activity in colon in control subjects and constipated patients (mean ± SD) at 24, 48 and 72 h. Regular points are marked down length of colon from 0 (cecal pole) to 100 (rectum) to define mean position of activity in bowel.

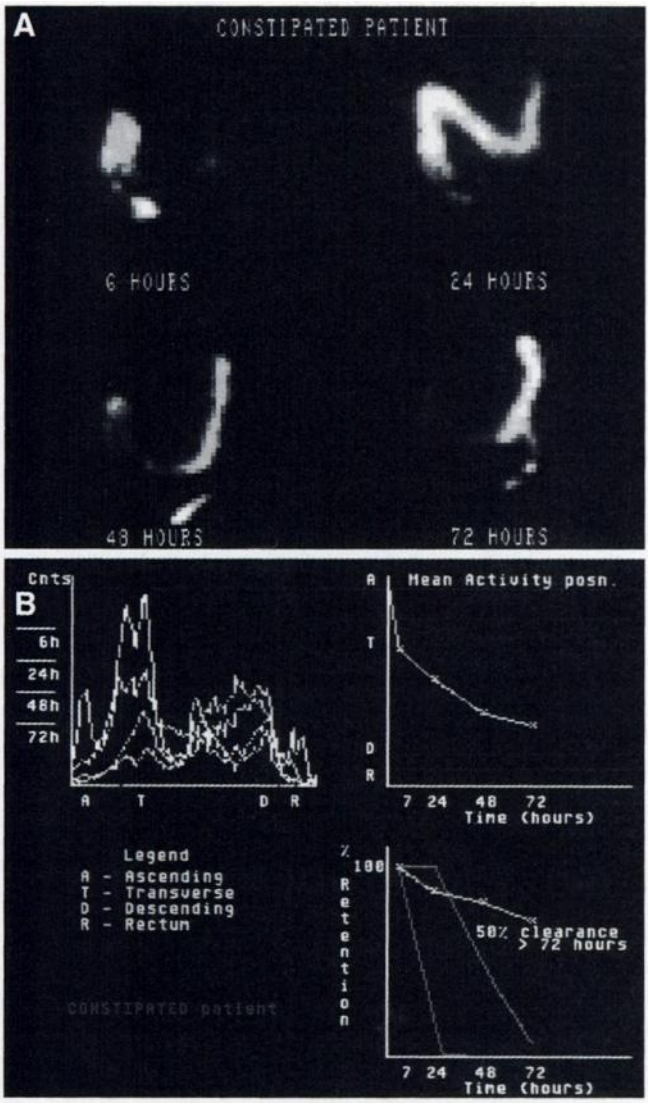

FIGURE 6. (A) ^{67}Ga-citrate colonic transit study in constipated patient. (B) Half-clearance time of tracer, mean position of activity and segmental activity profile.

The method of computer data analysis used in this study has been published previously for ^{111}In-DTPA. Geometric mean images are used in an attempt to overcome differences in attenuation caused by bowel position. Whereas the half-clearance time of tracer provides a single figure reflecting overall transit, segmental retention of tracer and mean activity profile are more useful data. The latter provides similar but not identical data to the geometric center of activity shown in other studies (*17*). They enable assessment of the site of regional delay in transit.

In both control subjects and constipated patients, there was a good correlation between the half-clearance time of tracer and the MCT using radiopaque markers. This has been shown previously with ^{51}Cr-labeled sodium chromate (*12*). We did not compare the regional motion of radiopaque markers with that of tracer because there is often overlapping of bowel segments that makes marker localization difficult, particularly when a single radiographic technique is used. Some studies have shown that whereas overall colonic transit is similar using radiopaque markers and isotope, regional differences may exist (*17*).

CONCLUSION

Constipation is a common and often chronic disorder. Most patients have mild symptoms but a small number have severe symptoms that can be difficult to manage. Accurate measurement of segmental colon transit with an inexpensive, safe and reliable test is important in these patients. The use of ^{67}Ga-citrate reduces the cost and increases the availability of colonic transit studies. The gallium was well tolerated by all patients and radiation dosimetry is low and compares well with other tracers used in colonic transit studies. In constipated patients, the dose can be reduced further by asking them to begin taking laxatives again after completion of the tests to rapidly clear any retained tracer. While reducing the cost of the test, oral ^{67}Ga-citrate provides quantifiable, objective data on segmental colonic transit in control subjects and those with chronic constipation.

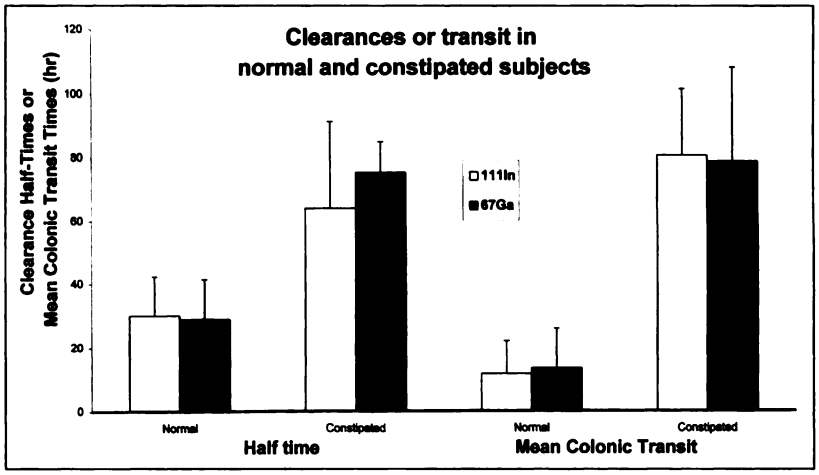

FIGURE 7. Comparison of half-clearance time of tracer ($t_{1/2}$) with mean colonic transit time calculated using radiopaque markers in control subjects and constipated patients using both tracers (mean ± SD).

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