# Colon Transit Scintigraphy in Health and Constipation Using Oral Iodine-131-Cellulose

Richard G. McLean, Richard C. Smart, David Gaston-Parry, Suzanna Barbagallo, Jennifer Baker, Norman R. Lyons, Catherine E. Bruck, Denis W. King, David Z. Lubowski, and Nicholas A. Talley

*Departments of Nuclear Medicine, Colorectal Surgery, and Gastroenterology, St. George Hospital, Kogarah, New South Wales, Australia*

The purpose of the study was to assess if a new scintigraphic method for noninvasive assessment of colonic transit could differentiate between subjects with normal bowel transit and those with constipation. Eleven normal subjects and 29 constipated patients were given 4 MBq iodine-131-cellulose ($^{131}$I-cellulose) orally and sequential abdominal scans were performed at 6, 24, 48, 72, and 96 hr from which total and segmental percent retentions were calculated. There were clear differences between the normal subjects and the constipated patients for the total percent retention at all time intervals, on a segmental basis in the right colon at 24 hr, and in all segments at 48 and 72 hr. Three-day urinary excretion of radioiodine was minimal; 2.4% ± 1.2% (mean ± s.d.) in constipated patients and 3.1% ± 0.8% in normals, with ~75% occurring in the first day. The use of oral radiotracers in the investigation of constipation appears promising.

**J Nucl Med 1990; 31:985-989**

Constipation is a common problem in the western world but patients frequently only seek medical attention when it becomes severe. The definition of constipation is primarily clinical and includes those patients who have two or less bowel motions per week or who strain more than 25% of defecating time (*1*). In many patients, the etiology is obvious (e.g., poor diet, irritable bowel syndrome, hypothyroidism, depression, or drug side effects) and no tests are needed to achieve optimum treatment (*2*). However, in some patients, further investigation is necessary and may include colonoscopy, anorectal physiology, and radiologic procedures such as defecating proctography and radio-opaque marker studies. In marker studies, the patient swallows a number of radio-opaque markers and their passage through the colon is monitored by radiologic examination of the abdomen or of the stools. This study gives information relating to the severity of the constipation and the site of delay. However, in its simplest and clinically applicable form it is prone to inaccuracy and in a more complex form is time-consuming, complicated, and involves significant patient radiation or suffers from the problems associated with stool collection over a number of days (*3-5*).

There are a small number of reports of radionuclide assessment of colonic transit that have relied on invasive techniques to instill the isotope into the cecum, either by oro-cecal tube or by colonoscopic intubation (*6-8*). However, they are not applicable in routine clinical practice. They may also be physiologically doubtful. Therefore, a noninvasive method which would also overcome the problems associated with the marker studies might have widespread appeal. Other groups have previously used iodine-131-cellulose ($^{131}$I-cellulose) for assessment of gastric and small intestinal transit (*9,10*), however, its potential role in the assessment of colonic transit is unknown.

We have, therefore, studied $^{131}$I-cellulose in normal subjects and in constipated patients to determine whether the patterns of tracer transit for the two groups of subjects would be sufficiently different to suggest that the test might give clinically useful information.

## MATERIALS AND METHODS

Two groups of subjects were studied, comprising 11 normal volunteers (two males, nine females, mean age 36 yr, range 23-61 yr) and 29 constipated subjects (5 males, 25 females, mean age 53 yr, range 20-80 yr). Normal subjects were not constipated, had no past history of bowel surgery, and were receiving no medications known to affect bowel function. Constipated subjects had two or less bowel motions per week or strained more than 25% of defecating time. This group was otherwise unselected and consisted of patients referred from the Colorectal Unit at St. George Hospital, from several gastroenterologists and a gynecologist.

Iodine-131-cellulose was prepared according to the method previously published (*11*). The volume of cellulose was <5 ml and was therefore thought unlikely to cause any alteration of bowel function. Following an overnight fast, 4 MBq $^{131}$I-cellulose was administered orally, together with a small meal of crackers, cheese, and water. All patients were asked to continue with their normal diet during the remainder of the

Received Sept. 21, 1989; revision accepted Jan. 9, 1990.

For reprints contact: R.G. McLean, FRACP, Department of Nuclear Medicine, St. George Hospital, Belgrave St., Kogarah, NSW Australia.

**TABLE 1**
Mean Total Percent Colonic Retention for Normal Subjects and Constipated Patients

| | Time (h) | | | |
|---|---|---|---|---|
| | 24 | 48 | 72 | 96 |
| Normal (±s.d.) | 48(28) | 11(11) | 3(4) | 0(1) |
| Constipated (±s.d.) | 84(23) | 63(28) | 43(28) | 30(25) |

study. Anterior abdominal scans were performed at 6, 24, 48, 72 and 96 hr using a large field of view gamma camera and high-energy collimator. Views were acquired for 10 min with simultaneous computer acquisition. A background image was similarly collected before the tracer was administered to enable subtraction of room background. Twenty-four-hour urine collections were performed for the first three days on 8 normal subjects and 17 constipated patients.

The absorbed doses and effective dose equivalents were calculated using the MIRD tables (*12*).

Using standard region of interest (ROI) analysis, three regions were defined: right colon (cecum to mid-transverse colon); left colon (mid-transverse colon to descending colon-sigmoid colon junction); and rectum and sigmoid colon. The amount of activity in the abdomen at 6 hr was taken as 100%. Using appropriate decay and background correction, total and segmental percent retentions were calculated at 24, 48, 72, and 96 hr for both groups of subjects. All results are expressed as mean ± 1 s.d.

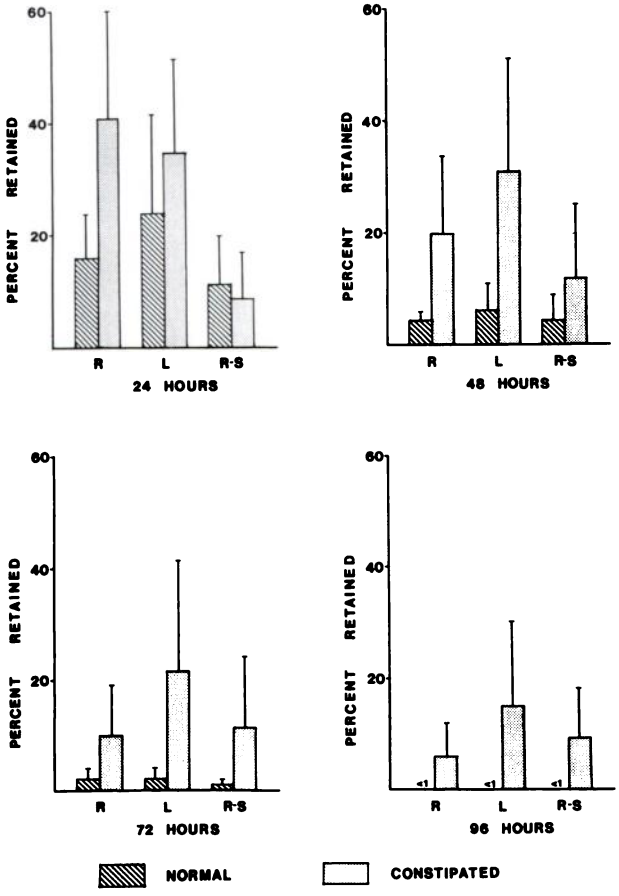


**FIGURE 1**
Mean segmental percent retention for normal subjects and constipated patients (R = right colon; L = left colon; and R-S = rectum and sigmoid colon).

## RESULTS

Mean total percent retention at 24, 48, 72, and 96 hr for normal subjects and constipated patients is shown in Table 1 and mean segmental percent retention in Figure 1. There is clear separation between the two groups for the right colon at 24 hr and for all segments in the 48-hr and later studies. Similarly, total percent retentions are markedly different at all times. For the 11 normal subjects, individual results are shown in Figure 2.

Representative images of a normal subject and of a constipated patient are shown in Figures 3 and 4. There is good outlining of the colon in both studies, with easy delineation of the three segments used for analysis. The regions used to define the different colonic segments are demonstrated in Figure 5.

In 11 patients, radio-opaque marker studies also were performed (*3*). For this study, the patients were given twenty short lengths of radio-opaque infant feeding tube by mouth and a plain abdominal radiograph performed at Day 5. If fewer than four markers were retained, the study was considered normal and if greater than four were retained the study was abnormal. In order to compare the results with the radionuclide colon transit study, total percent retention at 72 hr was used. A retention of >10% (i.e., >2 s.d. from the mean value for the normal subjects) was used as the upper limit of normal. Of the 11 clinically constipated patients, 5 had an abnormal marker study and ten had an abnormal radionuclide study.

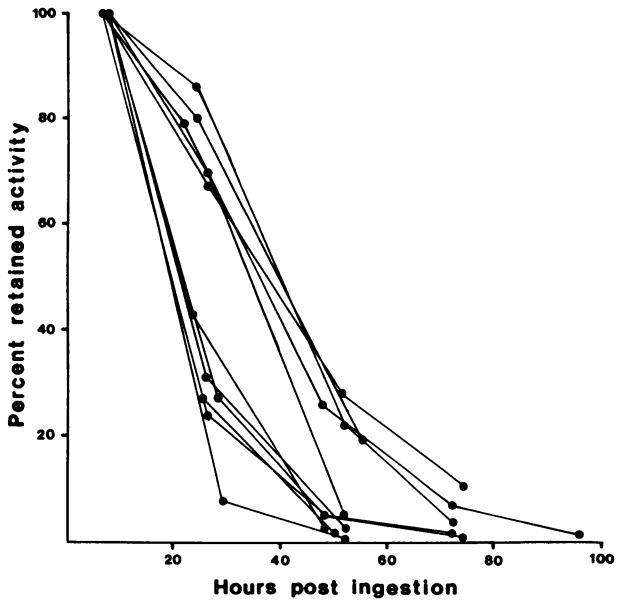


**FIGURE 2**
Total percent colonic retention for individual normal subjects.

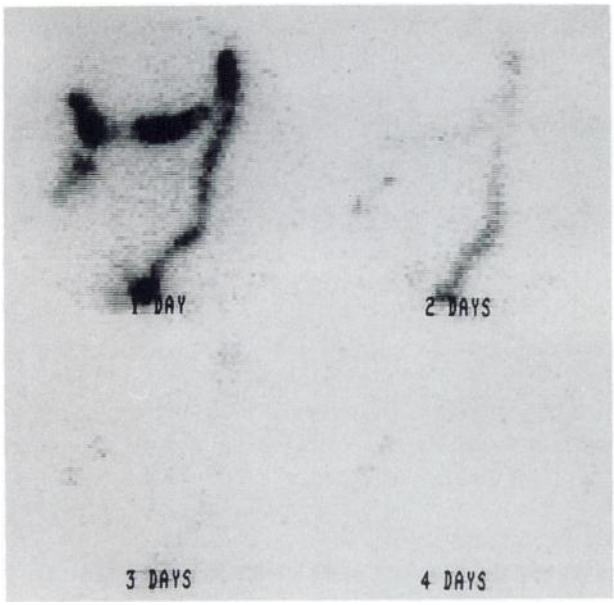


**FIGURE 3**
Representative images from a normal subject.

The urine collection showed a mean (±s.d.) urinary excretion of radioiodine of 3.1% (±0.8%) of the administered dose for normal subjects and 2.4 (±1.2%) for constipated patients. The majority of excretion occurred in the first 24 hr (2.5% and 1.7%, respectively). This indicates minimal dissociation of $^{131}I$ from cellulose in the bowel in both normal subjects and constipated patients. The absorbed doses and effective dose equivalents are shown in Table 2.

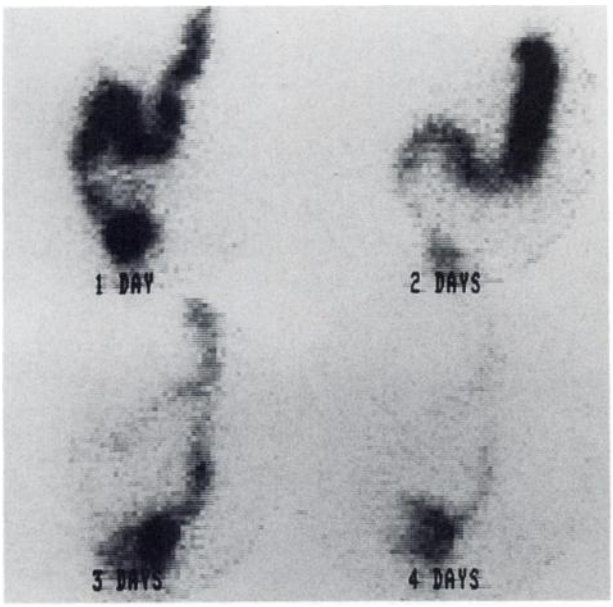


**FIGURE 4**
Representative images from a constipated patient.

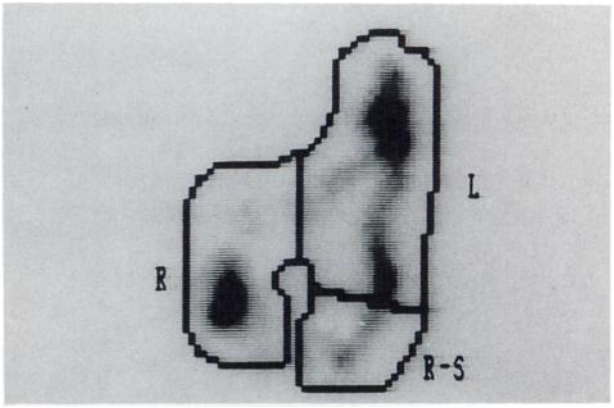


**FIGURE 5**
Representative image showing ROIs for different colonic segments (R = right colon; L = left colon; and R-S = rectum and sigmoid colon).

## DISCUSSION

The management of patients with constipation is becoming increasingly sophisticated as surgical procedures are added to previous conservative measures such as diet modification. Newer diagnostic techniques such as anorectal physiology greatly increase the clinician's understanding of the underlying disease processes and allow greater confidence in diagnosis. As a noninvasive test, radio-opaque marker studies, which give information concerning the severity, of constipation and the site of delay, have undergone many modifications since the initial description (*3*). These modifications include the use of different shaped markers, complex mathematical modeling, and radiologic examination of stools. However, none of the modifications is entirely satisfactory and none could be considered physiologic.

Although there have been previous reports of radionuclide colon transit, these have relied on invasive intubation methods and therefore are not suitable for routine clinical practice (*6–8*). Our study demonstrates that oral $^{131}I$-cellulose fulfills the criteria of a noninvasive test which gives diagnostic information and is applicable in routine practice.

**TABLE 2**
Dosimetry for Iodine-131-Cellulose

| | Normal Subject | Constipated Patient |
|---|---|---|
| Effective dose Equivalent (mSv) | 3.4 | 11.0 |
| Absorbed Dose (mSv) | | |
| Ovary | 1.2 | 3.8 |
| Lower Large Intestine | 28 | 80 |

Residence times assumed for dosimetry calculations:
Normal subject: upper large intestine = 8 h, Lower large intestine = 18 h, Constipated patient: upper large intestine = 2 days, lower large intestine = 3 days.

The procedure was well tolerated by all patients, no side effects were observed, and no patients reported altered bowel habit as a result of the small amount of added fiber. As each scan took only 10 min, it was possible to be flexible with scheduling and allow patients to attend at a convenient time. As all subjects were out-patients, this made attendance on multiple scanning days acceptable and patient compliance was complete. Computer analysis and quantitation was simple and only basic ROI analysis and decay correction were necessary. The operator was able to view all images from the study before drawing regions, which facilitated accurate demarcation of segments.

For this study, the only entry criterion was a clinical diagnosis of constipation and, therefore, the group included patients with constipation resulting from numerous causes. Eleven patients had a final diagnosis of slow transit constipation, five had obstructed defecation, three had diverticular disease, two had functional bowel disease, and in eight, no final diagnosis has been reached. In view of the heterogeneous nature of the group, we did not consider that a statistical comparison between the control and constipated groups would be fruitful. However, in comparing the results from individual constipated patients with the normal range (defined as mean + 2 s.d. for the normal group), three patients were within the normal range at all time periods, three patients had borderline abnormal results at all time periods, three were abnormal at 48 hr but normal at 72 hr with a visual pattern suggestive of outlet obstruction, and the remainder were markedly abnormal at all time periods. Although the number of normal subjects who have been studied is small, it would appear that the normal range will be relatively tight and therefore the test will discriminate well between normal and abnormal.

In a subgroup of 11 patients in whom radio-opaque marker studies were also performed, the radionuclide study was abnormal in 10 out of 11 patients, while the marker study was abnormal in 5 of 11 patients. The significance of this result is unclear as final diagnoses have not been established.

There are several issues relating to the radiotracer and to the imaging technique which need to be addressed. First, the preparation of the $^{131}$I-cellulose is a relatively time-consuming process and does require the services of a radiochemist. However, in view of the long half-life of the radioiodine, adequate material can be synthesized on a monthly basis for a number of patient studies. There was a small amount of dissociation of radioiodine from the cellulose and all patients received pretreatment with Lugol's iodine to prevent thyroid accumulation of radioiodine. The radiation dose from this quantity of radioiodine was relatively minor in normal subjects but there was significant dose to the critical organ (the lower large intestine) in severely constipated patients. Nevertheless, the ovarian dose in such patients (up to 3.8 mSv) is less than the dose from serial abdominal radiographs in radio-opaque marker studies, which may reach 6 mSv.

Second, several technical issues have become apparent. In this study, only a single anterior abdominal image was obtained. Although the colon is situated anteriorly in the abdomen throughout most of its length, the rectum is positioned more posteriorly. Therefore, calculated activity in this region will be underestimated due to attenuation. In addition, it may be preferable to divide the colon into shorter units for more precise analysis. When a bolus of activity is located at a junction between segments, different operators may calculate different results for segmental percent retentions although the total percent retention will be unaltered.

In order to overcome the relatively high dosimetry and the above technical problems, we have undertaken a pilot study comparing $^{131}$I-cellulose and indium-111-DTPA and used the geometric mean of anterior and posterior images to calculate the retained activity. If further study confirms the preliminary results, it should be possible to improve the procedure described here.

Radionuclide colonic transit using oral tracer is a promising technique which complements other tests of colonic function. The use of the study in clinical practice is still being assessed. Comparison of the percent retained activity with the normal range allows confirmation of the diagnosis and assessment of severity, while visual assessment of the pattern of transit may indicate the site of obstruction. However, this form of analysis is currently in a preliminary stage and will require further correlation with final diagnosis. With appropriate modifications, this technique may have a routine clinical role in nuclear medicine departments that service gastroenterologic and colorectal units.

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Selected manuscripts from the issues of the Journal of Nuclear Medicine published 15 and 30 years ago.
Edited by F.F. Mand

## JUNE 1975

### Vesicle Interactions with Polyamino Acids and Antibody: In Vitro and In Vivo Studies

June K. Dunnick, I. Ross McDougall, Sergio Aragon, Michael L. Goris, and Joseph P. Kriss

### In Vivo Distribution of Vesicles Loaded with Radiopharmaceuticals: A Study of Different Routes of Administration

June K. Dunnick, I. Ross McDougall, Michael L. Goris, and Joseph P. Kriss

Artificial spherules or vesicles, formed from phosphatidylcholine and gangliosides and enclosing $^{99m}TcO4$, survive intact in the circulation of the mouse. These vesicles remain intact when polyamino acids are incorporated into and onto them.

Studies of the distribution of polyamino acid-vesicles and protein vesicles in vivo uncovered that the latter distribute differently compared with standard vesicles or with free protein alone. In contrast, aromatic polyamino acid-vesicles concentrate in the liver and spleen to a greater extent than standard vesicles.

The permeability and stability characteristics of vesicles may be preserved then, when they are modified by the addition of protein or polyamino acids. This modification of vesicles may be associated with an alteration of their fate in vivo.

The potential exists, therefore, to use vesicles as carriers of radiopharmaceuticals and other drugs and to direct the vesicles preferentially to tissue targets in vivo.

The in vivo distribution of vesicles containing radiopharmaceuticals in their cavities was studied using three routes of administration: intravenous, subcutaneous, and intraperitoneal. In vivo distribution in mice was determined by dissection of the animals and calculation of radioactivity in the organs. In rats, the in vivo distribution was assessed by scintigraphy using a scintillation camera-digital computer unit.

After i.v. injection of vesicles, the radioactivity is concentrated in, to some extent, the liver and spleen, but the pattern of distribution is different from that of the corresponding free radiopharmaceutical. The permeability of the vesicular membrane to contain radiopharmaceutical has been shown to vary according to the chemical composition of the vesicles.

We conclude that vesicles can be used to introduce materials in vivo and that the potential exists for their specific targeting by coupling other molecules to their surfaces. ■

## JUNE 1990

### Half-Life

I. Ross McDougall

The article on vesicles, published 15 years ago in *The Journal of Nuclear Medicine*, was actually one of a pair of articles published back to back.

The laboratory work was done when I was a research fellow at Stanford University Medical Center. At that time (and now), one of the key problems was delivery of radiopharmaceuticals to target organs. In the course of discussion, the late Joe Kriss and I came across a series of articles in *Hospital Practice*, which dealt with the structure of cell membranes, including one about artificial membranes, liposomes, and vesicles. It occured to Joe and me that these might provide a mechanism whereby packages of radioactive tracers could be directed at target sites. Coincidentally, Michael Goris joined the faculty and was able to provide expertise in computing of in vivo distribution studies in animals. One hundred yards from the medical center, Harden McConnell, in the department of physical chemistry, was at the forefront of chemical studies using artificially prepared liposomes. The final building block was the good fortune of having June Dunnick, a PhD in chemistry, accompany her husband to his residency in diagnostic radiology. June was our "in-house" chemist; I was responsible for the biology and in vivo studies, Michael Goris for computer, statistical, and mathematical help, and Joe was our overall mentor. Our first publication, in the *Proceedings of the National Academy of Sciences*, demonstrated that vesicles loaded with radiopharmaceuticals could be injected into experimental animals and remain intact in circulation. The two articles published in *JNM* were corollaries to that article.

This was a very exciting period, but unfortunately I am not actively involved in vesicle research today. There are now companies devoted to the production of artificial lipid vesicles. Currently, George Segall, one of my colleagues, continues research with vesicles and I have a tinge of regret that time does not allow me to be more actively involved with his projects. ■