
Comparison of Oral Iodine-131-Cellulose and Indium-111-DTPA as Tracers for Colon Transit Scintigraphy: Analysis by Colon Activity Profiles

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In 11 normal subjects and 11 patients with a clinical diagnosis of constipation, oral ^{131}I -cellulose and ^{111}In -DTPA were compared simultaneously as tracers for radionuclide colon transit scintigraphy. Visual assessment of the images revealed no differences between tracers. Quantitation was performed using total and segmental percent retention and the derived value of clearance half-time. In addition, profiles of the activity distribution along the length of the colon were generated and the mean position of the activity in the colon calculated. For all indices, the results were similar in both normal subjects and constipated patients when comparing tracers, although marked differences were present between normal subjects and constipated patients for each tracer. Indium-111-DTPA was easy to administer and dosimetry was more acceptable than for ^{131}I -cellulose, especially in constipated patients. It is concluded that ^{111}In -DTPA is the preferred tracer for oral colon transit scintigraphy.

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The assessment of a patient with constipation involves a history and a physical examination, and sometimes, a barium enema or colonoscopy to exclude a structural abnormality. On the basis of these results, appropriate treatment can be instituted in most cases, however, in patients with severe constipation, further investigation is usually warranted. Determination of colonic transit plays an integral part in such evaluation. Previously, radiopaque marker studies have been used to provide an assessment of overall transit (1-3) and this technique has been supplemented by defecography, which may demonstrate a cause for obstructed defecation, such as an internal prolapse, rectocele, or paradoxical pelvic floor contraction (4,5). Radionuclide techniques have been applied to the investigation of colonic transit and have relied upon in-

vasive instillation of tracer (6-8). The preparation for such procedures and the procedures themselves are likely to disturb normal colonic transit, and despite the advantage of a bolus instillation to a precise site, their role in routine clinical practice is limited.

Recently, we have described a radionuclide colon transit procedure using oral ^{131}I -cellulose (9). Our study of 11 normal subjects and 29 constipated patients demonstrated clear delineation between normal and abnormal groups on the basis of total and segmental percent colonic retention over 4 days. However preparation of the tracer is complicated and the radiation exposure is high, particularly in constipated patients, and therefore we decided to investigate an alternative tracer. In this study, we report our results comparing our original tracer, oral ^{131}I -cellulose, with an alternative tracer, oral ^{111}In -DTPA, in 11 normal subjects and 11 patients with constipation. In addition, we have developed a more accurate method of displaying and characterizing colonic activity and of quantitating the passage of activity to allow comparison with normal ranges.

MATERIALS AND METHODS

Technique and Data Acquisition

Eleven subjects (two males, nine females, mean age 36 yr, range 23-61 yr) with normal bowel function and 11 patients (two males, nine females, mean age 58 yr, range 34-79 yr) with a clinical diagnosis of constipation (with two or fewer bowel motions per week or straining greater than 25% of defecating time) were studied. Following an overnight fast, 4 MBq of ^{131}I -cellulose, prepared by a trained radiochemist as previously described (10), and 4 MBq of ^{111}In -DTPA were given orally simultaneously, and serial images of the abdomen were obtained at 6, 24, 48, 72, and 96 hr. In some patients, the latter four views were obtained several hours later each day to coincide with the patient's domestic or work schedule. Dual-isotope imaging was performed using a LFOV gamma camera using 20% windows centered on the 364 keV photopeak for ^{131}I and the 173 keV photopeak for ^{111}In , with the patient positioned horizontally on a scanning bed. Phantom measurements demonstrated that the Compton downscatter from the ^{131}I contributed only 13% to the ^{111}In counts, due to the

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greater sensitivity of the camera to the 173 keV photons. On all occasions, anterior and posterior images of the abdomen were obtained on a digital computer for 10 min each using a 64×64 matrix. In addition, a single 10-min background image (for subtraction of room background) was obtained prior to the administration of the tracer. During the period of the study, patients continued on their normal diets and medications. In order to block thyroidal uptake of radioiodine, Lugol's iodine, two drops three times a day, was given for 7 days, commencing 2 days before tracer ingestion. Three successive 24-hr urinary collections were performed in eight normal subjects to assess urinary excretion of tracer.

Computer Analysis

In most patients, the total extent of the colon could not be defined on any one image so a composite image of the colon was obtained by merging together images recorded on multiple days. This was possible as any one segment of the colon was usually seen on at least two images. If necessary, the images were translated, either vertically or horizontally to align the images of the colon. A region of interest, ROI A, was marked as the outermost edge of the colon on the composite image. To define the course of the colon, up to 11 single pixel ROIs were marked, starting at the cecum and ending at the rectum. By joining consecutive points with straight line segments, a continuous "colon line" from cecum to rectum was thus obtained (Fig. 1).

At each data collection time, the room background image was subtracted from both the anterior and posterior images, a geometric mean image was calculated, and the above ROIs were superimposed. A value for the total activity at a particular point along the "colon line" was found by constructing a line perpendicular to the "colon line" and then summing counts in all pixels along this line that lay within the ROI A (Fig. 2). The distribution of activity within the colon could then be graphically displayed as an activity profile along the colon. The anatomical regions of the colon (ascending, transverse, descending, and recto-sigmoid) were marked on the display for alignment (Fig. 3).

In order to spatially quantify the passage of the activity along the colon, the mean position of the activity along the colon was calculated. To take into account the activity that had been passed from the rectum, this activity (determined as initial counts – retained counts) was added to the profile as point $n + 1$, where n was the number of points in the original profile.

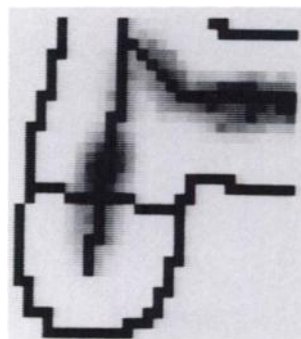


FIGURE 2. The counts at a particular point along the colon were found by summing the counts in the pixels of a line perpendicular to the line of the colon.

The mean activity position was then calculated as follows:

$$\text{mean activity position} = \frac{\sum_{i=1}^N \text{POS}(i) \times \text{ACT}(i)}{\sum_{i=1}^N \text{ACT}(i)},$$

where POS(i) is the i th position along the colon, ACT(i) is the profile activity at POS(i), and N is the number of points in the extended colon profile ($N = n + 1$).

The mean activity position was then normalized to a standard colon length of 100 points. A graphical display of the normalized mean activity position (Fig. 4) enabled any movement of activity within the colon to be clearly visualized and quantitated.

As well as spatial quantitation of colon activity, temporal quantitation was performed by determination of the clearance half-time. ROI A, around the total colon, enabled the total retained activity at any time to be calculated from the geometric mean images. Corrected for radioactive decay, the retained activity was plotted against time and the clearance half-time was found by linear interpolation (Fig. 5).

In addition to the new analyses described above, the geometric mean images were analyzed as described previously (9) using three colonic segments: (i) right colon (cecum to mid-transverse colon), (ii) left colon (mid-transverse colon to descending colon-sigmoid colon junction), and (iii) rectum and sigmoid colon.

Interoperator Reproducibility of Computer Analysis

Ten ^{111}In -DTPA colon transit studies, selected at random, were analyzed independently by two separate operators. The mean difference between the results of the two analyses were obtained for the total and segmental percent retentions, the

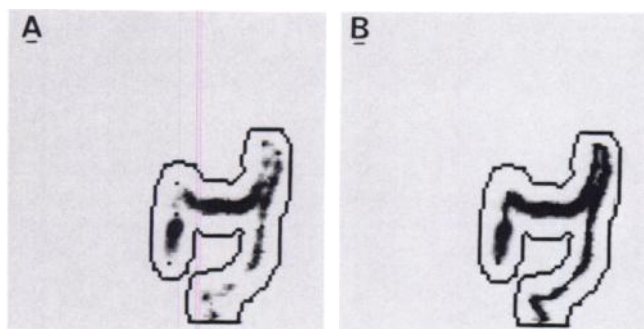


FIGURE 1. (A) A composite image of the colon together with the marked ROIs used to construct the colon activity profile. (B) The composite image together with the line formed by joining adjacent ROIs in Figure 1A by straight lines.

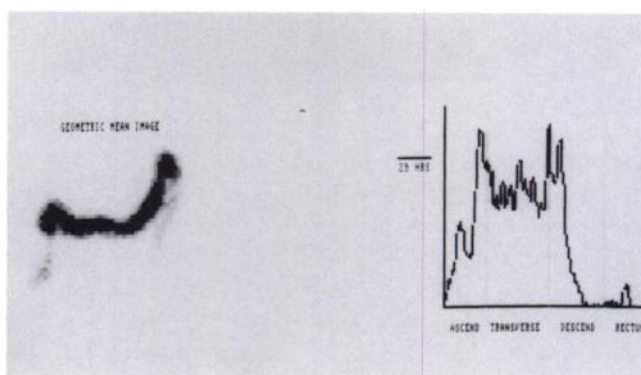


FIGURE 3. A geometric mean image with the corresponding colon activity profile from the cecum to the rectum.

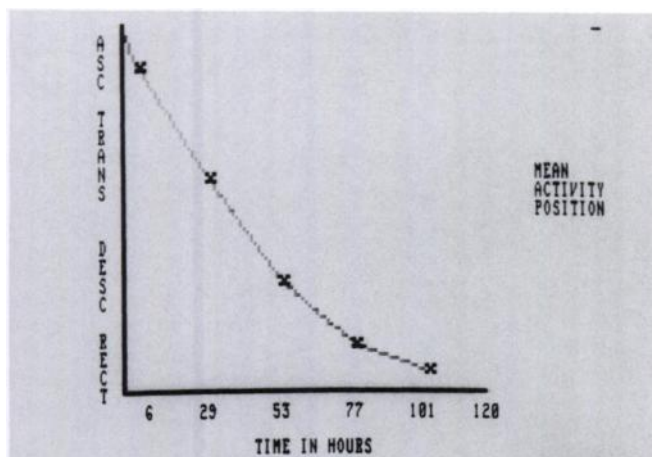


FIGURE 4. The position of the bolus in the colon, expressed as the mean position of the activity normalized to a colon length of 100 pixels against time for an individual patient.

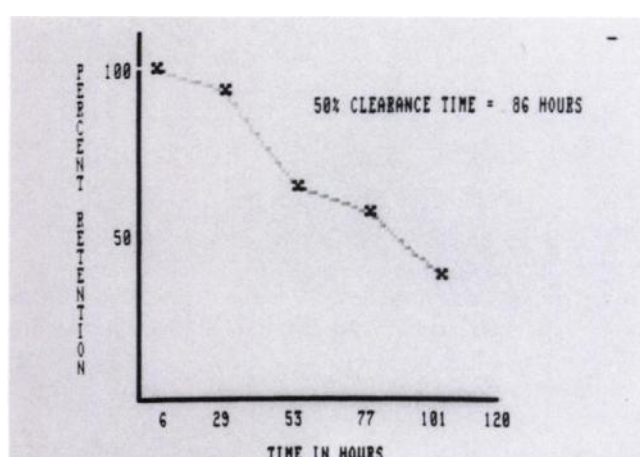


FIGURE 5. Total retained activity in the colon, expressed as a percentage of the activity at 6 hr against time for a particular patient.

clearance half-time and for the mean activity positions at 6, 24, and 48 hr.

Radiation Absorbed Dose

The absorbed doses and effective dose equivalents were calculated using MIRD tables (11).

Statistical Analysis

The significance of the differences between the colon retention of ^{131}I -cellulose and ^{111}In -DTPA in individual patients was assessed using the Wilcoxon signed rank test. The Wilcoxon rank sum test was used to compare the colonic retentions of each tracer between the normal controls and the constipated patients.

RESULTS

Segmental Percent Retention

Mean segmental percent retention of ^{131}I -cellulose and ^{111}In -DTPA at 24, 48, 72, and 96 hr for normal subjects is shown in Table 1 and for constipated patients in Table 2. Comparing ^{131}I -cellulose and ^{111}In -DTPA for each segment at each time period, the differences between mean values ranged from 0% to 3.2% for normal subjects and from 0% to 5.8% for constipated patients, however none was statistically significant. On a patient-by-patient basis, the difference in segmental percent retention between ^{131}I -

cellulose and ^{111}In -DTPA was also compared. For the normal subjects, 1 out of 12 comparisons was significant ($p < 0.05$). This occurred in the left colon at 48 hr. For the constipated patients, there were 2 of 12 significant comparisons, these occurring in the right colon at 24 hr ($p < 0.025$) and the right colon at 72 hr ($p < 0.005$). It must be noted that the differences between mean values of percent retention on these occasions were 1.2, 3.0, and 3.5%, respectively. However, these values are similar to the level of interoperator variability, and although the comparisons are statistically significant, they are therefore unlikely to be of major relevance.

Total Colonic Retention

Mean total colonic percent retentions for normal subjects and constipated patients with both ^{131}I -cellulose and ^{111}In -DTPA are shown in Figure 6. No significant difference was noted between tracers for either group. However there was a clear difference between groups for both tracers which was statistically significant at each time period. Examples of scans performed using ^{131}I -cellulose and ^{111}In -DTPA in a normal subject and in a constipated patient are shown in Figure 7. Scan appearances are virtually identical at all time periods, however the greater photon

TABLE 1
Segmental Percent Retention for Normal Subjects*

	24 hr			48 hr			72 hr			96 hr		
	R	L	R-S	R	L	R-S	R	L	R-S	R	L	R-S
^{131}I	15.8 (6.7)	25.7 (19.9)	14.7 (10.8)	3.0 (2.6)	4.5 (5.4)	5.5 (7.4)	0.8 (1.3)	1.0 (2.2)	0.5 (0.5)	0.2 (0.6)	0.1 (0.3)	0.0 (0.0)
^{111}In	12.6 (8.8)	27.3 (23.2)	16.6 (13.3)	1.7 (1.6)	3.3 (4.6)	6.5 (10.3)	0.5 (0.8)	0.7 (1.6)	0.3 (0.5)	0.1 (0.0)	0.0 (0.0)	0.0 (0.0)

* Expressed as mean segmental percent retention (s.d.).

R = right colon; L = left colon; and R-S = rectum and sigmoid colon.

TABLE 2
Segmental Percent Retention for Constipated Patients*

	24 hr			48 hr			72 hr			96 hr		
	R	L	R-S	R	L	R-S	R	L	R-S	R	L	R-S
¹³¹ I	36.7 (19.1)	36.7 (16.3)	18.1 (13.3)	18.1 (10.0)	33.3 (24.0)	22.4 (19.8)	8.6 (5.0)	18.2 (19.9)	19.2 (18.0)	4.4 (3.3)	12.6 (14.7)	15.6 (15.0)
¹¹¹ In	36.1 (22.6)	41.3 (26.3)	18.1 (18.4)	15.1 (11.7)	39.1 (37.5)	26.2 (25.8)	6.0 (5.8)	19.6 (35.3)	23.8 (24.0)	2.3 (2.3)	11.4 (16.1)	18.7 (20.7)

* Expressed as mean segmental group retention (s.d.).

R = right colon; L = left colon; and R-S = rectum and sigmoid colon.

flux obtained with ¹¹¹In resulted in images of greater count density. Total colonic retention, compared on a patient-by-patient basis showed no significant difference for either tracer in either group.

Clearance Half-Times

Mean clearance half-times for both groups and both tracers are shown in Table 3. No significant differences were seen between tracers, however, differences between groups were highly significant ($p < 0.001$).

Colonic Activity Profiles

Colonic activity profiles were plotted for all normal subjects and constipated patients and no differences were found when comparing the two tracers. An example is shown in Figure 8 in which activity profiles of the two tracers in a constipated patient are shown at 48 hr.

Mean Activity Position

By using activity profiles, mean activity positions were determined for all normal subjects and constipated patients at each time period. Mean values for this parameter are plotted against time in Figure 9. As with total colonic retention, there are no differences between tracers for either group but there are clear differences between the constipated patients and normal subjects for both tracers.

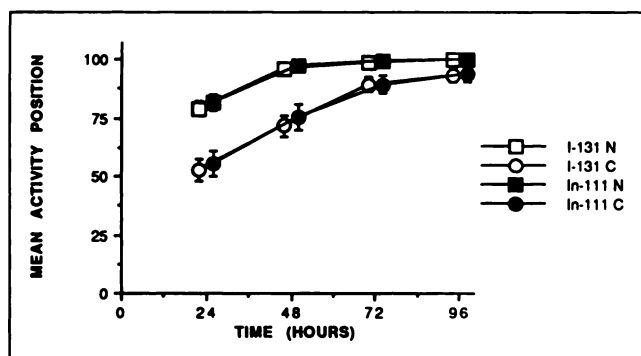


FIGURE 6. Total colonic percent retention vs time for normal subjects (N) and for constipated patients (C) using both tracers (mean \pm s.e.m.).

Mean activity position of the two tracers, compared patient-by-patient, showed one of four significant results for normal subjects [occurring at 48 hr ($p < 0.005$)] and none for constipated patients. However, on the occasion of the significant result, the difference between mean values was 1.7 points, less than the level of interoperator variability and therefore of questionable significance.

Interoperator Reproducibility of Computer Analysis

Clearance Half-time. In the ten patients in whom the reproducibility of the computer analysis was assessed the clearance half-times ranged from 17 to 94 hr. The mean difference between the values obtained by the two operators was 1.1 hr with a standard deviation of 1.6 hr and range of 0–4 hr.

Mean Activity Position. The mean \pm standard deviation for the difference between the mean activity position (expressed as percent of colon length) calculated by the two operators was $4.3\% \pm 4.6\%$ at 6 hr, $3.6\% \pm 4.7\%$ at 24 hr, and $3.0\% \pm 4.3\%$ at 48 hr. With the exception of one patient, the differences between operators, at all three times, lay in the range 0%–8%. In one patient, the differences were 16% at 6 hr, 15% at 24 hr, and 23% at 48 hr.

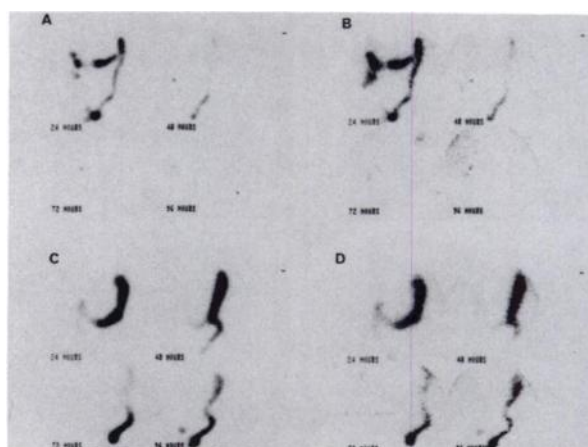


FIGURE 7. Scans at 24, 48, 72, and 96 hr of a normal subject using ¹¹¹In-DTPA (A) and ¹³¹I-cellulose (B), and of a constipated patient using ¹¹¹In-DTPA (C) and ¹³¹I-cellulose (D).

TABLE 3
Half-Clearance Times for Normal Subjects and Constipated Patients*

	Normal	Constipated
^{131}I	28.8 (10.0)	66.9 [†] (23.4)
^{111}In	28.6 (11.1)	68.0 [†] (24.8)

* Expressed as mean hr (s.d.).

[†] Significantly different from normal, $p < 0.001$.

Review of this patient's results revealed that although all the activity had entered the large bowel by 6 hr the extent of the cecum was not clearly defined, and the two operators had estimated the extent of the ascending colon differently, although the remainder of the colon had been defined similarly.

Total and Segmented Colonic Retention. The mean \pm standard deviation of all the differences between the total retained activity calculated by the two operators was $1.1\% \pm 1.2\%$ at 6 hr, $2.1\% \pm 2.5\%$ at 24 hr; and $2.2\% \pm 2.3\%$ at 48 hr. The mean difference for the percent retained in each of the three segments of the colon (right, left, and recto-sigmoid colon) was $<3.0\%$ at all times up to 48 hr.

Urine Analysis

For eight normal subjects, the mean \pm standard deviation urinary excretion over 3 days of ^{131}I was $3.1\% \pm 0.8\%$ and of ^{111}In was $0.1\% \pm 0.01\%$. We have previously shown that mean 3-day urinary excretion of ^{131}I in 18 constipated patients was $2.4\% \pm 1.2\%$ with approximately 75% excretion in the first day (9).

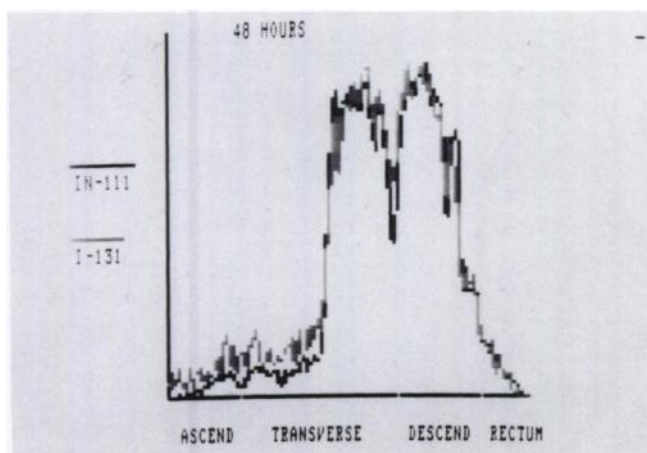


FIGURE 8. Colon activity profiles for a constipated patient using ^{131}I -cellulose and ^{111}In -DTPA at 48 hr.

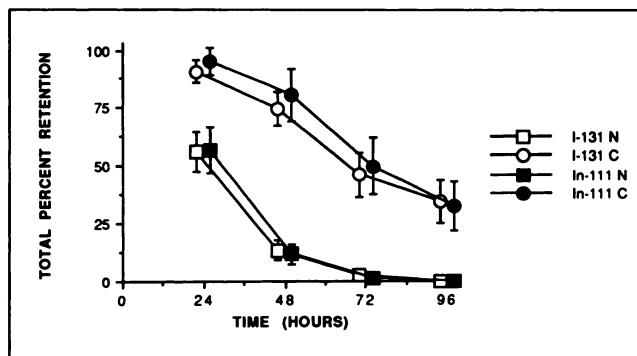


FIGURE 9. Mean activity position versus time for normal subjects (N) and for constipated patients (C) using both tracers (mean \pm s.e.m.).

Dosimetry

The absorbed doses and effective dose equivalents are shown in Table 4.

DISCUSSION

Most radionuclide techniques for the assessment of colonic transit have relied upon instillation of a radiotracer into the cecum (6-8). This required either a tube of 2 mm in diameter to be passed under fluoroscopic control in an antegrade fashion starting at the mouth until the tip of the tube reached the cecum, or intubation by colonoscopy. Kaufman et al. (12) have recently demonstrated that colonic transit obtained following jejunal instillation of radiopharmaceuticals was similar to that following cecal instillation however neither technique is routinely applicable on an outpatient basis.

Previously, we have described a technique for colon transit scintigraphy that avoided the requirement for either cecal or jejunal instillation (9). In a group of patients with constipation and a group of normal subjects, both on normal diets, ^{131}I -cellulose was given orally and its passage through the colon was monitored for up to 96 hr. This technique, which is both physiologic and routinely appli-

TABLE 4
Dosimetry

	^{131}I		^{111}In
Effective dose equivalent (mSv)	3.4	Normal	1.2
Critical organ dose (mSv)	11.0	Constipated	2.8
(lower large intestine)	80	Normal	6.4
Ovarian dose (mSv)	1.2	Constipated	11.6
	3.8	Normal	1.2
		Constipated	2.8
Residence times assumed for dosimetry calculations			
Normal transit	Upper large intestine 8 hr and lower large intestine 18 hr		
Constipated	Upper large intestine 2 days and lower large intestine 3 days		

cable, clearly demonstrated significant differences in colonic transit between the two groups. However ^{131}I is not an ideal radionuclide for imaging and may give rise to a significant radiation exposure to the colon in constipated patients, although the ovarian dose is less than that received in radiopaque marker studies.

The current study demonstrated that ^{131}I -cellulose can be replaced by ^{111}In -DTPA when given orally and that identical patterns of colonic transit are observed with the two tracers. Although statistically significant differences between ^{131}I -cellulose and ^{111}In -DTPA retention were noted in the left colon at 48 hr in the controls and in the right colon at 24 and 72 hr in the constipated patients, the magnitude of the differences ($< 3.5\%$) is of no clinical significance and is also no greater than the level of inter-operator variability. Indium-111-DTPA resulted in images of higher resolution, better counting statistics, lower absorbed dose to the patient, and negligible urinary excretion of ^{111}In -DTPA, indicating insignificant absorption of intact tracer. The possibility of tracer breakdown and absorption of altered components is possible, however even at low levels of colonic activity no liver activity was observed. Madsen and Jensen (13) have also used oral ^{111}In to measure large intestinal transit, however, they labeled the ^{111}In to plastic particles of 2-3 mm in diameter. Similarly, Hardy et al. (14) used both a non-disintegrating capsule and a multi-particulate system consisting of radiolabeled resin particles in a small number of normal subjects and patients with irritable bowel syndrome. Our results indicate that this is unnecessary, as ^{111}In -DTPA has an identical pattern of colonic transit to the physiologic cellulose fibre molecules.

Two groups of workers (12,13) have employed the analysis technique of Krevsky et al. (6), who used ROIs to delineate six colonic segments. Using counts in these regions together with calculated excreted counts, the geometric centre of the bolus of radioactivity was quantitated at time periods up to 48 hr. Our colon activity profile analysis has a number of advantages over the technique of Krevsky et al. Colon shape and length are very variable from patient to patient and the geometric centre analysis takes no account of the length of each of the segments. Furthermore, this analysis will be subject to interoperator variability in the drawing of the ROIs. Finally, if activity moves solely within a segment or any number of segments, this will not be reflected in a change in the geometric center.

The colon activity profile analysis makes no assumptions concerning the length or complexity of the shape of the colon. It produces a graphical representation of the distribution of radioactivity in the colon and enables the mean position of the activity in the colon to be found by integrating over the whole length of the colon (typically approximately 150 points in length) rather than over six arbitrary regions.

Our results indicate that the analysis is highly reproduc-

ible, with a mean difference of only 4% in the mean activity position when the results of two independent operators were compared. A larger difference (15%) was noted in one patient indicating that the definition of the cecum may be difficult in a small proportion of patients. The analysis can be easily performed in most patients, with the exception of those patients in whom there is overlap of the rectum with the cecum in the composite image, making definition of the colon line difficult. This problem did not arise in any of the patients reported in our study, although it has occurred occasionally in subsequent patients.

Most investigators have used the geometric mean of counts from the anterior and posterior images of the colon to attempt to correct for varying depth of the colon and therefore varying attenuation. This method of attenuation correction requires both the thickness of the patient and the attenuation coefficient to be constant over all areas of the abdomen. Hardy and Perkins (16) using radiolabeled particles administered orally to four normal subjects showed a relatively small variation (10%–15%) in geometric mean counts in comparison with either anterior or posterior counts alone during passage of the particles through the gastrointestinal tract. We have now measured colon transit using ^{111}In -DTPA in over 200 patients and have noticed that in some patients the decay-corrected geometric mean counts at 24 hr were significantly higher than at 6 hr. In these patients, the radioactivity at 6 hr was confined to the cecum, which was positioned low in the abdomen and was therefore subject to increased attenuation from the overlying pelvic bone on the posterior projection. When this occurred, the subsequent daily counts were normalized to the 24-hr value rather than to the 6-hr value without invalidating the procedure.

A radiologic technique using multiple radiopaque markers and a single abdominal radiograph to evaluate colonic transit has been proposed by Metcalf et al. (3). The values obtained by this group for mean colonic transit in normal subjects, although not directly comparable with our half-clearance time, are of a similar order of magnitude. However the radiologic technique uses a less physiologic marker than the radionuclide study and a single radiograph technique is less accurate than the multiple radiograph technique. In addition, there is a reliance on the ability to locate the markers accurately in the correct colonic segment. However in our study, we have seen a number of patients in whom a long sigmoid colon may overlie the rectosigmoid region or in whom multiple loops of sigmoid may be positioned above the pelvic rim. If an x-ray marker study was performed in these patients, markers may be incorrectly assigned to colonic segments leading to inaccuracies in calculating segmental and total transit.

The ideal test for assessment of colonic transit must be easy to perform, physiologic, quantifiable, reproducible, give low radiation dose, and produce clinically useful results. The test we have developed satisfies all these re-

quirements. It is easy to perform using a readily available radiopharmaceutical which behaves identically to cellulose fiber in its passage through the colon. The test is well tolerated by patients and can be performed easily on an out-patient basis, varying the imaging times so as not to interfere with the patient's work and domestic commitments. The radiation dose to the whole body is similar to that from an abdominal radiograph and is therefore acceptable in routine clinical practice. Finally, and most importantly, the test gives clinically useful information. It can confirm the presence of slow transit and therefore exclude normal transit constipation, and visual inspection of the images can suggest whether the likely diagnosis is idiopathic slow transit constipation or obstructed defecation. On the basis of this test, the attending clinician can have greater confidence when reaching a final diagnosis and instituting management. Oral radionuclide colon transit scintigraphy is likely to become an important test in the armamentarium of physicians dealing with constipation.

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