A Noninvasive Scintigraphic Assessment of the Colonic Transit of Nondigestible Solids in Man

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A noninvasive, scintigraphic technique for quantifying large intestinal transit time that provides low radiation doses was developed. The scintigraphic large intestinal transit (SLIT) method uses a total of 100 μCi of ^{111}In encapsulated in ten 2-cm nondigestible capsules, which are ingested after a 6-hr fast. Two hundred fifty microcuries of ^{99m}Tc-sulfur colloid were given to outline the gastrointestinal tract. Images were acquired at 4-hr intervals until all capsules were excreted. Normal volunteers (n = 10) consumed a standardized diet 2 days prior and during imaging. Segmental transit times were measured in the following: ascending, transverse, descending, recto-sigmoid colons; hepatic and splenic flexures. The radiation absorbed dose to the large intestine for the SLIT technique is less than half of that associated with other radiographic methods of colonic transit time measurement.

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The transit of solid and liquid food through the upper gastrointestinal (GI) tract is a well studied phenomenon. However, the transit of these same substances through the large intestine has suffered from a relative lack of investigation. The assessment of colonic motility has employed various methods such as direct observation (*1,2*), radiographic visualization of radiopaque markers (*3,4*), manometric and myoelectric measurement (*5–8*), and scintigraphic techniques (*9,10*). The ability to accurately determine total and segmental colonic transit is critical in diagnosing certain disease states of the large intestine. For example, the treatment for a person with colonic inertia, a disease primarily due to increased transit time on the right-side of the colon, is different from that of a person with functional recto-sigmoid obstruction, a disease of the rectum and sigmoid colon.

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Radiographic evaluation of colonic transit has taken two basic directions, one using radiopaque markers and the other using radionuclide techniques. The use of radiographic techniques to characterize bowel function was used as early as 1902 (*4*). Radiopaque granules or markers have been used by a number of investigators (*11–19*). These markers were usually given with a meal. By taking abdominal radiographs and counting the number of markers in each segment, the segmental colonic transit times were determined (*11,15*). For this method, the large intestine was divided into three segments; the right, left, and the recto-sigmoid colon. The principal drawbacks of these techniques were two-fold: data points were established at relatively infrequent intervals and a large abdominal radiation dose was delivered to the patient (263 mrem/abdominal film) (*20*). Exact intracolonic localization of the markers using an abdominal film may have been difficult because bony landmarks and gaseous outlines were used to determine the anatomical borders of the colon. In regions of the colon where there may be overlap, such as the regions proximal and distal to both flexures, there could have been much ambiguity as to which region the marker was located.

Scintigraphic evaluation of colonic transit has been performed in several fashions. In one study (*21*), 600 μCi of ^{51}Cr-tagged chromium chloride were given orally with 150 ml of water. After an overnight fast, a meal labeled with ^{99m}Tc-sulfur colloid was eaten by the patient. This study focused primarily on gastric emptying and simultaneous "gastro-colic reflex" events, therefore, it did not provide segmental colonic transit data.

An invasive method of colonic transit time quantification also has been developed (*22*). This technique required the oral insertion of a 4.5-meter long, 3-mm diameter tube to control the release of a radionucide. The tube was inserted into the cecum and ^{111}In-DTPA (50 μCi) was expelled. Subjects were subsequently fed and serial images were obtained and stored on a computer for analysis. Data processing was performed according to regions of interest (ROIs) by geometric center analysis (*23*). We have developed a scintigraphic technique that combines technologic simplicity and low radiation exposure with the noninvasive properties of radiopaque marker studies.

MATERIALS AND METHODS

The scintigraphic large intestinal transit (SLIT) technique measures the transit time of nondigestible solids through the large intestine. Small, nondigestible capsules containing ^{111}In were determined to be the optimal configuration for the SLIT technique. Capsules were made using 18 French (18FR = 6-ml outside diameter) nasogastric tubing (Argyle Salem Sump Tube, Sherwood Medical, St. Louis, MO) and a mechanical heat sealer (Vertrod Therma Impulse Heat Sealer, model 8H/8HTV, Vertrod Corp. Brooklyn, NY). The tubing had a wall thickness of 1 mm.

Ten capsules were made for each study, yielding a total activity of approximately 100 μCi. Measurement of the weight, length, and the encapsulated amount of ^{111}In in 50 capsules yielded the following (mean ± 1 s.d.): weight = 386 ± 2 mg, length = 21.6 ± 0.9 mm and activity 11.2 ± 1.1 μCi. Figure 1 illustrates several of these capsules.

In vitro testing of the capsule integrity, by immersion in human peptic acid, demonstrated no leakage of the radiotracer. Because the radiopharmaceutical is encapsulated in a nondigestible material, no additional precautions were necessary to guard against potential chemical toxicity. However, as an additional safeguard, the radiopharmaceutical compound used was ^{111}In-DTPA, which has been shown to be nonabsorbable in the human GI tract (*24*).

The capsules were administered with 150 ml of water containing 250 μCi ^{99m}Tc-sulfur colloid to provide an outline of the gastrointestinal tract.

Radiation dosimetry was estimated using the MIRD method. The dosimetry was calculated based on two different assumed distributions of the ^{111}In radioactivity; uniform and encapsulated sources (Table 1). It was assumed that the capsule walls completely attenuated all charged particles and low-energy (E < 27 kev) x-rays emitted during the radioactive decay of ^{111}In. A surface barrier semiconductor detector was used to verify that the capsule wall attenuated all particulate radiation originating from the ^{111}In (*25*).

The administration of 250 μCi of ^{99m}Tc-sulfur colloid gives the following estimated absorbed doses: stomach = 32 mrad, small bowel = 54 mrad, upper large intestine = 106 mrad, lower large intestine = 74 mrad, ovaries = 23 mrad, testes = 1.0 mrad, and total body = 4.0 mrad. These doses were calculated using the ICRP-30 GI tract model. The total absorbed dose for a single SLIT procedure is: stomach = 82 mrad, small intestine = 125 mrad, upper large intestine = 256 mrad, lower large intestine = 424 mrad, ovaries = 223 mrad, testes = 17 mrad, and total body = 29 mrad.

Prior to the commencement of experimental procedures, this study was approved by the Human Investigations Committee and the Clinical Research Center Advisory Committee of the University of Virginia Health Sciences Center. All procedures were fully explained to the volunteers and informed consent was obtained.

FIGURE 1. Several capsules after heat sealing. Ten microcuries of tracer in each. The scalpel has a centimeter scale ruler imprinted on it for reference.

Experimental Technique

The subjects (mean age = 26 yr, range 21–35; mean weight 176 lb, range 150–196; all within ± 10% ideal body weight) were required to have a bowel movement frequency in the normal range of 5–15 times per week. To estimate the reproducibility of the SLIT technique, all subjects underwent the SLIT protocol twice. Subjects were questioned as to the use of drugs or pharmaceuticals including laxatives, prokinetics, parasympathomimetics, and parasympatholytics. Subjects were also asked to refrain from strenuous exercise (long distance running or bicycling, etc.) during the experimental protocol.

For two days prior to commencing the scintigraphic study, each subject consumed a standardized diet established by the General Clinical Research Center. The standardized diet consisted of three meals and a small snack that yielded 2040 kcal per day. The daily macronutrient distribution was 50% carbohydrate, 30% fat, 20% protein and 18.2 grams of dietary fiber. Each subject submitted a three-day diet history prior to participation. Dietary analysis was accomplished with a commercially available nutrition analysis program (Nutripractor 6000, Practorcare, Inc., San Diego, CA).

On the third day after commencing the standard diet, following a 6-hr fast, each subject ingested ten capsules containing a total of 100 μCi of ^{111}In and 250 μCi of ^{99m}Tc-sulfur colloid in 150 ml of water. The subjects were positioned supine with an Anger camera (Raytheon Spectrum 150 DT, MEGA collimator, Raytheon Co. Melrose, IL) in the anterior position and sequential 1-min images were acquired for 3 hr (3-hr dual-isotope dynamic study). Static 1-min images were recorded at 4, 5, and 6 hr postingestion. Anterior and posterior images were acquired at these latter time intervals to correct for tissue attenuation. The subjects were allowed to eat the standard dinner meal after the capsules had undergone complete gastric emptying (3–6 hr postingestion).

The first image taken after this meal demonstrated at least one capsule in the cecum in all subjects studied. This image, 3–6 hr postingestion of the capsules, was considered the starting point or "time zero" for data analysis.

TABLE 1
Absorbed Dose Calculation Results Using an ^{111}In Radiopharmaceutical in the GI Tract: (A) Uniformly Distributed and (B) Encapsulated Distribution

Organ	Absorbed dose (mrad/100 μCi) A	B
S	68	50
SI	210	71
ULI	620	150
LLI	1100	350
Ovary	230	200
Testes	16	16
Total body	33	25

S = stomach, SI = small intestine, ULI = upper large intestine, and LLI = lower large intestine.

The subjects were allowed to ambulate between the acquisition of static images. A three-reference-point laser positioning system (model IL630, Gammex, Inc. Milwaukee, WI) was used to accurately reposition each subject. The images were stored on the hard disk of a SOPHY GPX+ digital computer (SOPHA Medical Systems, Columbia, MD).

At midnight, after the initial 6 hr of data collection was completed, the subjects had an 8-hr overnight respite. On the subsequent days beginning at 8:00 am, images were acquired in the anterior and posterior positions once every 4 hr with 8-hr breaks overnight. This sequence was repeated until 72 hr had passed or all capsules had been excreted, whichever came first. The ^{99m}Tc-sulfur colloid provided a colonic outline usually by the fourteenth hour postingestion.

Starting with this image, a set of ROIs were drawn around capsule activity (from the ^{111}In energy window). A separate ROI was drawn for each colonic segment containing capsules. To aid in the analysis of the sequence of images, a computer program was written to draw the ROIs automatically. This program also performed radioactive decay and geometric mean corrections. The geometric mean (square root of the product of the anterior and posterior counts in a given ROI) was calculated to correct for nonuniform tissue attenuation (*26*). These corrected images were then analyzed by geometric center analysis (GCA) (*22,23*). The geometric center was calculated for all image times. The geometric center allowed for quantification of the progression of the encapsulated ^{111}In through the colon. Table 2 shows the weights assigned to the different segments of the colon by Krevsky et al. (*22*) and the authors.

RESULTS

Figure 2 shows a series of anterior images, both ^{99m}Tc and ^{111}In energy windows, at various times during the course of one subject's SLIT study. Note that a colonic outline was visible early in the imaging sequence. The intra-colonic capsule location can be easily determined by comparing the image of the capsule activity (^{111}In image) to the colonic outline (^{99m}Tc image). Knowledge of the intra-colonic locations of the capsules provides the weighting values needed for geometric center analysis (see Table 2).

Because the colonic transit study was performed twice on each individual, it was possible to assess the reproducibility of this technique. Sixteen variables, which were measured from the progression of the geometric center or were derived from this progression, were assessed. A key to the variables and their definitions are listed in Table 3. Table 4 lists the means and standard deviations of these variables for the two trials, separately and combined. Note that the times for arrival of the geometric center of the radioactivity into the individual colonic segments is not mouth-to-segment, but cecum-to-segment. Table 4 also provides the same comparison for segmental transit data. The means were compared using Student's paired t-test with a statistically significant difference defined as $p < 0.05$.

The arrival times in the hepatic flexure (GC1.5), splenic flexure (GC2.5), and the time for complete excretion (GC5) had the largest numerical differences, 1.9 hr, 2.4 hr, and 2.4 hr, respectively, in their values when comparing

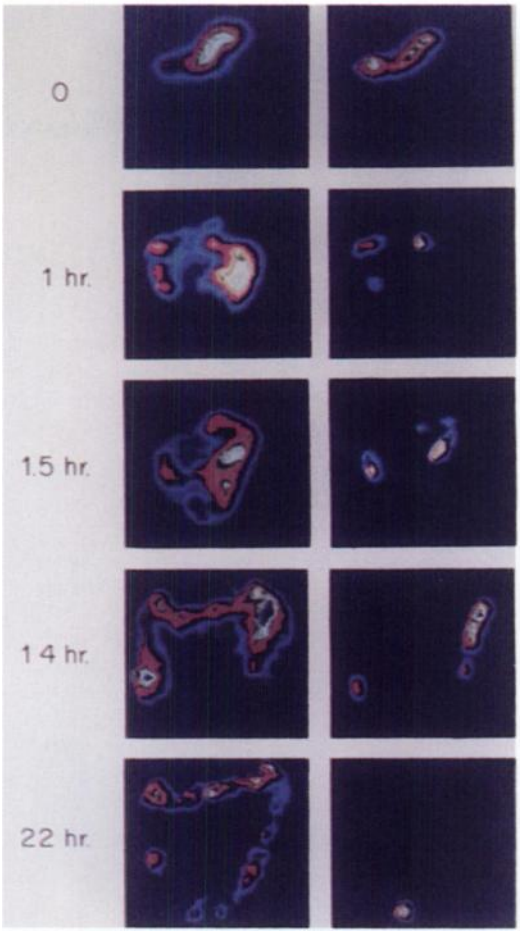

FIGURE 2. Illustration of the progression of the capsules (^{111}In window, left column) and liquid (^{99m}Tc window, right column) through the GI tract at various times during a typical SLIT scintigraphic study. The top pair of images (t = 0 hr) shows a complete gastric outline. The 1-hr images demonstrate small bowel filling by the ^{99m}Tc-SC and approximately 20% gastric retention of capsule activity. The 1.5-hr image shows complete gastric emptying of liquid and capsules. The 14-hr ^{99m}Tc-SC image shows an outline of nearly the entire colon and the ^{111}In image shows one capsule in the cecum with the remainder spread throughout the descending colon. The 22-hr image (2 hr post-bowel movement) demonstrates a complete outline of the distal colon and shows a single capsule in the rectum.

TABLE 2
Colonic Segment Weightings for Geometric Center Analysis

Location	Krevsky (22)	Stubbs
Small bowel	0	0
Ascending colon	1	1
Hepatic flexure	2	1.5
Transverse colon	3	2
Splenic flexure	4	2.5
Descending colon	5	3
Rectosigmoid	6	4
Excreted	7	5

TABLE 3
SLIT Technique Variable Definitions

Variable	Definition
Cecum	Cecal arrival time of first capsule.
GC1	Time for GC to reach a value of 1, minus "cecum," the cecal arrival time.
GCn*	Time for GC to reach a value of n, minus "cecum," the cecal arrival time.
MTAT	Mouth-to-anus-transit time.
#BM	Number of bowel movements during imaging period.
1st-EXC	Time required for first capsule excretion, minus "cecum," the cecal arrival time.
1 → 2	The difference in time required for the GC to progress from a value of 1 to 2.
1.5 → 2.5	The difference in time required for the GC to progress from a value of 1.5 to 2.5.
2 → 3	The difference in time required for the GC to progress from a value of 2 to 3.
3 → 4	The difference in time required for the GC to progress from a value of 3 to 4.
4 → 5	The difference in time required for the GC to progress from a value of 4 to 5.

* See Table 2 for the numerical value of "n".

TABLE 4
Comparison of Transit Time Variables (Hours)

	Trials 1 and 2		Trial 1		Trial 2	
Variable	mean	s.d.	mean	s.d.	mean	s.d.
Cecum	5.4	2.2	5.9	3.0	4.9	0.9
GC1	2.9	2.6	3.1	3.2	2.8	1.8
GC1.5	5.3	3.7	6.3	4.7	4.4	2.0
GC2	7.9	4.9	8.1	6.2	7.8	3.5
GC2.5	12.1	8.2	13.3	10.6	10.9	5.0
GC3	15.3	9.7	15.4	11.5	15.3	8.0
GC4	19.6	12.0	20.2	14.4	18.9	9.7
GC5	31.2	16.3	32.4	13.5	30.0	19.4
MTAT	21.4	8.2	21.6	8.9	21.2	7.9
1st-EXC	17.4	8.9	16.7	9.4	18.1	8.7
#BM	3.1	1.3	3.6	1.3	2.6*	1.2
1 → 2	5.5	4.4	5.4	5.8	5.5	2.6
1.5 → 2.5	7.3	6.6	7.6	8.5	7.0	4.5
2 → 3	7.4	6.7	7.2	7.3	7.5	6.4
3 → 4	4.3	3.1	4.9	3.6	3.7	2.5
4 → 5	11.6	9.8	12.1	9.6	11.0	10.6

* $p < 0.05$, Student's paired t-test. Note that the segmental transit times were determined for each individual subject and the descriptive statistics calculated on those values, rather than simply taking the difference in the mean segmental arrival times.

trial 1 to trial 2. These differences were not statistically significantly different; $p = 0.096$, $p = 0.465$, $p = 0.659$ for the variables GC1.5, GC2.5, and GC5, respectively. The arrival times in all colonic segments were shorter (faster transit from cecum to segment) in trial 2 than trial 1. Cecal arrival time (cecum) was also faster in trial 2 (4.9 hr) than trial 1 (5.9 hr). However, the mouth-to-anus transit time was nearly identical for trials 1 and 2, 21.6 hr and 21.2 hr, respectively ($p = 0.849$). Although the segmental arrival times were quicker in trial 2, the segmental transit times were not significantly different ($p > 0.25$ for all transit variables). In fact, there was less than a 10% difference in transit time values for all variables except transit time from descending colon to rectosigmoid colon (3 → 4). The mean number of bowel movements (#BM) was statistically significantly different ($p = 0.0229$) between trials 1 and 2.

Figure 3A illustrates the progression of the geometric center through the colon. The wide standard deviations are indicative of large intersubject variability. Figure 3B shows the temporal progression of the mean geometric center of trials 1 and 2 for all ten subjects. There was no statistically significant difference in the time required to reach any geometric center value between trials. This was indicative of small intrasubject variability.

The geometric center of the capsules, as illustrated in Figure 3, appeared to traverse the colon in a temporally linear fashion. A linear regression was computed between the geometric center and the elapsed time (minus cecal arrival time) of the corresponding image for all subjects. This relationship between geometric center and time proved to be linear (mean $r = 0.94$, range 0.88–0.998). Table 5 shows the transit rate, in colonic segments per hours, calculated from each linear regression. The mean transit rate was 0.171 segments per hour (range 0.055–0.407 segments per hour). While the individual temporal progression of the geometric may not be perfectly linear ($r = 1.00$), taken as a whole the group of subjects exhibited highly linear colonic transit ($r = 0.94$).

Linear interpolation was used to calculate the time required for the geometric center to reach values corresponding to the colonic segments (see Table 2, column 2). The amount of time between images, relative to the total colonic transit time, is small enough (by our method) that the assumption of linear transit, during that time interval, is valid. The linear regression results in Table 5 were derived using the geometric center values as calculated at the specified image times, not the interpolated geometric center values.

Recalling that $t = 0$ hr is the time that the first of the capsules reached the cecum (5.4 hr postingestion), the equation describing the temporal progression of the geometric center is:

$$GC(t) = 0.97 + 0.171*(t),$$

where time, t, has the units of hours. This equation was derived from the data in Table 5.

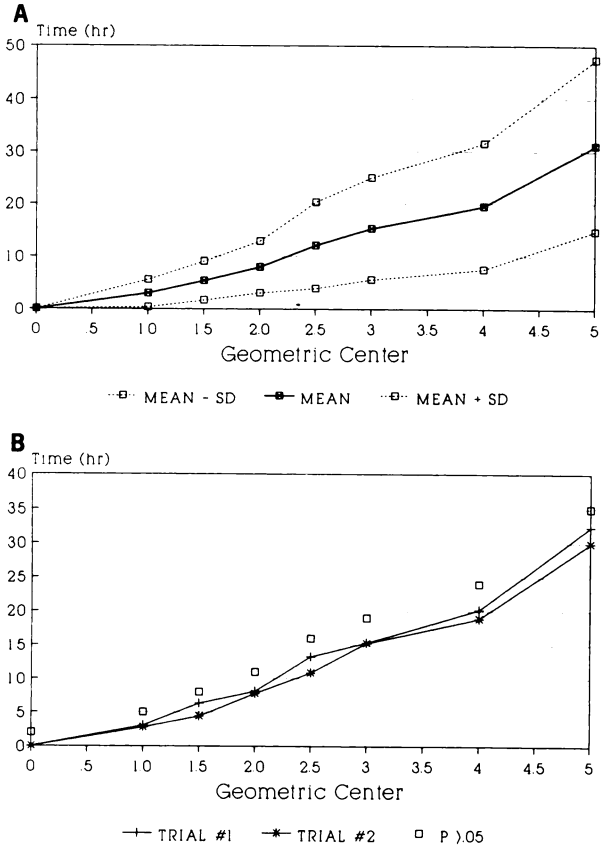

FIGURE 3. (A) Temporal progression of the geometric center through the colon (also known as geometric center analysis) for both trials in all subjects (n = 10). The solid line represents the mean and the broken lines are ± 1 s.d. (B) Temporal progression of the geometric center through the colon for trials 1 and 2. The boxes indicate that the mean values for the two trials are not significantly different ($p > 0.05$).

Time-activity and activity distribution analyses of the SLIT technique mean data are shown in Figure 4. It is readily seen that the time required for the percent of radioactivity in a colonic segment to reach its peak value increases as one moves distally in the colon. There is also a rapid rise in excreted radioactivity from 12 hr (2%) to 18 hr (34%), which tapers off after 24 hr, then "asymptotically" approaches 100% excreted. The apparent "asymptotic" rise to 100% excreted is due to two subjects whose colonic transit study lasted over 60 hr.

TABLE 5
Transit Rate Results for Linear Regression of Geometric Center Value with Elapsed Time from Cecal Arrival

Subject	Transit rate (segment/hour) Trial 1 rate	Trial 2 rate
A	0.139	0.187
B	0.118	0.165
C	0.110	0.160
D	0.190	0.295
E	0.146	0.073
F	0.114	0.275
G	0.111	0.347
H	0.055	0.063
I	0.147	0.407
J	0.209	0.111

Mean colonic transit rate = 0.171 segments/hr.

The average caloric intake for 3 days of diet history was 2735 kcal/day, with a caloric distribution of 48% carbohydrate, 15% protein, and 37% fat. This indicated a higher amount of fat consumed *ad lib* as compared to the standard diet (30% versus 37%). The usual mean daily caloric intake of the subjects was 695 kcal higher than that for the standard diet.

One subject differed substantially from the others in height, weight, and caloric intake, but not in his macronutrient distribution. Removal of his data gives the study group the following mean values: 2440 kcal/day; 48% carbohydrate; 15% protein; 37% fat. The subject in question had a mean 3-day caloric intake of 5500 kcal/day, but the macronutrient distribution was identical to the mean of all subjects. All values for the variables listed in Table 4 for this subject fell within one standard deviation of the mean with the exception of the mean values for flexure-to-flexure transit time (1.5 → 2.5) and transverse-to-descending colon transit time (2 → 3). All results reported herein include this subject's data.

The *ad lib* mean total dietary fiber intake (USDA-AOAC method) calculated from the diet histories was 13.5 g per day, whereas the dietary fiber intake for the standard diet was 18.2 g per day. No subjects reported any side effects attributable to increased fiber intake, i.e., gas, bloating, or abdominal cramps.

DISCUSSION

Although these SLIT capsules are not chymous in nature (i.e., a "physiologic" tracer) they do serve a role in quantifying GI tract motility. The GI tract does transport nondigestible solids and these capsules serve as a measure-

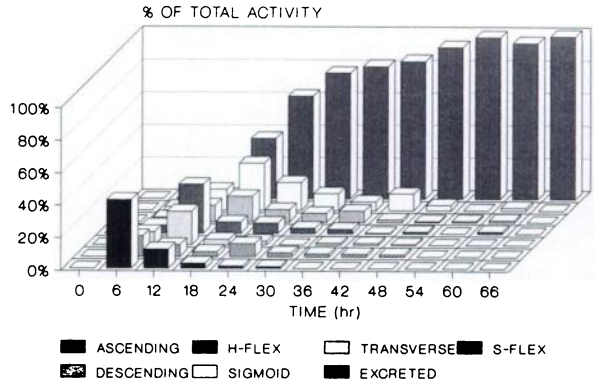

FIGURE 4. Combined time-activity and activity distribution analysis of the mean data (n = 10) for the SLIT technique. Geometric center analysis, Figure 3, is a simpler and more quantitative reduction of the above data.

ment method for this transport function. In addition, the slight perturbation of the GI tract caused by transit of these capsules is certainly more "physiologic" than techniques requiring oral (or rectal) intubation.

It has been reported that the gastric emptying of nondigestible solids up to 2.5-cm in length is the same as that of solids 2-mm in length (*27*). Several articles have described methods for measuring GI transits (*27,28*), including colonic transit (*29*), and the use of radiopaque markers of 10 ml in length. Kaus (*29*) describes the GI transit of a single "Perspex" capsule measuring between 19.54 mm and 20.88 mm in length and 6.93–7.49 mm in diameter. Therefore, the SLIT capsules are within the size range of previously investigated markers. At the present time, there are no methods capable of detecting the "non-physiologic" effects of the transit of objects this size through the colon.

Scintigraphic methods involving radiolabeled fiber (*32, 33*) and cation exchange resin beads (*26*) have been proposed recently. These techniques measured the movement of fluid-like substances through the bowel and were subject to the problems inherent in having a radiolabeled fluid first traverse the stomach and small intestine with a resultant wide distribution of arrival time of the tracer into the colon. Assessment of gross movements were possible but detailed quantification of segmental transit times were not.

In spite of the expected moderately-high intersubject variability, the colonic transit of the SLIT capsules was highly reproducible in each subject and for the group as a whole. Strict adherence to dietary and imaging schedules contributed to the high degree of reproducibility.

The difference in fiber intake between the standard and *ad lib* diets may have had a small effect on colonic transit. We do not feel that the increased fiber level was cause for the significant difference in the mean number of bowel movements because all subjects consumed the same diet during both trials, which were separated by at least a 1-wk interval.

As expected, the encapsulation of ^{111}In further reduced the absorbed dose to the GI tract. To extract the same quality information as achieved by our technique, radiopaque marker methods would yield a colonic absorbed dose of several rad.

Data acquisition, which gives a detailed description of segmental colonic transit and residence times, requires frequent imaging. Segmental transit data can provide clues to bowel function, localized drug interactions and specific sites of certain pathologic conditions. One example of the differential diagnostic capability of the SLIT method concerns constipation. Colonic inertia may be easily differentiated from functional outlet pseudo-obstruction. We have begun studies in patients with altered bowel function to assess the efficacy of the SLIT technique in this patient population.

The SLIT technique requires no invasive procedures, thus reducing bowel function perturbation and increasing the safety and patient tolerance of this diagnostic procedure. This technique can be performed on outpatients, thereby reducing the cost and complexity associated with assessment of colonic function.

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