## CONCLUSION

We have shown by a quantitative method that sex-specific changes are observed by bone scintigraphy which also reveals the association of serum biochemical markers with skeletal uptake.

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# Opioid and Opioid-Like Drug Effects on Whole-Gut Transit Measured by Scintigraphy


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We studied the effects of several drugs on gastrointestinal transit (tramadol HCl, acetaminophen with codeine and placebo) in a randomized, double-blind, crossover study. **Methods:** Combined gastric emptying, small bowel and colonic transit scintigraphy was performed in 12 normal subjects. Each subject received a standardized diet and study drug on Days 1–5. On Day three, subjects received a radiolabeled solid and liquid phase meal. **Results:** No significant difference in the gastric $T_{1/2}$ (mean ± s.e.m.) of solids for placebo (69 ± 7 min), APAP/C (74 ± 15 min) or tramadol (686 ± 8 min) ($p = 0.86$) were seen. Similarly there was no significant difference in the $T_{1/2}$ of liquids for placebo (31 ± 4 min), APAP/C (41 ± 6 min) or tramadol (41 ± 7 min) ($p = 0.29$). Orocecal transit times were not significantly different for placebo (237 ± 20 min), APAP/C (311 ± 26 min) or tramadol (311 ± 10 min) ($p = 0.12$). Colon geometric centers (GC) for placebo at 24, 48 and 72 hr were 4.6 ± 0.35, 6.0 ± 0.28 and 6.8 ± 0.08. The GC for tramadol and APAP/C were all significantly lower at 72 hr, 6.4 ± 0.17 and 6.2 ± 0.17, respectively compared to the placebo. The GC of tramadol at 24 and 48 hr (3.8 ± 0.4, 5.4 ± 0.26) were not significantly different from placebo. In contrast, the GC for APAP/C at 24 and 48 hr (3.3 ± 0.31, 5.0 ± 0.26) were significantly delayed. All subjects recorded a significant increase in constipation on drugs compared to placebo ($p = 0.04$). **Conclusion:** Tramadol and APAP/C had no effect on gastric emptying or small bowel transit. At equianalgesic doses, tramadol caused less delay in colonic transit than APAP/C for 48 hr and delay in the GC agreed with the subjective complaints of constipation on both drugs.



**Key Words:** gastric emptying; small bowel transit; colon transit; opioid drugs

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Analgesics are widely prescribed for acute and chronic pain. Codeine, a commonly used opioid analgesic, frequently causes constipation (*1*). Tramadol hydrochloride, a new, opioid-like centrally acting analgesic may result in less constipation (*2*), but this effect has never been quantified.

We have previously shown that scintigraphy can be used to quantify changes in gastrointestinal transit in response to medications including opioid analgesics (*3,4*). The purpose of this study was to compare the effects of tramadol, acetaminophen with codeine (APAP/codeine) and placebo on gastrointestinal transit times in healthy male subjects. Additionally, we sought to refine our technique for performing combined gastric emptying, small bowel and colon (whole-gut transit) scintigraphy and to correlate the findings of quantitative scintigraphy with the clinical symptoms of constipation.

## MATERIALS AND METHODS

We performed a randomized, double-blind, placebo controlled crossover study comparing the effect of 100 mg tramadol HCl to acetaminophen 600 mg with codeine 60 mg (APAP/codeine) on gastric emptying, small bowel and colon transit.


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Under a protocol approved by the Temple University Research Review Committee, 12 normal healthy male subjects were enrolled into the study. The subjects ranged in age between 22 and 39 yr (mean age 26.8 yr). Inclusion criteria included: (1) male subjects at least 18 yr of age; (2) ability to take oral medication; (3) judged to be in good health and without a history of prior gastrointestinal disease based on: medical history, physical examination and routine laboratory blood testing; and (4) history of 6-to-10 spontaneous bowel movements weekly. Specific exclusion criteria included: (1) prior abdominal surgery (except appendectomy); (2) known significant medical disease; (3) renal or hepatic dysfunction; (4) history of seizure disorder; (5) narcotic abuse or alcoholism; (6) any known contraindication to opioids or acetaminophen; (7) participation in another investigational study within the last 30 days; (8) use of aspirin, other nonsteroidal anti-inflammatory drugs or other analgesic within 72 hr prior to the start of the study; and (9) the use of anti-diarrhea or laxative medications within the last seven days.

Medical history, clinical laboratory measurements, physical examination and an evaluation of usual dietary habits were performed during a prestudy screening. After subjects completed all three phases of the study, follow-up laboratory and physical examinations were performed. All subjects were given a diary for each study period to record symptoms of constipation or changes in bowel habits as well as any adverse events.

After giving informed consent, all subjects were randomized to receive either tramadol, APAP/codeine or a matching placebo in a randomized, double-blind, three-period crossover design. Dosing frequency was four times daily for each five-day study period. In a double-blind manner, the subjects were randomly assigned to one of the three study drugs. Upon completion of that study they entered into succeeding periods until all three studies had been completed. At the completion of each study period all subjects took a mild laxative (30 cc milk of magnesia) to clear the bowel of any residual radioactive material. A 2-wk washout interval was imposed between the initiation of each study period.

Compliance with diet and drug/placebo administration was assured by admitting the subject to the General Clinical Research Center of Temple University Hospital for each entire study period.

An admission history and physical exam and baseline laboratory studies were performed for each study period. Each subject was allowed to choose meals from a standardized "house diet". The diet provided 2000–2500 kcal daily and consisted of approximately 250 g carbohydrate, 85 g protein, 90 g fat and 3–4 g of fiber.

On Day 1 through Day 5 subjects received the study drug. On the morning of Day 3 the subjects received a radiolabeled meal consisting of two large scrambled eggs labeled with 500 $\mu$Ci (18.5 MBq) of $^{99m}$Tc sulfur colloid served between two pieces of white toasted bread. The subjects were required to complete the egg-sandwich meal within 5 min. Each subject then drank 300 ml of water containing 125 $\mu$Ci (4.6 MBq) of $^{111}$In-DTPA. Immediately after ingestion of the water, gamma camera imaging was begun using a large field of view camera and a dedicated nuclear medicine computer. The stomach was positioned at the upper edge of the field of view such that the entire abdomen was included in the field of view below the stomach (Fig. 1).

From 0-to-120 min after the patients meal ingestion, images were acquired as for a dual-isotope, combined solid and liquid phase gastric emptying study. Imaging began immediately after consumption of the liquid phase of the meal and was repeated every 15 min for up to 120 min. Each four-image sequence included upright, 128 × 128 byte mode, 30 sec anterior, followed by posterior images of the whole abdomen using a 140 KeV photopeak with a 20% window. These images were immediately

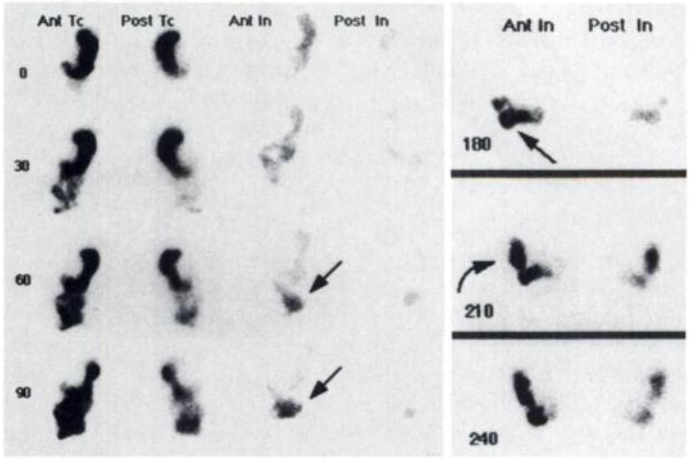


**FIGURE 1.** Image sequence for whole-gut transit scintigraphy. (A) Initial $^{99m}$Tc and $^{111}$In images are shown from 0–90 min for a normal subject (placebo). Liquid emptying (indium) is more rapid than solids (technetium) and is complete by 90 min. A typical build-up of activity in the "reservoir" area of the distal ileum can be seen (arrows). (B) After 120 min $^{111}$In images only are acquired. By 180 min activity has moved into the cecum (straight arrow) and at 210 min the ascending colon is identified.

followed by supine anterior and posterior 60 sec images of the whole abdomen using a 247 KeV photopeak for $^{111}$In with a 20% window.

Supine anterior and posterior, 60 sec abdominal images were then acquired using only the $^{111}$In photopeak from 120-to-360 min after meal ingestion to continue recording the small bowel transit of the $^{111}$In-DTPA in water.

Whole abdomen images were acquired at 24, 48 and 72 hr after meal ingestion (Fig. 2). These were supine, anterior and posterior, 128 × 128 byte mode images of the $^{111}$In activity in the colon. These were acquired for 4 min using a 247 KeV photopeak with a 20% window.

## Data Analysis

*Gastric Emptying Analysis.* A manual region of interest (ROI) corresponding to the stomach was determined for all images from

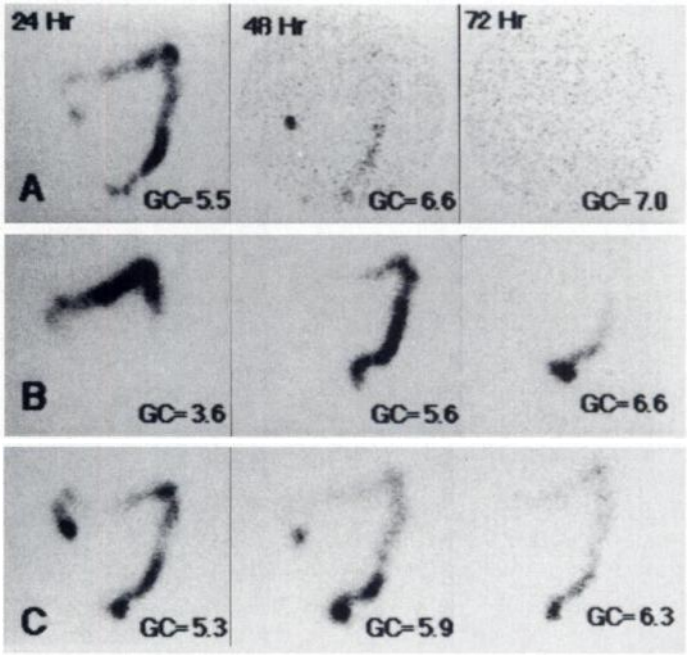


**FIGURE 2.** Colon images at 24, 48 and 72 hr for each drug are shown (same subject) (A = placebo, B = APAP/codeine and C = tramadol). GC = geometric center values. (A) shows normal transit and (B) shows a delay compared to C (most marked at 24 hr).

0-to-120 min. The percent of gastric activity for solids and liquids was calculated for all times from the geometric mean ((anterior counts × posterior counts)$^{1/2}$) of gastric counts. After correcting for decay, the percent of gastric activity for solids and liquids was normalized to 100% for maximum gastric counts. The half-emptying time, $T_{1/2}$, was calculated as the time to 50% emptying. In addition the percent of liquid retention at 120 min was recorded for all studies.

### Small Bowel Analysis

The average of small bowel counts from each image between 120–360 min was used to define 100% of total small bowel activity (TSBA) for the small bowel transit measurements. To obtain the small bowel counts a large rectangular ROI was drawn to include all the activity within the stomach and entire abdomen in both anterior and posterior views. A ROI was then drawn over the stomach in both the anterior and posterior images to obtain the geometric mean of gastric counts. The difference between the geometric mean of total abdominal counts and gastric counts was taken as the small bowel counts at that time.

In order to evaluate the variation associated with the geometric mean correction of small bowel counts, the coefficient of variation of small bowel counts for all images from 120-to-360 min was calculated for the placebo study in all 12 subjects.

Cecal arrival time was used as the measure of small bowel transit time. This was obtained by first identifying the image where the cecum and/or ascending colon was most clearly visualized in the $^{111}$In-DTPA images. A manual ROI was drawn over the cecum and proximal ascending colon in the anterior and posterior images. This ROI was then positioned over the same area of the cecum and ascending colon of all earlier images. The cecal arrival time was then defined as the time that the geometric mean cecal and ascending colon counts first became greater than or equal to 10% of TSBA.

### Colon Transit Analysis

Using 100% of the TSBA obtained on Day 1 as the counts available to fill the colon, a geometric center of decay corrected colon counts was calculated from the geometric mean of anterior and posterior images of the colon at 24, 48 and 72 hr. To calculate the geometric center, a ROI for each of six anatomical segments of the colon was drawn as previously described (*5*). Each region was assigned a numerical value as follows: cecum-acending colon = 1; hepatic flexure = 2; transverse colon = 3; splenic flexure = 4; descending colon = 5; recto-sigmoid = 6; and excreted feces = 7. The value for the counts in excreted feces was calculated by subtracting the geometric mean of total counts in the colon from the TSBA. The geometric center is a weighted average of the counts in each region and is given by the following equation:

$$\text{Geometric center} = \sum_{i=1}^{i=7} (R_i \times C_i)/C_{tot}, \qquad \text{Eq. 1}$$

where $R_i$ = region number (i = 1, 2, . . .7), $C_i$ = region counts and $C_{tot}$ = total small bowel activity.

A low geometric center (*1–2*) indicates that the majority of the radiolabel is closer to the cecum and a higher value (*5–7*) indicates that most of the activity has progressed to the left side of the colon or has been eliminated as stool. With this approach a continuous numerical value provides a measure of transit through the colon.

The geometric centers of colon activity were analyzed using a three-period crossover analysis of variance model at each evaluation (24, 48 and 72 hr). Comparisons were performed using the Kaplan-Meier analysis for the gastric half-emptying and cecal arrival times. Statistical comparisons for cecal arrival times were performed using the log rank test. To compare the frequency of subject reported constipation, pairwise treatment comparisons were performed using the McNemar chi-square analysis. All statistical analyses were performed using SAS System software (SAS Institute Incorporated, Cary, NC).

## RESULTS

Eleven of the 12 subjects completed all three periods of the study. One subject discontinued the study during period three due to nausea experienced after the second drug study dose on Day 2. This was the only significant adverse experience encountered in the study.

Table 1 summarizes the subjective bowel symptoms. There were no reported symptoms of constipation for any subject while on placebo. There was a significant difference in the number of symptoms of constipation for tramadol verses placebo ($p = 0.04$) and for APAP/codeine versus placebo ($p = 0.04$) but not for tramadol versus APAP/codeine ($p = 0.72$).

For the solid phase of the meal there was no significant difference in the half-emptying time ($T_{1/2}$) (mean ± s.e.m.) measurements of gastric emptying for placebo (69 ± 7 min) versus APAP/codeine (74 ± 15 min) or tramadol (68 ± 8 min) ($p = 0.87$). Similarly, there was no significant difference in the half-emptying time measurements of gastric emptying of liquids for placebo (31 ± 4 min) versus APAP/codeine (41 ± 6 min) or tramadol (41 ± 7 min) ($p = 0.29$). There were also no significant differences in liquid retention in the stomach at 2 hr for placebo (9% ± 1% min) versus APAP/codeine (16% ± 1% min) or tramadol (10% ± 4% min) ($p = 0.24$).

Three of the subjects on placebo failed to visualize the cecum or ascending colon by 360 min. This occurred in five of the tramadol studies and six of the APAP/codeine studies. The mean cecal arrival times, however, showed no significant differences for placebo (237 ± 20 min) versus APAP/codeine (311 ± 26 min) or tramadol (311 ± 10 min) ($p = 0.12$). Table 2 summarizes the distribution of cecal arrival times for all studies.

Both tramadol and APAP/codeine influenced colonic transit (Fig. 3). At 72 hr the mean geometric center of colon activity for both tramadol and APAP/codeine were significantly delayed

**TABLE 1**
Summary of Subject Reported Bowel Movement Symptoms

| | Tramadol | APAP/Codeine |
|---|---|---|
| Significant change in bowel movement | 6 | 6 |
| 72-hr periods without bowel movement | 1 | 3 |
| Stool Frequency | | |
| Normal | 0 | 0 |
| Less frequent | 6 | 6 |
| More frequent | 0 | 0 |
| Stool Consistency | | |
| Loose | 0 | 0 |
| Soft | 0 | 0 |
| Normal | 3 | 1 |
| Hard | 3 | 3 |
| Very hard | 0 | 2 |
| Difficulty with stool | | |
| No difficulty | 1 | 0 |
| Some difficulty | 5 | 3 |
| Much difficulty | 0 | 3 |
| Impacted | 0 | 0 |
| Pain at defecation | | |
| None | 5 | 3 |
| Mild | 1 | 2 |
| Moderate | 0 | 1 |
| Severe | 0 | 0 |

**TABLE 2**
Distribution of Cecal Arrival Times

| Cecal arrival time (min) | Placebo (n = 12) Number (%) | APAP/Codeine (n = 12) Number (%) | Tramadol (n = 11) Number (%) |
|---|---|---|---|
| 120–180 | 3 (25) | 2 (17) | 0 (0) |
| 210–270 | 5 (42) | 1 (8) | 2 (18) |
| 300–360 | 1 (8) | 3 (25) | 4 (36) |
| >360 | 3 (25) | 6 (50) | 5 (45) |

compared to placebo. At both 24 and 48 hr the geometric center for APAP/codeine was significantly delayed compared to placebo, whereas tramadol was not.

The mean coefficient of variation for small bowel counts between 120–360 min was 0.07 with a range of 0.04–0.10. These results indicate little variation in the geometric mean correction of small bowel counts. This is similar to a report by Hardy and Perkins who found a range of 0.09–0.11 (*6*).

## DISCUSSION

Tramadol hydrochloride is a new centrally acting analgesic which has been marketed internationally but has only recently been introduced into the United States. The analgesic activity of tramadol is believed to be derived from two synergistic modes of action: attachment to the $\mu$ opioid receptor, and inhibition of noradrenaline and serotonin reuptake (*7–9*). This dual action provides effective pain control, and does not appear to cause additive adverse effects (*10,11*). Our results indicate that at equianalgesic doses, neither tramadol nor APAP/codeine significantly affects gastric emptying or small bowel transit. While they both delay colonic transit, tramadol appears to slow colonic transit less in the first 24 to 48 hr. These results suggest less of an effect of tramadol on the right colon. The fact that the effect of tramadol was only significant at 72 hr (compared to APAP/codeine at 24, 48 and 72 hr), may explain the clinical observation that tramodol is less constipating.

The use of scintigraphy for the clinical evaluation of patients with suspected upper gastrointestinal motor disorders is well established. Gastric emptying scintigraphy has become the "gold standard" for assessing motor function of the stomach.

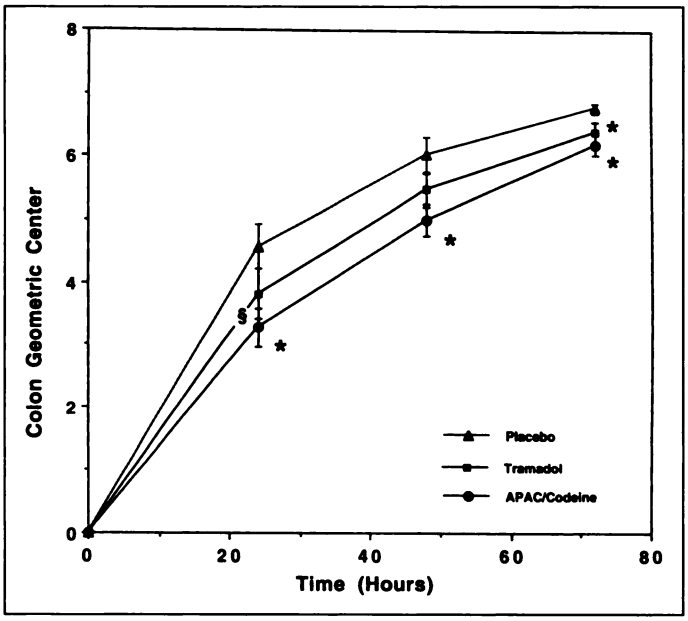


**FIGURE 3.** Geometric centers of colon activity for all three drugs at 24, 48 and 72 hr. (*p < 0.05 versus placebo, §p < 0.05 versus C/APAC).

While gastric emptying studies are frequently performed, however, the clinical use of scintigraphy for measurement of small bowel and colon transit is uncommon. The slow acceptance of scintigraphy for measuring small bowel and colon transit is due to the lack of a practical method for performing these measurements.

Several investigators have shown that oral $^{111}$In-DTPA can be used to measure colon transit (*4,12,13*). We have used $^{111}$In-DTPA in liquid given orally, to perform combined small bowel and colon transit studies (*4*). Our colon transit measurements by the oral method correlate well with our previous studies using direct cecal intubation (*5,14*).

Other methods for measuring colon transit that require the preparation of special capsules designed to release $^{111}$In resin beads into the ileum have been described. To measure colon transit these capsules are coated with methacrylate which dissolves at a pH of 7.2–7.4 in the environment of the terminal ileum (pH = 7.4) (*15–17*). The clinical utility of performing combined gastric emptying, small bowel and colon (whole-gut) transit scintigraphy with such capsules has recently been reviewed (*18*).

We have refined our method by using a dual-tracer, oral method to perform whole-gut transit scintigraphy. The method is well suited for quantitative studies of the effect of drugs on whole-gut transit and uses radiopharmaceuticals that are routinely available in most nuclear medicine facilities.

If measurement of solid phase gastric motility is not a concern the $^{99m}$Tc sulfur colloid measurements can be eliminated. Because of technical limitations with our computer we used only a single isotope peak for imaging both $^{99m}$Tc and $^{111}$In. Imaging times could be shortened for $^{111}$In if both the 171 and 245 KeV photopeaks were used. No correction for scatter was necessary for the activities of $^{99m}$Tc and $^{111}$In used in this study. Measurements in our laboratory for 15, 20 and 30% windows showed less than a 1% scatter contribution into either photopeak.

Measurement of small bowel transit time can be difficult since the input of a meal into the small intestine depends on gastric emptying. We chose in this study to use cecal arrival time as a measure of small bowel transit. This is analogous to the use of hydrogen and $^{14}$C breath tests which measure the leading edge arrival of the meal in the colon. Prior comparisons have demonstrated good correlation between scintigraphy and hydrogen breath testing with lactulose. In one comparison, Caride et al. reported a mean small bowel transit of 73.0 ± 6.5 min for scintigraphy and 75.1 ± 8.3 min for the hydrogen breath test (*19*).

It has been shown that lactulose itself, however, may accelerate small bowel transit (*20*). In a separate study we have confirmed that the hydrogen breath test correlates well with scintigraphy (*21*). We found that the mean orocecal transit time in normal volunteers was 56 ± 4 min for the hydrogen breath test and 43 ± 4 min for simultaneously performed scintigraphy. When the subjects had scintigraphy performed without lactulose, the mean orocecal transit time was 231 ± 37 min, similar to the results of the present study (*21*).

While relatively simple and practical to perform, there are several potential limitations to the use of orocecal transit time as a scintigraphic measure of small bowel transit. First is the possible effect of delayed gastric emptying. It has been shown, however, that liquid gastric emptying is usually not significantly delayed unless there is severe gastroparesis (*22*). In this study, liquid gastric emptying was consistently 85%–95% complete at 2 hr for all three study groups and therefore did not limit measurement of small bowel transit or the TSBA between

120–360 min. In addition we found, as have others, that there is a very wide range of normal cecal arrival times. In some normal subjects imaging beyond 360 min may be needed to define cecal arrival.

Use of the orocecal transit time also requires that one can accurately visualize and separate the cecum and ascending colon from loops of small bowel. We have found that supine, as opposed to upright, imaging reliably permits identification of the cecum and ascending colon. Typically the distal small bowel first appears as a reservoir where counts accumulate prior to visualization of the cecum or ascending colon (Fig. 1A). Read described that the terminal ileum "is a region of relative stasis" prior to filling of the colon (*23*). This localization of activity in the distal small bowel usually permits adequate separation of the small bowel and cecal regions of interest (Fig. 1B). In this study three of the placebo subjects did not show filling of the colon by 360 min. The need to image beyond 360 min would present practical limitations in most clinical settings.

All analyses in this study utilized a geometric mean correction of anterior and posterior counts. While not a perfect correction for attenuation, it can minimize the attenuation changes that occur as activity moves through the abdomen (*6*). We confirmed a small coefficient of variation in total small bowel counts between 120–360 min.

## CONCLUSION

The proper treatment of patients with symptoms suggesting bowel dysmotility depends on an accurate assessment of motility throughout the entire gastrointestinal tract. Gastric emptying studies are routinely used to evaluate upper gastrointestinal motility and whole-gut studies are now being introduced into clinical practice (*18*). In performing the current investigation, we have had the opportunity to refine a whole-gut scintigraphic method which can be applied in most nuclear medicine laboratories. Such studies not only advance our understanding of the mechanism of action of pharmaceutical agents but also afford an opportunity to obtain normative data which can then be applied to clinical studies.

Whole-gut transit scintigraphy can be performed and applied clinically to study patients with suspected dysmotility involving the stomach, small bowel and/or the colon.

## ACKNOWLEDGMENT

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