Gastrointestinal Transit of Technetium-99m-Labeled Cellulose Fiber and Indium-111-Labeled Plastic Particles

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We introduce two new nondigestible solid markers for gastrointestinal transit measurements. One is technetium-99m-labeled cellulose fiber [^{99m}Tc]CF, the other is indium-111-labeled plastic particles [^{111}In]PP of 2- to 3-mm diameter. In six healthy male volunteers gastric emptying and small intestinal transit of the two markers were obtained simultaneously. Large intestinal transit of [^{111}In]PP was also obtained. Technetium-99m CF had acceptable stability properties in the proximal gastrointestinal segments. Indium-111 PP was almost completely stable in all segments. Mean gastric emptying time was 1.13 ± 0.24 hr (mean ± s.d.) for [^{99m}Tc]CF and 1.94 ± 0.78 hr for [^{111}In]PP. The difference was significant ($p < 0.05$). Mean small intestinal transit time was 3.85 ± 0.61 hr (mean ± s.d.) for [^{99m}Tc]CF and 4.03 ± 0.34 hr for [^{111}In]PP. The difference was not significant ($p < 0.5$). Mean large intestinal transit time of [^{111}In]PP was 23 ± 11 hr (mean ± s.d.). We also suggest a simple deconvolution principle for the interpretation of the small intestinal and the large intestinal transit data.

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Gastric emptying measurements of digestible solid food components by means of gamma camera technique have proven useful in both research and clinical studies. The recommended radiolabeled markers are broken down into fine particles before their discharge into the small intestine where they are hydrolyzed and almost completely absorbed (*1–4*). In contrast, measurements of small intestinal and large intestinal transit require stable nondigestible markers to obtain reliable quantitative results.

This study was undertaken to evaluate the applicability of two new nondigestible markers of different physical character: Technetium-99m-labeled cellulose fiber ([^{99m}Tc]CF) and indium-111-labeled plastic particles ([^{111}In]PP). The markers were used simultaneously to measure gastric emptying and small intestinal transit. In addition, [^{111}In]PP was used to measure large intestinal transit. We also wanted to provide an accurate interpretation of the small intestinal and the large intestinal transit data on the basis of deconvolution principles.

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MATERIALS AND METHODS

In Vitro Studies

Technetium-99m CF synthesis. Two hundred milligrams of a cellulose fiber ion exchanger (Whatman DE 23, Whatman Ltd., Maidstone Kent, UK) was weighed out and incubated with 2 ml of 0.9% saline, 1.4 ml of 0.1% stannous chloride in 0.5 N hydrochloric acid, 2.5 ml of 8% sodium acetate, and 80 MBq [^{99m}Tc]pertechnetate in 2 ml of 0.9% saline for 30 min. Subsequently the fiber was washed with 30 ml of 0.9% saline. One capsule of pancreatic enzymes (Pankreon, Kali-Chemie, Hannover, FRG) was incubated with 3 ml of 8% sodium acetate for 30 min at 37°C. The fiber was then agitated with the sodium acetate containing enzymes for 60 min at 37°C. Finally the fiber was washed with 30 ml of 0.9% saline.

Indium-111 PP synthesis. A target of silver was bombarded in a cyclotron with 1 to 2 C of 24 MeV alpha particles. Two days later 200 mg of grains of ~ 100 μm were grinded from the target which now contained indium-111. The grains were fixed to the surface of 15 ml of 2- to 3-mm diameter and 1.13 g per ml density plastic particles (Ultramid B 3K, BASF, Ludwigshafen, FRG) by addition of 3 ml of 10% polystyrole in chloroform in a rotating evaporator at 50°C. After evaporation of the chloroform, the particles were sieved with a 2.8-mm screen and washed with 200 ml of 0.9% saline.

In vitro stability. At 37°C, four 100-mg samples of [^{99m}Tc]CF and 2-ml samples of [^{111}In]PP were incubated with 3 ml of gastric juice (pH 1.2) for 3 hr, and subsequently with 3 ml

of small intestinal juice (pH 5.3) for 6 hr. Finally the samples of [^{111}In]PP were incubated with 3 ml of feces for 63 hr. At the end of each incubation period the activity distribution between the markers and the incubation media was measured by well counting of each phase separately.

In Vivo Studies

Six healthy male subjects of mean age 23 yr (range 21 – 25 yr) and mean-body mass index 22.5 kg per m^2 (range 21 – 25) participated after giving informed consent. The protocol for the studies had been previously approved by the local ethical committee. During the studies the energy distribution and the fiber fraction of the diet were maintained (44% of carbohydrate, 33% of fat, 23% of protein, 3.6 g of fiber per 1,000 kJ). The total daily energy supply, however, was body weight dependent (below 70 kg; 7,700 kJ, between 70 to 75 kg: 9,500 kJ, above 75 kg: 11,000 kJ). The diet was consumed according to a fixed schedule (9:00 a.m., 1:00 p.m., 5:00 p.m., 9:00 p.m.). The subjects drank ~ 2,000 ml of liquids per day. They avoided coffee, tea, alcohol, tobacco, and vigorous physical activity the day before and during the study.

Radiolabeled Standard Meal. The standard meal given at the start of each study consisted of 400 g of mixed solid and liquid components (80 g of bread, 30 g of cheese, 10 g of butter, 50 g of yogurt, 230 g of water) of an energy value of 1,600 kJ. 40 MBq [^{99m}Tc]CF and 2 MBq [^{111}In]PP were added to the yogurt fraction.

Gastric emptying and small intestinal transit. The studies began at 9:00 a.m. after an overnight fast and recent bladder emptying. After having ingested 400 mg of potassium perchlorate in order to block thyroid uptake of any free [^{99m}Tc]-pertechnetate, the subjects consumed the labeled standard meal within 10 min. Right after the meal imaging was performed in the upright position using a large field-of-view gamma camera with a medium-energy, parallel-hole collimator. Imaging was repeated at 30-min intervals until no activity could be detected in the small intestine. Anterior and posterior images were obtained using a 15% energy window over the 140-keV ^{99m}Tc photopeak, and 15% and 22.5% energy windows over the 174- and 247-keV ^{111}In photopeaks, respectively. Each acquisition lasted 2 min. First acquisitions yielded ~ 250,000 counts in the ^{99m}Tc window and 50,000 counts in the ^{111}In windows. Data were stored on a computer for later analysis. Subjects were encouraged to sit upright or walk between imaging for the first 4-hr period.

On each image and for each marker, regions of interest (ROIs) were delineated manually around the stomach, the small intestine, and the large intestine. Examples of images are shown in Figure 1. The count rates were corrected for downscatter from ^{111}In into the ^{99m}Tc window, attenuation, and radioactive decay. A mean downscatter fraction of 0.35 was computed on data obtained from a single supplementary study where, after ingestion of [^{111}In]PP only, the ^{111}In activity was registered in both the ^{99m}Tc window and the ^{111}In windows. Geometric mean of corresponding anterior and posterior count rates were used as attenuation correction (*5,6*).

Paired Student's t-test was used to compare gastric emptying and the small intestinal transit of [^{99m}Tc]CF and [^{111}In] PP.

Large intestinal transit. Until all markers had cleared from the large intestine feces was collected in separate samples. The total clearance of activity from the large intestine was established by abdominal scintigraphy, first performed after 72 hr and then, if necessary, at 24-hr intervals. The ^{111}In activity was measured in each sample with the same gamma camera equipment. To eliminate geometric errors caused by variation in counting efficiency depending on shape of feces sample, the samples were placed 40 cm from the surface of the collimator. Four minutes of acquisition was used.

Calculations. Areas of activity present in either the stomach or the large intestine could be well delineated in almost all images and were, therefore, selected as the primary ROIs for subsequent analyses. Contrary to this, the small intestinal region was difficult to delineate reliably on some images. For that reason, the small intestinal region was only used qualitatively to decide whether the markers had cleared from that region.

As a result of slight differences in counting efficiency in the stomach and the large intestine the corrected count rates were expressed as fractions of first and last count rate respectively. Corrected count rate for each single feces sample was converted into fraction of the summed up count rate for all samples.

On the assumption that the activity output from the large intestine was zero in the first hours of the study the fraction of activity in the small intestine (B) could be estimated from the fraction of activity in the stomach (A) and in the large intestine (C) by use of the equation:

$$A + B + C = 1. \quad (1)$$

The small intestinal transit function T(t), which is the activity versus time curve to be expected from a unit input at time zero, can be found by deconvolution of the small intestinal signal B(t) on the gastric output dA(t). As the measurements are performed at discrete time intervals (30 min), the continuous functions A(t), B(t), C(t), T(t) . . . are replaced by time series A_n, B_n, C_n, T_n . . . . Setting up the equations for the measured small intestinal signal B_n we get, as time progresses:

$$\begin{aligned} B_1 &= dA_1 \cdot T_1 \\ B_2 &= dA_1 \cdot T_2 + dA_2 \cdot T_1 \\ B_3 &= dA_1 \cdot T_3 + dA_2 \cdot T_2 + dA_3 \cdot T_1 \\ &\cdot \\ &\cdot \\ &\cdot \\ B_n &= \sum_{i=1}^{n} dA_i \cdot T_{(n-i+1)} \end{aligned} \quad (2)$$

where $dA_n = A_{n-1} - A_n$.

This system of n equations with the n unknown T_n's can be solved, thus giving the transit function for the small intestine.

A similar system of equations can be set up for the large intestinal time signal C_n. TT_n denotes the large intestinal transit function:

$$C_n = \sum_{i=M}^{n} dB_i \cdot TT_{(n-i+1)}. \quad (3)$$

This series of equations is first started at a time $t_M = M \cdot 30$ min, when the first activity shows up in the large intestine. In principle, the inputs dB_n to this system could be calculated from the previously found values for dA_i and T_n. However, it is easier to note that as long as no activity has passed with

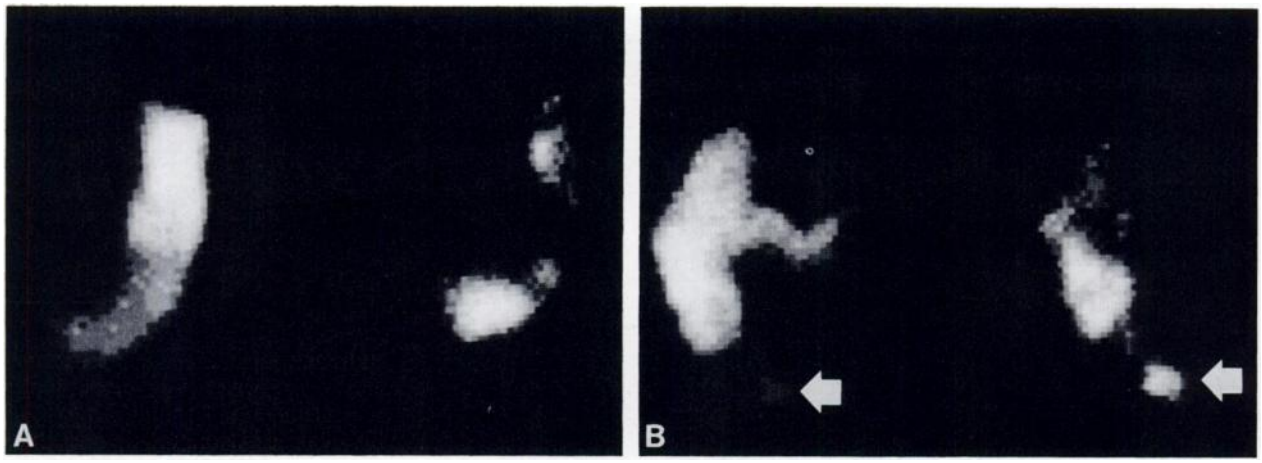

FIGURE 1
A: Anterior images representing distribution of [^{99m}Tc]CF (left) and [^{111}In]PP (right) at 0 hr. Activity outlines the stomach. B: Anterior images representing distribution of [^{99m}Tc]CF (left) and [^{111}In]PP (right) at 5 hr. Activity outlines the small intestine (arrows) and the large intestine.

feces the sought dB_i is simply identical to the increase in large intestinal signal:

$$-dB_i = dC_i. \quad (4)$$

Using Eqs. (3) and (4) we get TT_n.

Data reduction. Mean transit times (Mn) were calculated for the gastric, small intestinal, and large intestinal transit functions (X_n) from the equation:

$$Mn = \sum_{1}^{\infty} (x_{n+1} - x_n) \cdot (n + \tfrac{1}{2}) \cdot 30 \text{ min}. \quad (5)$$

Marker stability. Blood samples, drawn 3, 6, and 9 hr after marker consumption were examined for ^{99m}Tc and ^{111}In activity by well counting. Count rates were scaled up to an estimated blood volume of 5,000 ml and expressed as fractions of the dose given. Besides, activity in urine collected over the 9-hr period was expressed as fraction of the dose given.

RESULTS

In Vitro Studies

The dissociation of activity from markers into the incubation media is shown in Table 1.

In Vivo Studies

The time taken until no activity could be detected in the small intestine ranged between 6 and 7.5 hr. No subjects passed activity in feces during that period. All subjects cleared all activity from the large intestine within 72 hr.

Gastric emptying, small intestinal, and large intestinal transit results are shown in Table 2. Gastric emptying of [^{99m}Tc]CF was considerably faster than that of [^{111}In]PP ($p < 0.05$), whereas no difference could be found in the small intestinal transit of the two markers ($p < 0.5$). An example of the computed gastric emptying, small intestinal, and large intestinal transit functions is shown in Figure 2.

Results of the marker stabilities are shown in Table 3.

DISCUSSION

The scintigraphic technique is noninvasive and makes it possible to obtain quantitative results for the main gastrointestinal segments. In addition, the properties of the radiolabeled markers can be adjusted according to various clinical needs (determination of mechanical, enzymatic or bacterial degradation, or propulsive action). Still, a number of assumptions and corrections may be required.

In our procedure, the delineation of ROIs was a subjective process and, therefore, susceptible to errors

TABLE 1
In Vitro Radioactivity Dissociation (%, mean ± s.d.)

	Gastric juice	Small intestinal juice	Feces
	3 hr	6 hr	63 hr
[^{99m}Tc]CF	3.1 ± 0.6	2.7 ± 0.6	
[^{111}In]PP	0.4 ± 0.1	0.1 ± 0.1	0 ± 0

n = 4

TABLE 2
Mean Transit Time (hr, mean ± s.d.)

	[^{99m}Tc]CF	[^{111}In]PP
Stomach	1.13 ± 0.24	1.94 ± 0.78
Small intestine	3.85 ± 0.61	4.03 ± 0.34
Large intestine	—	23 ± 11

n = 6

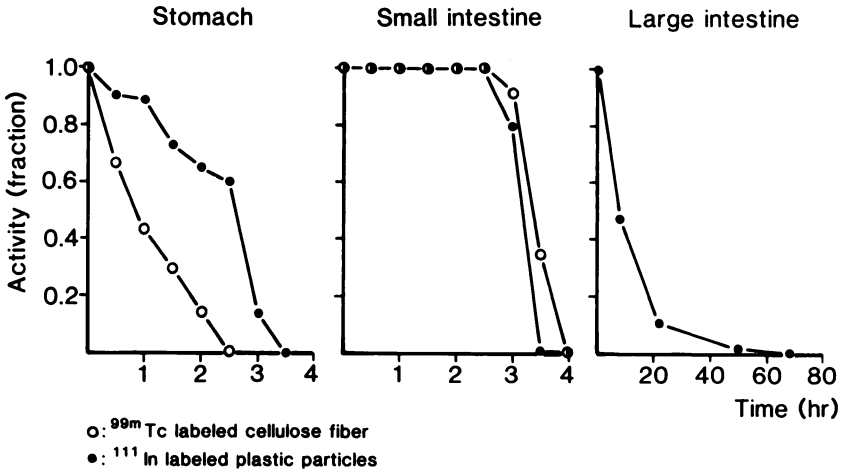

FIGURE 2
Computed gastric emptying, small intestinal, and large intestinal transit functions in one subject.

in the interpretation. However, the two regions used in the analysis, the stomach and the large intestine, were reasonably identifiable in virtually all images, in particular when sequential images were displayed forwards and backwards in time, showing the movement of the markers.

The corrected maximum count rates in the large intestine were 5% to 10% higher than in the stomach, probably a result of differences in counting efficiency. Since, only the markers leaving the stomach could eventually enter the large intestine, the count rates were converted into fractions of the maximum count rate in that region before deconvolution. Thus, we consider this error to be of minor importance.

The data given for [^{99m}Tc]CF could be influenced by error caused by inaccurate correction of the ^{111}In scatter. However, this error was reduced considerably by using a dose of ^{99m}Tc ~ 20 times as high as that of ^{111}In.

Approaches to the analyses of gastric emptying data consist of defining one or more parameters, which are expected to reflect quantitatively the examined process and which allow statistical comparison. An often given parameter is the time of emptying a certain fraction of the dose given (*7–9*). However, this parameter disregards the remaining part of the emptying process. Characterizing the process in its whole by linear, mono- or power-exponential parameters might be relevant alternatives (*10–13*). In most of our studies, however, this would imply large approximations. Therefore, we computed a balanced mean value of the emptying process [mean transit time, Eq. (5)].

TABLE 3
In Vivo Radioactivity Dissociation (%, mean ± s.d.)

	[^{99m}Tc]CF	[^{111}In]PP
5 1 blood 3. hr	1.5 ± 0.8	0 ± 0
— 6. hr	1.2 ± 0.5	0 ± 0
— 9. hr	1.0 ± 0.4	0 ± 0
Urine 0–9 hr	2.6 ± 1.0	0 ± 0

n = 6

We introduce two new simple and probably physiologic markers for gastrointestinal transit of nondigestible components. The one, [^{99m}Tc]CF, has acceptable stability for gastric and small intestinal measurements and might be a readily prepared alternative to the iodine-131-labeled cellulose fiber (*14*). The other, [^{111}In]PP, can be due to almost complete stability and suitable radionuclide half-life be used for measuring the propulsive action of all gastrointestinal segments.

Gastric emptying depends among many other factors on the properties of the material emptied. Liquids are emptied faster than solids, and nondigestible solids of unit density are emptied progressively faster as diameters are decreased (*15*). Accordingly, we have found a faster gastric emptying of [^{99m}Tc]CF than of [^{111}In]PP. On the basis of previous studies (*15–18*) gastric emptying rates of [^{99m}Tc]CF (thin and flexible) and [^{111}In]PP (2- to 3-mm diameter) might be expected to correspond to the more fast and the more delayed emptying rates applied to nondigestible physiological components. In addition, the composition of the diet (e.g., the fiber content) supplied during the study might have important influence on the obtained transit times. As a general standardization was not given we chose to supply an ordinary hospital diet (Rigshospitalet, Copenhagen, DK).

In agreement with previous reports we could not prove any difference in progress along the small intestine due to difference in physical character of the material (*18,19*).

For the small intestine the deconvolution technique was initially described by Malagelada and colleagues (*19*). However, their method involved polynominal curve fitting and an iterative numerical process to construct a transit spectrum. Our restricted system of equations is adapted directly to the raw data and might, therefore, be a more accessible alternative.

CONCLUSION

We conclude that the two new radiolabeled markers are useful for studying the propulsive action of the gastrointestinal tract, and that this propulsive action reflects the physical properties of the markers. We find that our method of deconvolution is a valuable data interpretation which yields the most comprehensive physiologic parameter: the transit function.

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