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Colonic Transit Scintigraphy Labeled Activated Charcoal Compared with Ion Exchange Pellets

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Scintigraphic measurement of colonic transit is currently performed by delivering ^{111}In ion exchange resin pellets to the colon in a methacrylate-coated capsule. However, use of this method is constrained by the need for an investigational drug permit. We have demonstrated previously optimal adsorption in vitro of commonly used radioisotopes (e.g., ^{99m}Tc or ^{111}In) to activated charcoal in milieus that mimicked gastric and small intestinal content. The aim of this study was to compare the transit profiles of radioactive activated charcoal and resin pellets delivered to the colon in the same methacrylate-coated capsule. **Methods:** In 10 healthy volunteers, we compared the colonic transit profiles over 32 hr of simultaneously administered resin pellets labeled with ^{111}In and activated charcoal mixed with ^{99m}Tc-diethylenetriaminepentaacetic acid. Transit was summarized as the geometric center (weighted average of counts) in the colon at each scanning period. **Results:** Colonic transit profiles were virtually identical with the two markers, with less than 0.1 geometric center unit differences in the transit profiles over the 32-hr periods. **Conclusion:** Activated charcoal is a suitable alternative to resin pellets when delivered in a methacrylate-coated, delayed-release capsule to the colon for measurement of transit by scintigraphy.

Key Words: colonic transit; charcoal; scintigraphy

J Nucl Med 1997; 38:1807–1810

Measurement of colonic transit is a useful clinical and research technique for evaluating patients with suspected motility disorders of the colon. The radiopaque marker method (*1*) is widely available and is relatively inexpensive and reproducible (*2*), but it requires patients to be available for 4–7 days in order to evaluate the transit profile in the colon. The need to have a test with a faster completion time and more detailed assessment of regional colonic motor function has led us to develop a radioscintigraphic approach (*3*) that has since been simplified (*4*) and used clinically (*5*). It involves radiolabeling ion exchange resin pellets with isotopes such as ^{99m}Tc or ^{111}In and delivering these to the colon in a delayed-release, methacrylate polymer-coated medication capsule that dissolves in the alkaline pH of the terminal ileum. These initial research studies also have led to novel insights into the pathophysiology of the colon in diseases such as irritable bowel syndrome, idiopathic constipation and carcinoid diarrhea (*2,6,7*). Clinical utilization of the test (*5*) required a great deal of administrative support to meet regulatory requirements when using radiolabeled pellets under an investigational new drug application. In a clinical venue, this becomes administratively burdensome because the test only can be done after the patient has signed an informed consent form and reduces considerably the cost efficacy of the method; moreover, reimbursement by third-party payers is complicated because the informed consent is required to use the markers with an investigational new drug.

Our aim was to develop a new marker to be used in measuring colonic transit in human subjects. The characteristics of such a new marker would need to match the ideal properties we have previously noted when using labeled ion exchange pellets (*3–5*). The method would ideally involve "radiolabeling," a substrate that fulfills U.S. Pharmacopeia standards for synthesis; moreover, radiolabeling should be achieved with one of the commonly used radioisotopes, ^{99m}Tc or ^{111}In. The association between radioisotope and substrate must be optimal in the ranges of pH between 2 and 7.5 that are observed in the gastrointestinal tract and in the presence of pancreatic enzymes and conjugated bile acids. Finally, the marker's colonic transit

Received Sep. 16, 1996; revision accepted Jan. 13, 1997.
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profile should be virtually identical to that of the currently used 1–2 mm ion exchange pellets.

Activated charcoal is a fine, odorless and tasteless black powder that is free of grittiness (*8*). It is prepared from vegetable matter by carbonization processes intended to confer a high adsorbing power. It is practically insoluble in all usual solvents and is relatively nontoxic in humans after typical single, 50–100-g administrations at a recommended dilution of 20 g in 240 ml of water. It can adsorb a wide range of plant and inorganic poisons and many drugs, but being nonionic, charcoal does not bind or adsorb on ion exchange particles. It rarely causes vomiting when administered orally. Activated charcoal is approved for use as a medicinal. In a previous in vitro study, we showed that ^{99m}Tc and ^{111}In adsorbed effectively on activated charcoal and were retained (*9*) during incubations of up to 3 hr in milieus that mimicked gastric and small bowel contents (*10*).

Our hypothesis was that ^{99m}Tc adsorbed on activated charcoal and would have virtually identical colonic transit profiles as labeled ion exchange resin pellets in healthy volunteers.

MATERIALS AND METHODS

Participants

Ten healthy volunteers (5 men, 5 women; age range 18–43 yr) who were not taking any medication on a regular basis, were recruited by public advertisement. All signed the written informed consent of the research protocol, which was approved by Mayo's Institutional Review Board and Radiation Safety Committee. All volunteers were screened for gastrointestinal symptoms by a validated questionnaire developed for identifying functional gastrointestinal diseases (*11*). All female participants previously had undergone sterilization or had a negative pregnancy test within 48 hr of receiving the radiolabels.

Preparation of Radioactive Markers

Five milligrams of activated charcoal were mixed with 8 mCi (296 MBq) ^{99m}Tc-diethylenetriaminepentaacetic (DTPA) by addition of the radioisotope and evaporating the aqueous phase to dryness at 90–100°C. Ten milligrams of Amberlite 120 IR Plus resin pellets were radiolabeled with 0.1 mCi (3.7 MBq) $InCl_3$ as in previous studies (*12*). Radioisotope dosages were selected to ensure optimal colonic imaging up to 32 hr after ingestion. The activated charcoal dosed with ^{99m}Tc-DTPA and the radiolabeled ion exchange pellets were placed into one gelatin medication capsule (size 1). The capsule was then coated with one layer of the pH-sensitive polymer, methacrylate (*3*). This polymer dissolves at alkaline pHs that are only achieved in the distal ileum in humans (*13–15*).

Performance of Transit Studies

Participants attended the General Clinical Research Center Physiology Core Laboratory at St. Marys Hospital after an overnight fast. The capsule was ingested at time 0, patients ate meals ad libitum, and dual (anterior and posterior) gamma camera scans were obtained with the subject standing at 0, 2, 4, 6, 8, 24, 28 and 32 hr after ingestion of the capsule. The windows for ^{99m}Tc and ^{111}In were 140 keV ± 20 and 247 keV ± 20, respectively.

Data Analysis

A region of interest program was used to estimate the amount of radioactivity in the ascending (AC), transverse (TC), descending (DC), sigmoid and rectum (SR) and stool (ST). These were designated as regions 1–5, respectively, as in previous studies (*2–7*), for estimating the geometric center (weighted average) of counts for colonic transit. The geometric mean of anterior and posterior counts was estimated (square root of product of anterior and posterior counts), and, for each scan, the proportion of isotope in the region was estimated by dividing the counts in that region by the total counts of radioactivity in the entire colon. For ^{99m}Tc counts, crossover from the ^{111}In window was first estimated using a downscatter factor of 0.8 and subtracted from the total counts. A geometric center (or weighted average of counts in the five regions described above) was calculated as a summary of the transit profile for each isotope at 4, 6, 8, 24, 28 and 32 hr using the following formula:

(%AC * 1 + %TC * %DC * %RS * 4 + %ST * 5)/100.

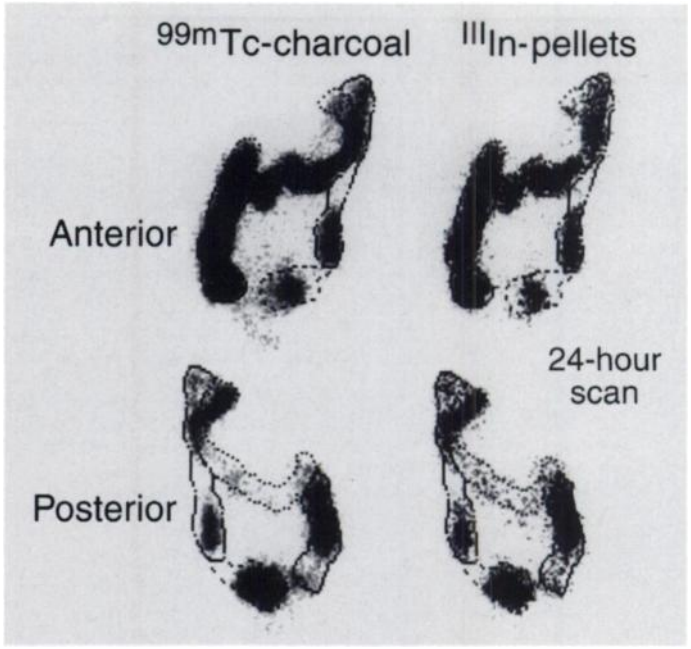

FIGURE 1. Anterior and posterior scintiscans of ^{99m}Tc-charcoal and ^{111}In-pellets showing distribution of radioisotope in the colon at 24 hr after ingestion of a delayed-release capsule containing both markers in a healthy volunteer's colon.

Statistical Power and Analysis

To be deemed equally accurate in estimating colonic transit, the profile of transit of radiolabeled activated charcoal would need to be within 10% of the transit profile of radiolabeled ion pellets. A sample size of 10 provided >80% power to detect such an agreement between the two markers at $\alpha = 0.05$.

First, the data were plotted as geometric center at each time point to assess intraindividual differences in transit profile using the two markers. Second, we plotted the differences in geometric center at each time point and the 95% confidence intervals on either side of the median difference. If the confidence interval of this difference in geometric center at each time point overlapped with a difference of zero, it would suggest that the colonic transit profiles of the two markers were not different.

RESULTS

None of the subjects had any significant gastrointestinal symptoms, including any functional gastrointestinal disorder, and all subjects completed the studies without complications. All scans were obtained as planned except for two subjects (9 and 10), who were unable to attend the laboratory for the final scan at 32 hr. Figure 1 shows an example of anterior and posterior colonic silhouettes containing ^{99m}Tc-charcoal and ^{111}In-pellets. The distribution of radioisotopes at 24 hr was similar with the two radioactive markers (Fig. 1). Figure 2 shows a comparison of the time-activity curve for colonic radioactivity of the two markers in one individual. The curves are virtually identical.

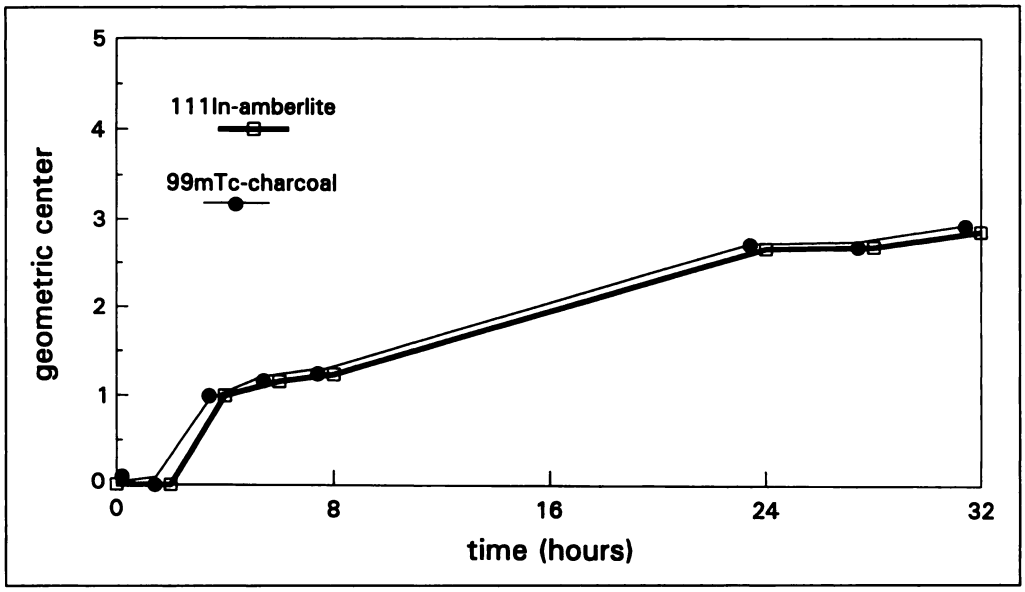

FIGURE 2. Time-activity curve of ^{111}In-Amberlite pellets and ^{99m}Tc-charcoal in the colon over 32 hr after ingestion. Geometric center 0, ileocolonic junction; 1, hepatic flexure; 2, splenic flexure; 3, end of descending colon; 4, end of rectum; 5, stool. Note the virtually identical transit profiles of the two radioisotopic markers.

Figure 3 plots the difference in geometric center at the different times of imaging. Note that the highest difference in geometric center units observed was 0.1, which represents 10% or less of one of the colonic regions studied. Figure 4 plots the 95% confidence limits above and below the median difference in geometric center at each scanning time. Note the overlap of each of the 10 variances with the zero difference line, negating the null hypothesis that the transit profiles of the two markers were significantly different.

DISCUSSION

This study shows that the transit profiles through the colon of ^{99m}Tc-activated charcoal particles and ^{111}In-labeled ion exchange resin pellets in healthy adult human participants were virtually indistinguishable. The average size of the two solid particles was 1.5 mm for the ion exchange pellets and 0.1–0.2 mm for the activated charcoal particles, suggesting that particle size below 2 mm does not appear to influence the colonic transit profile. This is unlike the situation noted previously, when particles of 6 mm radiopaque markers traversed the colon more rapidly than the average 1.5 mm ion exchange pellets (*3*). The normal transit profile of activated charcoal particles suggests that the adherence of the charcoal to intracolonic residue was greater than its adherence to the colonic mucosa. This was an important consideration, since the marker must reflect movement of intracolonic residue to be useful for measuring colonic transit.

Activated charcoal is not ionically charged and, therefore, does not bind to ion exchange pellets in vitro. Therefore, the similarity of the transit profiles does not reflect the binding of charcoal to the pellets but reflects similar movement of the two markers as part of the intracolonic residue. Charcoal may have certain advantages over the pellets; for example, it binds to vegetable residue by virtue of its high adsorptive power and therefore truly traverses the colon with those residues.

One needs to consider the potential pitfall that ^{99m}Tc might bind to the ion pellets rather than being adsorbed to the activated charcoal. This is unlikely, since the ion exchange pellets used were cation binders, whereas the marker adsorbed on charcoal, ^{99m}Tc, was part of an anion (DTPA). The in vitro studies (*9*), showing the high adsorption and retention of radioisotope on the activated charcoal particles, suggest that the ^{99m}Tc was associated closely with the charcoal particles during

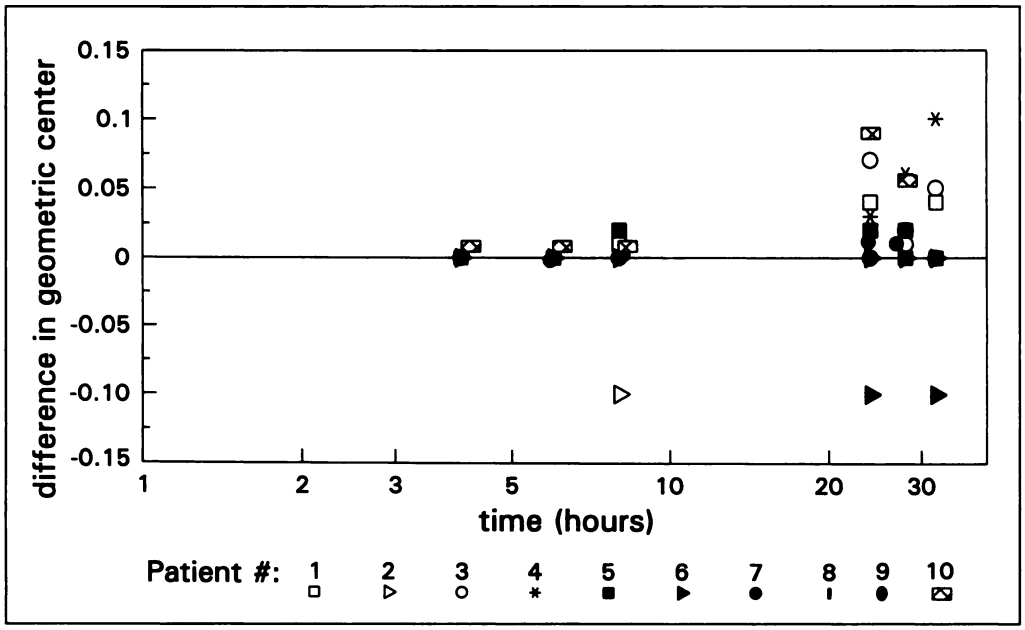

FIGURE 3. Difference in geometric center of ^{99m}Tc-charcoal and ^{111}In-pellets at each scan time for each individual identified by a different symbol. Note that the highest difference at any scan time is less than 0.1 of a geometric region.

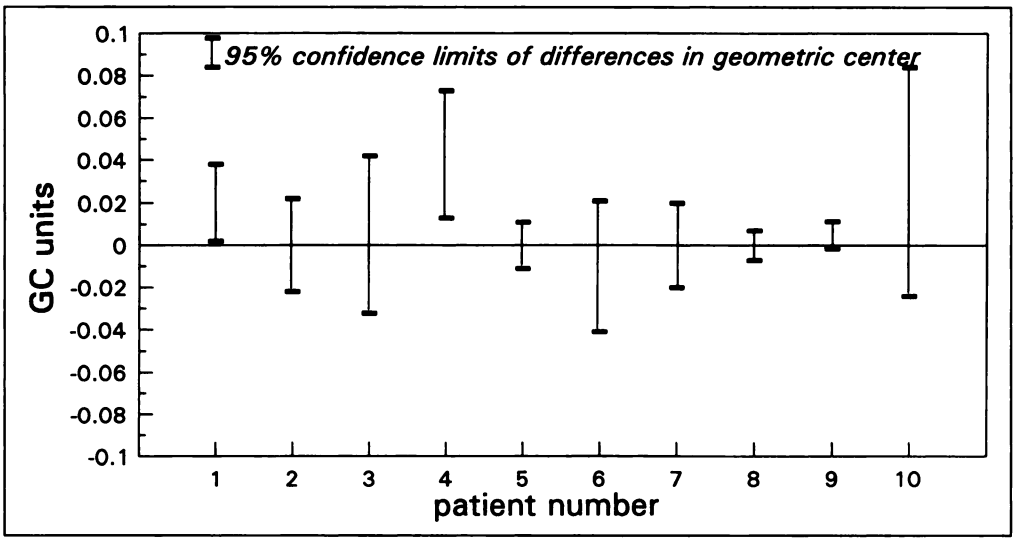

FIGURE 4. Variance of the difference in geometric center of ^{99m}Tc-charcoal and ^{111}In-pellets at all scan times in 10 healthy participants. Note that the 95% confidence intervals overlap the zero line in 9 of 10 participants, proving that the transit profiles of the two markers are not significantly different.

its transit through the colon. Similarly, the excellent binding characteristics of ^{111}In to ion exchange pellets make it highly unlikely that ^{111}In dissociated from the ion exchange pellets and adsorbed on the charcoal or on other particles in the colonic residue.

Activated charcoal binds medications and some nutrients, and this might be disadvantageous if the charcoal was allowed to mix with food constituents in the stomach or small bowel. However, since the charcoal carrier of the radioisotope is given in small quantities (5 mg or less) and the charcoal is within a delayed-release capsule during its passage through most of the small intestine, the likelihood of any deleterious effect of the charcoal on nutrient or medication adsorption is negligible. Moreover, since the method is being developed as a test, it is unlikely that most patients would require more than occasional ingestion of the activated charcoal for measurement of colonic transit.

CONCLUSION

We have documented the in vivo use of a radioisotope adsorbed on activated charcoal as a marker for colonic transit; the new marker has features that are comparable to those of radiolabeled ion exchange pellets. The activated charcoal is inexpensive, readily adsorbs radioactive markers, can be delivered to the human colon in a delayed-release capsule that is identical to one used in over 1000 patients in the past 5 yr at our institution and fulfills U.S. Pharmacopeia standards for patient use. This method has the potential to become a generally available scintigraphic method for measuring colonic transit noninvasively in health and disease states. Further studies are necessary in patients with disorders of colonic motility. Because colonic transit profiles can be accurately assessed over a 24-hr period (*4*), the starting dose of ^{99m}Tc can probably be reduced to 4 or 5 mCi (148 or 185 MBq), with adequate residual counts for accurate measurements of colonic geometric center. At this dose, H_E is 360 mrad, and organ exposures are summarized in Table 1.

ACKNOWLEDGMENTS

This study was supported in part by General Clinical Research Center grant RR0085 from the National Institutes of Health, supporting the Physiology Core Laboratory, and by the Samsung Colonic Motility Research Fund at Mayo Foundation. We thank Cindy Stanislav for typing and preparing this manuscript. This work was presented at the American Motility Society Meeting, October 1996. An abstract of this work has been published (*16*).

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TABLE 1
Radiation Exposure (mrad) with 4 mCi Technetium-99m-Activated Charcoal

Activity	Body	Stomach	SI	ULI	LLI	Marrow	Gonads	H_E
4 mCi	72	960	960	1840	1120	536	336	360

SI = small intestine; ULI = upper large intestine; LLI = lower large intestine.