Detection of Esophageal Ulcerations with Technetium-99m Albumin Sucralfate

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Technetium-99m albumin-sucralfate ([^{99m}Tc]Su) can be used to demonstrate peptic ulcer disease in man and animals. We evaluated the usefulness of [^{99m}Tc]Su for detecting various grades of esophagitis. [^{99m}Tc]Su adhered to the distal esophagus for up to 3 hr in five of six patients with esophageal ulcers but adhered to only two of nine with lesser degrees of esophagitis. No adherence was seen in five patients without esophagitis. Thus, [^{99m}Tc]Su may not be useful for detecting any but the most severe grade of esophagitis. Based on these results, we speculate that the previously documented beneficial effects of sucralfate on mild to moderate esophagitis may be due to other mechanisms besides adherence to the ulcerated mucosa.

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Sucralfate (the aluminum salt of sulfated sucrose) has been shown to heal gastric and duodenal ulcers (*1–2*). It probably has two mechanisms of actions. In acid, it becomes a viscous substance that avidly binds to protein. Consequently, it readily adheres to ulcerated mucosal surfaces, and provides a protective barrier to further damage from acid and pepsin (*3*). Sucralfate also increases local tissue prostaglandin levels that promote healing and cytoprotection (*4,5*).

Previously, the specific adherence of sucralfate to ulcers has been demonstrated by either endoscopy or gastrostomy (*1,3*). Preliminary studies with technetium-99m- (^{99m}Tc) labeled sucralfate have demonstrated localized, prolonged adherence of the sucralfate to gastric and duodenal ulcers in animals and man (*6, 7*). The ^{99m}Tc-labeled sucralfate study results suggest that one might be able to use this noninvasive scanning technique to diagnose peptic ulcer disease.

A few reports have suggested that sucralfate might be useful for healing esophagitis (*8–11*). In particular, a small randomized trial from Germany found 72% healing of esophagitis with sucralfate therapy while only 40% of their placebo group healed (*11*). Sucralfate has been shown to prevent in vivo and in vitro esophageal injury in rabbits (*12,13*). Why sucralfate promotes healing of esophagitis remains unclear.

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If one hypothesizes that sucralfate exerts its beneficial effect on esophagitis by adhering to the ulcerated mucosa, as it does in peptic ulcer disease, then one might be able to use ^{99m}Tc-labeled sucralfate to diagnose the presence of an ulcerated esophagus. A noninvasive scan would be much better tolerated by patients than esophagoscopy and might be more accurate than a barium swallow which is frequently nondiagnostic in patients with esophagitis. The purpose of this study was to determine if a [^{99m}Tc]albumin-sucralfate ([^{99m}Tc]Su) suspension could be used to diagnose various grades of esophagitis.

MATERIALS AND METHODS

Twenty patients with complaints of heartburn or reflux who were being scheduled for esophagogastroduodenoscopy (EGD) were randomly recruited for the study from the gastroenterology clinic or wards at our institution. After obtaining informed consent, each subject had a routine EGD and a [^{99m}Tc]Su scan within 72 hr of the EGD. Biopsies were not done during the EGD. The study was approved by the Human Subjects Committee at the University of Colorado Health Sciences Center on 1/13/84.

The sucralfate labeling procedure was essentially the same as that of Vasquez et al. (*6*), with only slight modifications. Stannous tartrate and bovine albumin were both obtained commercially.* Technetium-99m was obtained by milking a ^{99}Mo/^{99m}TcO$_4$ generator.† Sucralfate was obtained commercially as 1-g tablets.‡

These tablets were then crushed to a fine powder. Instant thin-layer chromatography (ITLC-SG) paper was also obtained commercially.[§]

Approximately 12.5 mg stannous tartrate was dissolved in 0.25 ml concentrated HCl (37% w/w) and warmed under tap water to facilitate dissolution. This acid solution was then diluted to 25 ml with nitrogen-purged distilled water, and 0.25-ml aliquots were placed into 10-ml vials. The vials were again purged with nitrogen gas and frozen. Each aliquot contained ~0.12 mg stannous tartrate per 0.25 ml.

Ten milligrams bovine albumin was diluted with 0.5 ml normal saline. To this was added an aliquot of the diluted stannous tartrate solution (0.12 mg/0.25 ml) followed by 5–7 mCi (185–259 MBq) of $^{99m}TcO_4$ generator eluate. This mixture was shaken intermittently over a 30-min period after which the percent labeling efficiency of the albumin was determined by chromatography on ITLC-SG with methylethylketone as solvent. Greater than 98% of the ^{99m}Tc was normally found labeled to the albumin.

The labeled albumin from above was added to a slurry consisting of 1 g of sucralfate (one crushed tablet) in 3 ml of 0.06N hydrochloric acid, and the total activity was determined in a dose calibrator.[¶] The slurry was then twice-washed by centrifuging at 300 *g* for 5 min, a speed that pellets sucralfate but leaves any free ^{99m}Tc-albumin in the supernatant. After each centrifugation, the supernatant was removed and the slurry was resuspended with ~3 ml of water. The final activity of the preparation was determined in the dose calibrator and the percent labeling efficiency was calculated. The activity ranged from 3.5 to 6 mCi (130–222 MBq) per g of sucralfate with >95% of the ^{99m}Tc activity bound to the sucralfate. The pH of the administered [^{99m}Tc] albumin-sucralfate was 7.

Each subject ingested 1 g of the Tc-Su solution with a small volume of water. Scans of the esophagus and stomach were subsequently obtained at 30, 60, 120, and 180 min after the ingestion using a gamma camera.[**] One-minute scans were made with the patient sitting upright. They were not allowed to recline during the entire duration of the study. The patients were asked to drink a minimum of 8 oz of water between the 60- and 180-min scans to assess the degree of adherence of the Tc-Su to the esophageal mucosa.

Assessment of the degree and duration of localization of the [^{99m}Tc]Su in the esophagus was made by a radiologist who was unaware of the EGD results. A scan was considered positive if there was persistent radioactivity in the esophagus at 60 min postingestion, and if the 60-min activity did not exceed the 30-min activity that would suggest reflux rather than adherence to the esophagus. Similarly, scans at 120 and 180 min were not considered positive if the activity in the esophagus greatly increased over the previous time interval.

RESULTS

Fifteen of the 20 patients had moderate to severe esophagitis demonstrated at EGD. Six of these had deep, 0.5–1.0 cm, ulcerations (three secondary to recent sclerotherapy with 3% sodium tetradecyl sulfate). The other nine patients had superficial ulcers or diffuse exudative esophagitis involving the distal one-third of the esophagus. Five patients had completely normal or only erythematous distal esophageal mucosa despite their positive heartburn/reflux histories (Table 1).

Of the 15 patients with erosions, friability, and ulcerations in the distal esophagus, seven had positive scans and eight had negative scans. Those with a positive result at 60 min had persistently positive scans at 120 and 180 min (Fig. 1). Three scans in patients with initially negative scans showed increased distal esophageal activity in later scans indicating reflux. These scans were not considered positive. Five of the six patients with deep ulcerations had positive scans, while only two of the nine patients with lesser degrees of mucosal abnormalities had positive scans. None of the five patients with intact mucosa had positive scans.

DISCUSSION

Sucralfate is a unique compound that, in the presence of acid, becomes a viscous material that readily adheres to the proteinaceous base of ulcers in the stomach and duodenum (*3*). While adherent to the ulcer, sucralfate protects it from acid, bile, pancreatic enzymes, and pepsin. Sucralfate also increases local tissue prostaglandins that further aid in ulcer healing (*4,5*).

Berges et al. in 1981 found that in a small group of patients with severe esophagitis 69% improved and 46% healed after 12 wk of sucralfate therapy (*10*). Laitinen et al. demonstrated 54% complete healing of esophagitis

TABLE 1
Results of Scans Grouped by Type of Esophageal Mucosa

Patient no.	Endoscopic diagnosis	Scan results (min)		
		60	120	180
1–3	Normal	Neg	Neg	Neg
4, 5	Erythema	Neg	Neg	Neg
6	Sclerotherapy ulcers	Pos	Pos	Pos
7	Sclerotherapy ulcers	Pos	—	—
8	Sclerotherapy ulcers	Neg	Neg	Neg
9	Large ulcer, Barrett's	Pos	Pos	Pos
10, 11	Large ulcer	Pos	Pos	Pos
12	Superficial ulcerations	Pos	Pos	Pos
13–16	Superficial ulcerations	Neg	Neg	Neg
17	Exudative esophagitis	Pos	Pos	Pos
18–20	Exudative esophagitis	Neg	Neg	Neg

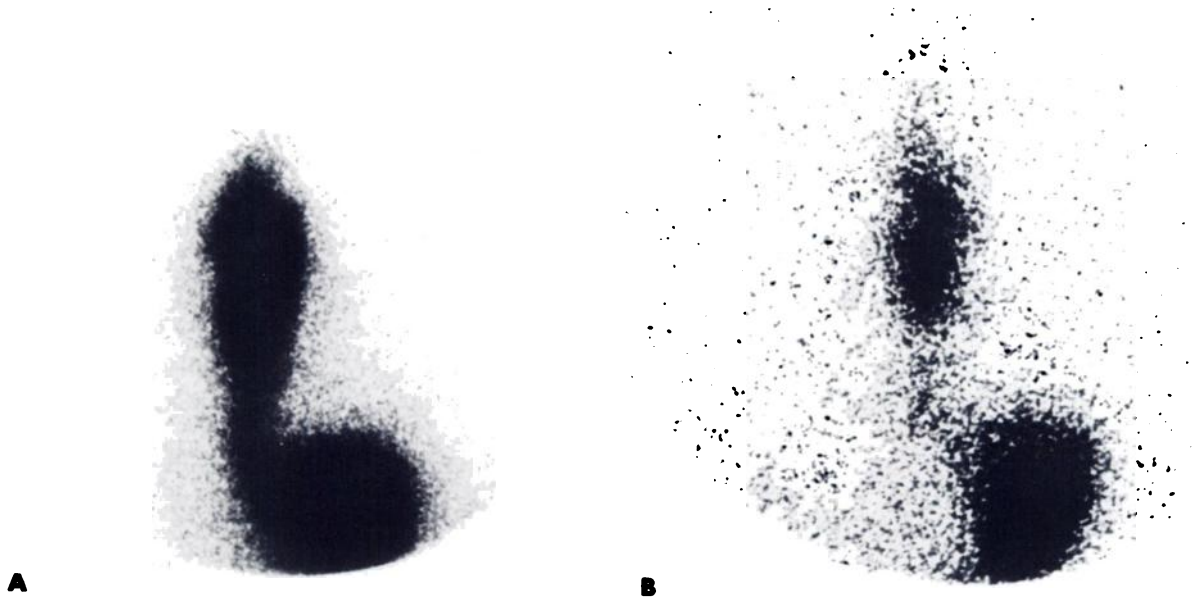

FIGURE 1
A: Scan at 1 hr from Patient 11 (see Table 1) with large esophageal ulcer showing localized activity in distal esophagus.
B: Same patient 3 hr later with continued localized activity in distal esophagus

at endoscopy after 6 wk of sucralfate therapy (*9*). The best study looking at the effects of sucralfate on human esophagitis is a randomized, double-blind placebo controlled trial in 47 patients reported by Weiss et al. (*11*). They found 72% healing after 12 wk of therapy with sucralfate compared with only 40% healing in the placebo group ($p < 0.05$). Similarly, reports in animals have suggested that sucralfate can protect the esophagus from injury (*12,13*).

If sucralfate is truly effective in healing esophagitis one would presume it accomplishes its beneficial effect by the same mechanism as it does in the stomach or duodenum. Since ^{99m}Tc-labeled sucralfate has been shown to localize to gastric and duodenal ulcers (*6*), we felt the same technique could be used to see if sucralfate would localize to areas of the esophagus with disrupted mucosa (esophagitis) and remain there for prolonged periods of time. If this was the case, we would have evidence to support the hypothesis that sucralfate heals esophagitis by forming a protective coating.

The major advantage of demonstrated adherence of [^{99m}Tc]Su to esophagitis would be that it could possibly be used as a diagnostic tool. Rarely, a specific diagnosis of esophagitis can be made on a barium swallow. Severe inflammation may create a ragged appearance to the mucosa in the lower esophagus or a deep ulcer can be detected but lesser degrees of inflammation do not alter the mucosa enough to produce an abnormal radiograph. Consequently, one must resort to EGD, which is more invasive and costly, to make a specific diagnosis of esophagitis. Unfortunately, the results of our study do not allow us to conclude that [^{99m}Tc]Su can be used to diagnose lesser grades of esophagitis. [^{99m}Tc]Su appears to be quite reliable for detecting large or deep esophageal ulcers, but its lack of demonstrable adherence to lesser grades of esophagitis makes it no better than a barium swallow. None of these patients had strictures or achalasia. In those conditions, [^{99m}Tc]Su could remain in the esophagus but not be truly adhering to the mucosa. To prevent such a misinterpretation, a scan done within 5 min of ingestion showing little or no counts in the stomach would be diagnostic.

The reason for the lack of adherence to mild to moderate esophagitis is not readily apparent. It is possible that there is not enough proteinaceous exudate overlying lesser degrees of esophageal inflammation, but this seems unlikely, especially in our patients with severe exudative esophagitis. The more likely explanation is that our suspension of sucralfate was inadequately suspended or inadequately activated which decreased its ability to adhere to the disrupted mucosa as it passed through the esophagus. This may be very important since the exposure time during a swallow is limited. It has been suggested that a better suspension can be obtained with 95% alcohol or Tween 80 (*14*). The other factor potentially effecting the [^{99m}Tc]Su adherence is the amount of albumin bound to it. Theoretically, this could decrease its binding ability since some of the binding sites are blocked by the [^{99m}Tc] albumin. Further studies with better suspensions of radiolabeled sucralfate may yet find it to be a useful diagnostic tool.

Despite the poor adherence of [^{99m}Tc]Su in many of our patients the important finding is that, in those to

whom it adhered, the duration of the adherence was at least 3 hr. This means that the reported healing of esophageal ulcers after sucralfate treatment may be produced by the protective coating created by the sucralfate or by its ability to stimulate local tissue prostaglandin synthesis once it becomes adherent, as has been previously demonstrated in the stomach and duodenum. Our results suggest that a crude suspension of sucralfate may be useful for treating deep esophageal ulcers because of its likelihood to adhere to these lesions.

Though we detected little adherence of sucralfate to lesser degrees of esophagitis, this should not be used as evidence to negate the prior studies demonstrating clinical improvement in esophagitis after treatment with sucralfate. Rather, other reasons for these results should be considered. Since we observed [^{99m}Tc]Su reflux in several patients over the course of the study, one might hypothesize that in patients with lesser degrees of esophagitis, sucralfate produces healing by the same mechanism as alginic acids. That is, reflux of the sucralfate slurry might occur rather than reflux of the acidic gastric secretions, resulting in decreased esophageal inflammation because of less exposure to the irritating acid.

FOOTNOTES

* Sigma Chemical Company, St. Louis, MO.

† DuPont Diagnostic Imaging Div., North Billerica, MA.

‡ Marion Laboratories, Inc., Kansas City, MO.

§ Gelman Sciences, Inc., Ann Arbor, MI.

¶ Capintec, Inc. (Radioisotope Calibrator CRC-30), Ramsey, NJ.

** Technicare, Solon, OH.

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