The Source of Gallium-67 in Gastrointestinal Contents: Concise Communication

David C. Chen, Ursula Scheffel, Edwaldo E. Camargo, and Min-Fu Tsan

The Johns Hopkins Medical Institutions, Baltimore, Maryland

The sources of Ga-67 in gastrointestinal (GI) contents, and factors affecting its secretion were studied in rats. To prevent loss of fecal Ga-67, the anus was sutured before intravenous injection of Ga-67 citrate. Secretion of Ga-67 into the contents of the GI tract was rapid, 3, 6, and 9% of the injected dose were secreted at 1, 6, and 24 hr after injection, respectively. In contrast, Ga-67 concentration in the GI tissues remained relatively constant throughout this period. Analysis of Ga-67 contents of various parts of the GI tract revealed that small intestine is its major source, contributing 60% while the bile contributes 20%, large intestine 10%, esophagus and stomach 10%. Feeding had no effect on the Ga-67 secretion into GI contents. In contrast, the serum unbound iron-binding capacity (UIBC) played an important role in the GI secretion of Ga-67; reducing the serum UIBC reduced the Ga-67 secretion into GI contents.

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Gallium-67 continues to be widely used for the detection of neoplasms as well as inflammatory lesions, but interpretation of intra-abdominal disease is often complicated by the physiological accumulation of Ga-67 in the gastrointestinal (GI) tract (*1,2*). However, little is known about the source of Ga-67 in the GI contents. Newstead et al. (*2*) noticed that the concentration of Ga-67 in human bile was high, and suggested that fecal Ga-67 was primarily derived from biliary excretion. On the other hand, Taylor et al. (*3*) found that ligation of the common bile duct did not affect the fecal Ga-67 excretion in rats, and suggested that it is secreted primarily through the bowel mucosa. In this study, we performed experiments in rats to determine the source of Ga-67 in GI contents and factors affecting its secretion.

MATERIALS AND METHODS

Sprague–Dawley rats weighing between 200–350 g were used. After a 24-hr fast period, the anus was sutured to prevent any loss of the intestinal contents. Carrier-free Ga-67 citrate (5 μCi/100 g body weight) was then administered intravenously by tail vein. At various intervals after injection, the animals were anesthetized with intraperitoneal pentobarbital (10 mg/100 g body weight). The abdominal and chest cavities were then opened and the rats were exsanguinated by cardiac puncture. Ligatures were applied around the upper esophagus, gastroesophageal junction, pylorus, terminal ileum, and rectum. After dissecting the mesentery from the intestine, the entire alimentary tract was removed and washed once in normal saline. It was then divided into esophagus, stomach, small intestine, and large intestine, and the radioactivity in each section was determined, along with a standard in a gamma well counter using a window setting of 80–320 keV. The esophagus, stomach, small intestine, and large intestine were then everted and their contents removed by repeated washing with normal saline. The radioactivity of these organs, now free of their contents, was determined as described above. The radioactivity in the contents was derived from the difference before and after the contents were removed.

To determine the contribution of various parts of the GI tract in the secretion of Ga-67, the pylorus and terminal ileum were ligated, in addition to the anal suture, before the intravenous injection of Ga-67. A sham operation was done in the control group by simply opening

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For reprints contact: Min-Fu Tsan, MD, PhD, 615 N. Wolfe St., Baltimore, MD 21205.

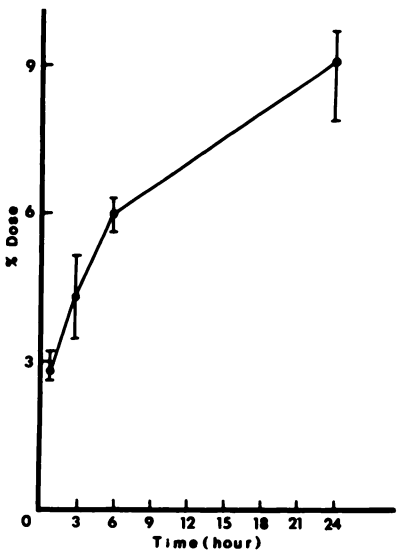

FIG. 1. Time course of Ga-67 secretion into GI contents. Results are mean and range of three rats.

the abdominal cavity. To determine the contribution from the bile, the common bile duct was ligated in addition to the ligation of pylorus and terminal ileum. In some animals, a duodenal loop was created by ligating the pylorus and at 10 cm caudal to this junction. Tc-99m dimethyl acetanilide iminodiacetic acid (Tc-99m HIDA, 5 μCi/rat) was used to ensure the complete ligation of the common bile duct.

To determine the effect of feeding on the Ga-67 secretion into GI contents, the animals were not fasted but were allowed free access to diet after the injection of Ga-67. To determine the role of serum unbound iron-binding capacity (UIBC) on Ga-67 secretion into GI contents, rats were treated with weekly intramuscular injection of iron dextran (25 mg/wk) for 2 or 5 wk to reduce their UIBC. The measurement of serum UIBC was performed using the Res-O-Mat Fe-59 Diagnostic Kit.*

Statistical differences were determined by Student's t-test for independent means (*4*).

RESULTS

Secretion of Ga-67 into gastrointestinal contents. This process was rapid (Fig. 1). At 1 hr after injection, 3% of the injected dose was found in the GI contents, 6% at 6 hr and 9% at 24 hr. Figure 2A shows the time course of Ga-67 secretion into the contents of various parts of the GI tract. The radioactivity in the contents of esophagus and stomach was small and remained constant. The radioactivity in the small intestine was high, reaching a plateau at 6 hours after injection. In contrast, the activity in the large intestine was initially small, but increased steadily over the next 24 hr. At 6 hr after injection, more than 50% of the total activity in the GI contents was found in the small intestine, but at 24 hr 60% was in the large intestine. This finding suggested that part of the gallium in the large intestine might come from the upper GI tract. Figure 2B shows the time course of gallium in

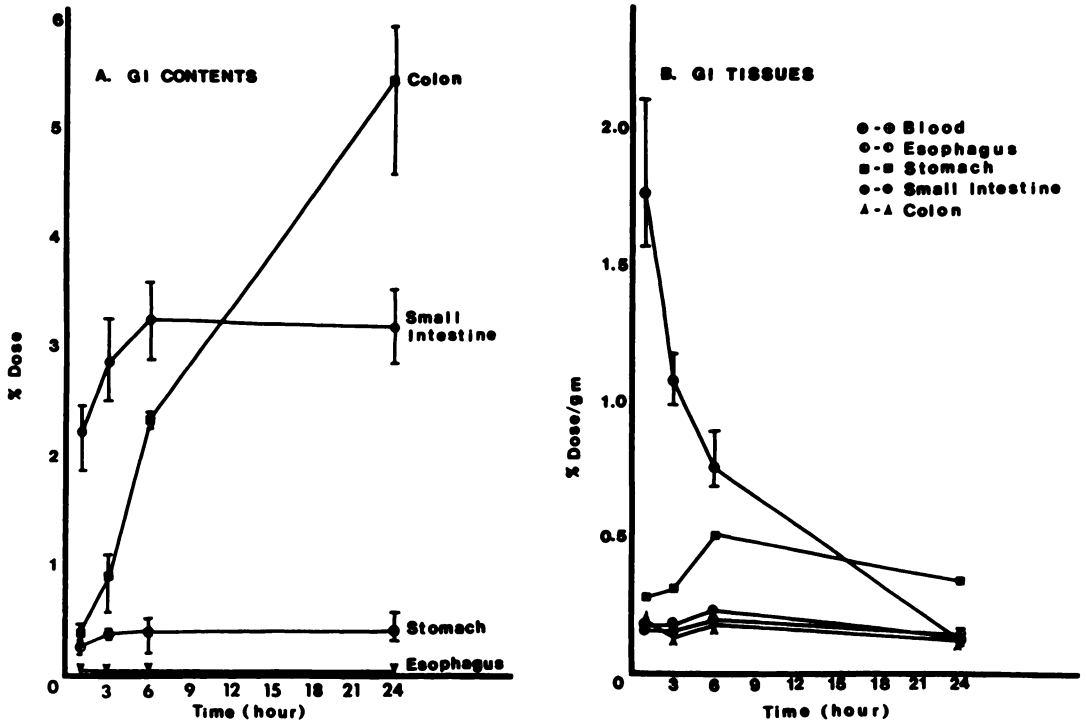

FIG. 2. Time course of Ga-67 in contents (A) and tissues (B) of various parts of GI tract. Results are the mean (and range) of three rats.

TABLE 1. SOURCE OF Ga-67 IN THE GI CONTENTS

	Esophagus* and stomach	Small intestine*	Large intestine*	UIBC†
Control (3)‡	0.40 (0.21–0.53)	3.27 (2.88–3.57)	2.32 (2.27–2.34)	283.6 (241.2–338.6)
Sham Operation (3)	0.62 (0.58–0.69)	2.63 (2.59–2.66)	2.19 (2.13–2.31)	315.7 (266.8–365.7)
Pylorus, terminal ileum ligated (7)	0.57 (0.34–0.86)	5.05 (4.52–5.56)	0.53 (0.4–0.63)	303.9 (242.4–307.7)

* The results were obtained at 6 hr after i.v. injection of Ga-67 citrate and expressed as percent dose injected (mean and range).

† mg/100 ml (mean and range).

‡ Number of animals.

the tissue of the GI tract. In contrast to the radioactivity in the GI contents shown in Figure 2A, the activity in the tissue remained relatively constant over the entire experimental period. The radioactivity in the stomach was higher than that of the esophagus, and small and large intestines. The radioactivity in the blood is also shown in this figure.

Location of the source of Ga-67 in the GI contents. Attempts were then made to locate more clearly the source of Ga-67 in the GI tract. In this experiment, ligation at the pylorus and terminal ileum, in addition to the anal suture, was performed before the intravenous injection of Ga-67. The results obtained at 6 hr after Ga-67 injection are shown in Table 1; there was no difference between control and sham-operated groups. In contrast, when the pylorus and terminal ileum were ligated before the injection of Ga-67, the radioactivity in the contents of the small intestine was markedly increased, whereas that in the large intestine was markedly reduced. Under this circumstance about 80% of the total activity in GI contents was in the small intestine. The serum UIBC was determined in each rat. As shown in this table, there was no difference in the serum UIBC among these three groups. Thus the results suggest that the majority of Ga-67 in GI contents comes from small intestine.

The role of bile in the secretion of Ga-67 into GI contents. Since about 5–10% of the injected Ga-67 is concentrated in the liver (*1,2,5*) and the concentration of Ga-67 in the bile is about one third of that in the liver (*2*), we studied the contribution of bile to the Ga-67 secretion into the GI contents. For this purpose, the common bile duct was ligated in addition to the ligation at the pylorus and terminal ileum. As shown in Table 2, there was no difference in the radioactivity in the contents of esophagus, stomach, and large intestine. In contrast, when the common bile duct was ligated the radioactivity in the small intestine was reduced. This suggests that part of the Ga-67 in the small intestinal content is derived from the bile.

To further quantitate the amount of Ga-67 excreted in the bile, a duodenal loop was created by ligating the pylorus and at 10 cm below this junction. Tc-99m HIDA was used to verify the complete ligation of the common bile duct. Table 3 shows that at 6 hr after injection more than 60% of the injected Tc-99m HIDA was excreted into the duodenal loop in the control animals, whereas less than 0.2% was in the loop in the group with the ligated common bile duct. Similarly, 1.7% of the injected Ga-67 was found in the duodenal loop in the control group, whereas only 0.5% was found there in the groups with the ligated common bile duct. Thus, about 1.2% of

TABLE 2. THE ROLE OF BILE EXCRETION ON THE Ga-67 SECRETION INTO GI CONTENTS

	Esophagus* and stomach	Small intestine*	Large intestine*	UIBC†
Control	0.58 ± 0.19 (7)	5.05 ± 0.36 (7)	0.53 ± 0.07 (7)	303.9 ± 51.0 (7)
Common bile duct tied	0.60 ± 0.16 (6)	3.92 ± 0.43 (6)	0.44 ± 0.10 (6)	315.4 ± 78.1 (6)
p value	>0.80	<0.001	>0.80	>0.20

* Ligations were made at the pylorus and terminal ileum (in addition to the anal suture) before Ga-67 citrate was injected intravenously. The results were obtained 6 hr later and expressed as percent dose injected (mean ± 1 s.d.).

† μg/100 ml (mean ± 1 s.d.).

TABLE 3. QUANTIFICATION OF BILE SECRETION OF GA-67

	Duodenal Loop*	
	Ga-67	Tc-99m HIDA
Control (3)†	1.71	62.16
	(1.45–1.87)	(52.36–68.79)
Common bile	0.46	0.13
duct tied (3)	(0.34–0.58)	(0.09–0.19)
p value	<0.005	<0.001

* Ligations were made at the pylorus and 10 cm from this junction before the i.v. injection of Ga-67 citrate and Tc-99m HIDA. The results were obtained 6 hr later and expressed as percent dose injected (mean and range).

† Number of animals.

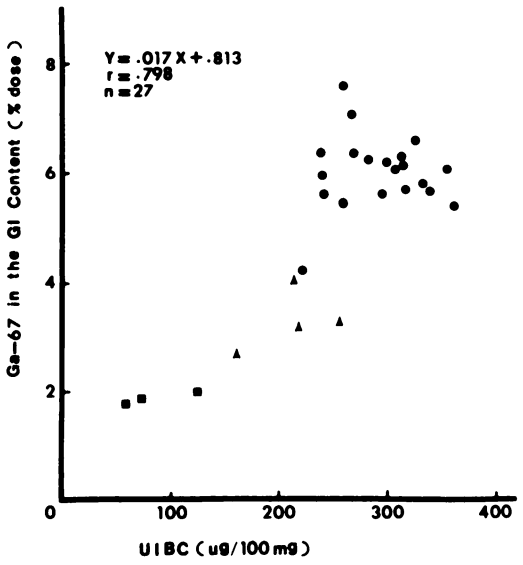

Fig. 3. Relationship between serum UIBC and amount of Ga-67 secreted into GI contents. Results were obtained 6 hr after Ga-67 injection. ●, control rats; ▲, iron-dextran treated rats (2 wk); ■, iron-dextran treated rats (5 wk).

the injected dose was excreted through the bile. This amount represents about 20% of the total Ga-67 secreted into the GI contents.

The effect of serum UIBC on Ga-67 secretion into GI contents. The serum UIBC plays an important role in the body retention and distribution of Ga-67 (*6*). The results presented so far were obtained from normal rats, and there was no difference between the serum UIBC of the control and experimental groups. To determine the effect of serum UIBC on Ga-67 secretion into GI contents, animals were given intramuscular injections of iron dextran for 2 or 5 wk to reduce their serum UIBC. As shown in Fig. 3, the serum UIBC and the amount of Ga-67 secreted into GI contents were markedly reduced in the group treated with iron dextran. Furthermore, there was a significant correlation between the serum UIBC and the amount of Ga-67 secreted into GI contents ($r = 0.79$). Analysis of Ga-67 in various parts of the GI contents revealed that the reduced Ga-67 secretion in the rats treated with iron dextran was evenly spread throughout the entire GI tract.

The effect of feeding on the Ga-67 secretion into GI contents. The above experiments were performed in fasted animals. Since it has been shown that feeding affects the biodistribution of Ga-67 (*7*), we studied the effect of feeding. As shown in Table 4, feeding had no effect on the Ga-67 secretion into GI contents.

DISCUSSION

The foregoing results suggest that secretion of Ga-67 into GI contents in rats is rapid—9% of the injected dose being secreted in 24 hr. The small intestine is the major source of Ga-67 secretion, contributing 60%, while the bile contributes 20%, large intestine 10%, and esophagus and stomach 10%. Whether this information is applicable to humans is not clear.

Secretion of Ga-67 into the GI tract has been studied previously by collecting the stool from animals (*3*), but this method suffers from several disadvantages. The stool

TABLE 4. EFFECT OF FEEDING ON THE Ga-67 SECRETION INTO GI CONTENTS

	Esophagus*	Stomach*	Small intestine*	Large intestine*	Total content*	UIBC
Fasting (3)‡	0.02	0.38	3.27	2.33	6.00	283.6
	(0.01–0.02)	(0.20–0.52)	(2.89–3.58)	(2.28–2.37)	(5.69–6.38)	(241.2–338.6)
Feeding (4)	0.02	0.38	2.78	2.61	5.78	274.1
	(0.02–0.03)	(0.22–0.49)	(2.22–3.06)	(1.77–3.08)	(4.23–6.39)	(220.2–317.6)
p Value	>0.5	>0.09	>0.1	>0.4	>0.7	>0.7

* The results were obtained 6 hr after i.v. injection of Ga-67 citrate and expressed as percent dose injected (mean and range).

† μg/100 ml (mean and range).

‡ Number of animals.

collected at any particular time may not represent what is secreted into the GI tract. In animals, contamination of the stool by urine poses additional problems. These may explain the divergent results described in the literature (*1–3*). In our study, we sutured the anus before the intravenous injection of Ga-67 to prevent any loss of GI contents. With the exception of the mouth and pharynx, the entire alimentary tract was then removed. Thus, we have studied the amount of Ga-67 present in GI contents much more completely. Furthermore, this technique enables us to study the role of various parts of the GI tract by ligating at appropriate levels.

The mechanism of Ga-67 secretion into GI contents is not clear. We have observed that the serum UIBC plays an important role: reducing the serum UIBC reduced the secretion of Ga-67 into GI contents. This may suggest that transferrin binding of Ga-67 is important for the GI secretion of Ga-67. Alternatively, the reduced GI secretion of Ga-67 in iron-treated rats could be due to the reduced Ga-67 plasma level as a result of enhanced urinary excretion.

We have assumed that the amount of Ga-67 present in GI contents is the amount of Ga-67 secreted into the GI tract. However, this assumption is valid only if there is no reabsorption of the secreted Ga-67. Taylor, et al. (*3*) have shown that there is practically no absorption of Ga-67 citrate by the GI tract. However, it is not clear whether the secreted Ga-67 is protein-bound and whether any of it is reabsorbed. Further study is required to clarify this point.

· FOOTNOTE

* Mallinckrodt Nuclear, St. Louis, MO.

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