Controlled Gastric Emptying. III. Gastric Residence Time of a Nondisintegrating Geometric Shape in Human Volunteers

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INTRODUCTION

The performance of controlled-release dosage forms can depend on the location of the dosage form within the gastrointestinal (GI) tract (1). The ability to retain a dosage form in a specific location of the GI tract, preferably the stomach, would provide constant exposure of the entire absorptive surface of the intestine to the drug being released, thereby optimizing conditions for maximal control of drug absorption (1).

In previous studies reported from this laboratory, a nondisintegrating geometric shape (2.0-cm open tetrahedron) was identified which reproducibly remained in the stomach of 11- to 15-kg beagle dogs for 24 hr (2). Additionally, potential erodible polymers were identified which indicated that it was feasible to construct such a device which would erode and exit the stomach within a desired time interval (3).

While a useful and commonly employed animal model for gastric residence studies, beagle dogs may represent a fairly narrow band in terms of subject size and body weight. To determine whether or not the tetrahedrons perform as desired in a more diverse population, gastric residence studies were conducted in larger dogs (American foxhounds) and in human volunteers. The results of these studies are reported here.

MATERIALS AND METHODS

Materials

Indium-111-oxine was obtained in a sterile, pyrogen-free saline solution from Amersham Corporation, Arlington Heights, Illinois. Preparation of ^{99m}Tc sulfur colloid was accomplished using a Mallinckrodt (St. Louis, Missouri) 99-molybedenum/99m-technetium generator and a Syncor sulfur colloid kit. Durelon dental adhesive was from Premier Dental Products, Norristown, Pennsylvania. Low-density polyethylene was obtained from Aldrich, Milwaukee, Wisconsin.

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Device Manufacture

Open tetrahedrons (2.0-cm arms) were fabricated from low-density polyethylene as described previously (2). The tetrahedrons were folded and placed in gelatin capsules immediately prior to dosing. The devices contained 15% BaSO4 to permit visualization by standard X-ray techniques in the stomach or GI tract of dogs. For external visualization in the human study, the devices were also labeled with ^{111}In for gamma scintigraphic localization. Since dental-grade adhesive adheres poorly to polyethylene, a narrow band of heat-shrink tubing was attached to each tetrahedron, and ^{111}In (in dental-grade adhesive) was applied to this band. *In vitro* studies indicated that there was no significant loss or leaching of the label from the adhesive over a 24-hr period in simulated gastric fluid. In order to prevent transit of the tetrahedron after gastric emptying, a single suture (ca. 65 cm) was tied to the device and threaded through a pinhole in the gelatin capsule (Fig. 1). After swallowing the device-containing capsule, the suture was attached to the cheek area of the subject for subsequent use in retrieving the device.

Dog Studies

American foxhounds (30–40 kg) were fasted for 18 hr prior to administration of the capsule containing the tetrahedron. Food was withheld for the duration of the experiment. Water was available throughout the course of the study. The device was loaded in a No. 000 gelatin capsule, and after dosing, each dog was administered 15–50 mL of water. An X-ray examination (CRG compact X-ray unit No. 726B951G) was performed immediately after administration to assure that the device was in the stomach. Gastric retention of the device was monitored by X-ray at various time intervals over a 24-hr period.

Human Volunteer Studies

Ten healthy male volunteers 18 to 35 years of age were selected for participation in this study. Volunteers were determined to be in good health and required to be from 5 ft 7 in. to 5 ft 11 in. tall and weigh 134–165 lb. An informed consent was obtained from the volunteers and the study was approved by the University of Kansas Medical Center Human Subjects Committee.

In both legs of this two-way crossover study, volunteers fasted (no food or liquid except water) from 10 PM the day preceding the study. In one leg. subjects continued the fast throughout the study (12-hr maximum). In the crossover leg, subjects received meals at −0.5, 4 and 10 hr relative to dosing. Meals were of a consistent nutritional content (Beyer Test Diet). Fixed fluid volumes (up to 100 mL) were given during each meal period and at regular intervals thereafter. A position finding marker was affixed to the subject's skin immediately over the xiphoid cartilage. The subject was placed in front of the gamma camera, aligning the xiphoid marker with a mark on the camera face. At 8 AM (t = 0 hr), the subject swallowed an ^{111}In-labeled and tethered tetrahedron, contained in a gelatin capsule, along with 200 mL of water containing ^{99m}Tc sulfur colloid as a gamma-emitting label.

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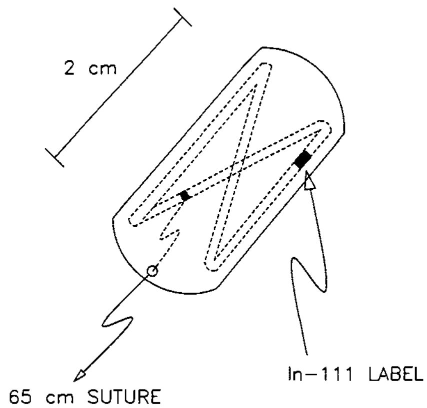

Fig. 1. Schematic of open tetrahedron compressed inside No. 000 hard gelatin capsule.

The tether was externally attached (taped to cheek area) to prevent passage of the device through the GI tract once it exited the stomach. The tether was also used to retrieve the device after the study period. Differential gamma scintigraphy was used in the anterior–posterior and lateral positions for localization of the device. Imaging of the ^{111}In device and the ^{99m}Tc sulfur colloid labeled water was intermittent for the first 15 min to define the stomach and to confirm the positioning of the tetrahedron in the stomach. Subsequent to the initial 15-min scan, additional scans were performed (with the xiphoid aligned) at least every 30 min for 12 hr or until the device exited the stomach. During the study, subjects were allowed to sit or move about at will, but were not permitted to assume a reclining position. Additional ^{99m}Tc sulfur colloid washes were administered, as needed, to redefine the stomach. When the tetrahedron exited the stomach, or at a maximum of 12 hr, the device was retrieved with the attached suture.

Gamma Scintigraphy

Two Siemens Pho-Gamma LFOV cameras were used for the imaging studies. Window settings were as follows: 247 keV, 15%, and 171 keV, 15%, for ^{111}In; and 140 keV, 20%, for ^{99m}Tc. The data were acquired and analyzed on a Medical Data systems computer (Ann Arbor, Michigan).

RESULTS AND DISCUSSION

Each of eight fasted dogs received the tetrahedron on one to four occasions. In some cases, studies were terminated due to difficulties in establishing the initial location of the tetrahedron as being in the stomach. A total of 24 measurements was recorded.

The results of these studies in larger dogs were distinctly different from those previously seen in beagle dogs (2,3), where greater than 90% retention in the stomach was seen at 24 hr. In 50% of the cases, the tetrahedron exited the stomach within 2 hr. In 79% of the cases, the devices exited the stomach in less than 8 hr. In only four experiments (17%) did the tetrahedron remain in the stomach for 24 hr. A clear reason for the discrepancy between beagles and the larger foxhounds is not readily apparent. An examination of the literature regarding the size of the pyloric opening did not provide definitive information. In general, most of the reports indicated pyloric openings of approximately 0.9–1.9 cm in humans and dogs (4–6), although any relation to body size was not reported. Comparative data on myoelectric activity and antral contractile forces in various breeds of dogs do not appear in the literature. Regardless of the mechanistic reason, the preliminary conclusion from the dog study was that the performance of the tetrahedron as a gastric retention device was apparently dependent on the breed (and possible size) of dog utilized in the study, and it was not known which breed more closely represented the performance of the device in man.

Direct determination of the gastric residence time of the tetrahedron in man was undertaken to clarify the questions raised in the previous dog studies. The individual results of the fed versus fasted two-way crossover in 10 volunteers are shown in Fig. 2. In only one subject (during the fed state) did the device remain in the stomach for the 12-hr duration of the experiment. In the fasting state, the gastric retention time was a median of 3 hr (range, 0.5 to 6.0 hr). The device was retained in the stomach for a longer time (median, 6.5 hr; range, 3.5 to >12.0 hr) in all subjects when they were given regular meals. These data confirm previously reported effects of food on inhibiting the "housekeeper contractile wave" and allowing prolonged gastric retention of nondigestible solids (7). Aside from confirming the retarding effect of food on gastric emptying of the tetrahedrons in human volunteers, the results of this study clearly show that there are distinct differences in gastric retention of nondigestible solids between beagle dogs and humans. The observation seen in the larger American foxhounds more closely resembles that seen in human volunteers. Sarna *et al.* (8,9) have reported similar gastric motility patterns in dogs and humans, which suggests that this activity may not be the causative agent in the observed differences in retention of the tetrahedron. Meyer *et al.* (10,11) have examined emptying of solid meals and found gastric emptying to be significantly slower in dogs than in humans. Therefore, even though myoelectric activity patterns appear qualitatively similar between dogs and humans, differences in solid emptying between dogs and humans have been previously observed. Some other factor(s) must be responsible for the differences

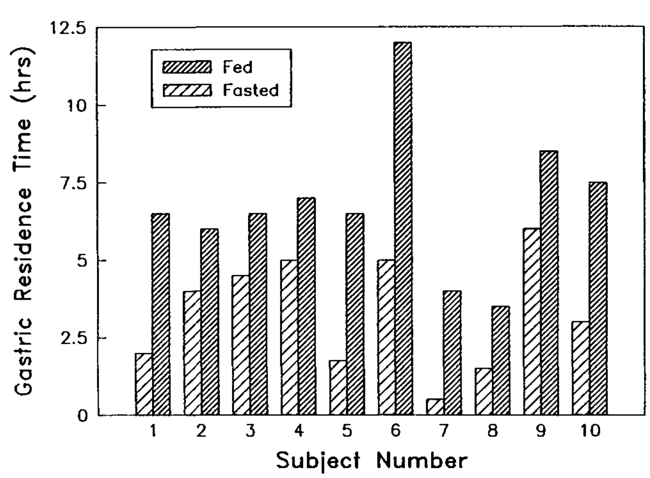

Fig. 2. Individual data for gastric residence time of open tetrahedron in human volunteers.

observed in retention of the tetrahedrons, but it is not known if this is the same factor(s) which influences gastric emptying of solid meals (e.g., study by Meyer *et al.*).

Numerous studies have been reported describing attempts to increase the gastric residence times of controlled-release dosage forms or gastric retention devices: flotation (12,13), swelling (14,15), inflation (16), and adhesion (17,18). In many cases, as in the initial studies performed in this laboratory (2,3), these studies were performed in dogs. The data reported here indicate that, while dog studies may be useful for relative screening of different gastric retention approaches, the results do not necessarily transfer successfully to man. At this point, it is not known what causes the difference in gastric retention of the tetrahedron in beagle dogs and man. Regardless of the cause, it is clear that the tetrahedron does not function similarly in beagle dogs and man.

The results of this study, together with those previously reported (2,3), lead to several conclusions. First, although the tetrahedron appears to function well in beagle dogs as a gastric retention device, this device does not perform well in larger dogs or man and does not appear to have utility in man in this regard. Second, there may be intrinsic differences in the efficiency of the "housekeeper wave" in dogs (especially beagles) and man which influence the gastric retention of undigestible solids. Third, the beagle dog model must be evaluated with certain reservations when extrapolating experimental gastric retention data to what could be expected in man. While dog studies are certainly useful in comparing relative approaches to increasing gastric residence times and identifying promising lead approaches, the ultimate answer on performance must still be determined in human studies.

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