Perfluorochemicals as Gastrointestinal Contrast Agents for MR Imaging: Preliminary Studies in Rats and Humans


The ability to distinguish bowel from other intraabdominal structures is essential for the accurate diagnosis of intraabdominal disease with MR. Because perfluorochemicals have no protons, they cause no MR signal. Since they are immiscible with water, they create a signal void in bowel independent of bowel contents and thus are suitable as oral contrast agents. Furthermore, they are tasteless and odorless and have no side effects. We evaluated the use of perfluorochemicals by performing MR scans of the abdomen in rats after the oral administration of unemulsified perfluorohexylbromide or perfluorocetyl bromide. Since the latter is approved as an investigational drug for oral use in humans, two volunteers were also studied.

Both compounds created signal void in the bowel of both rats and human subjects allowing identification of the gastrointestinal tract. The results suggest that these compounds have potential as oral contrast agents for MR imaging.

Paramagnetic solutions are the only oral contrast agents so far described for use in MR imaging [1, 2]. When used to identify bowel they have several shortcomings, the most important of which is the dependence of signal intensity on concentration. Since they are water soluble, their concentration in the bowel, and therefore their resultant signal intensity, depends on bowel content. Furthermore since the MR signal is increased by these agents, it is possible to confuse bowel with other structures. We therefore sought an agent that decreases signal from the bowel lumen on both T1- and T2-weighted images and that is independent of bowel content.

Perfluorochemicals (PFC) are organic compounds in which hydrogen atoms have been replaced by fluorine. Perfluorohexylbromide (PFHB) (C₆F₁₃Br) and perfluorocetyl bromide (PFOB) (C₆F₁₇Br), compounds that are radiopaque because of the bromine, have been used as experimental radiographic oral contrast agents in animals [3, 4] and humans (Long DM, unpublished data). Unemulsified PFCs have potential as MR gastrointestinal contrast agents for the following reasons: (1) Lacking hydrogen, these compounds cause no MR signal. Therefore, like air, they create a signal void on both T1- and T2-weighted images. (2) Being immiscible with water and having high mass density (1.9 g/ml), PFCs layer out in water. Therefore, the signal void produced would be independent of bowel content. (3) These compounds have rapid transit through the bowel because of their low surface tension [4]. (4) They are tasteless and odorless, and have no side effects [3, 4].

Consequently, we performed studies in rats and man to evaluate PFCs as gastrointestinal contrast agents for use in clinical MR imaging.

Materials and Methods

Animal Study

We evaluated the effect of dose (13 or 16 ml/kg) and method of administration (single or double bolus) on the extent and degree of filling of the gastrointestinal tract as seen on MR
scans performed before and after giving PFHB or PFOB. Fifteen rats weighing approximately 300 g were sedated with ketamine (30 mg) and acepromazine (0.6 mg), and MR images of the abdomen were obtained. When the animals fully recovered (2-3 hr), they were resedated with ether, a nasogastric tube was placed in the stomach, and PFC was administered. Because of its ultra-short action (1-2 min), ether was used to minimize the anesthesia effect on gastrointestinal motility.

One rat was given 13 ml/kg and another rat was given 16 ml/kg PFHB as a single bolus 15 min before rescanning. Two rats were given 13 ml/kg, and another two rats were given 16 ml/kg PFHB as a single bolus 30 min before rescanning. As controls, two animals were given nothing.

Two rats were given a total volume of 13 ml/kg and another three rats were given 16 ml/kg PFOB. The total dose was divided into two equal boluses, given 30 and 15 min before rescanning. Since these five rats required two ether sedations, two additional controls were included.

MR scans were performed by using the head coil on a GE 1.5-T Signa system. Spin-echo sequence TR = 2 sec and TE = 25 and 50 msec were used with a 256 x 256 matrix, 5-mm scan thickness, and 20-cm field of view.

Immediately after the second MR study, the rats were sacrificed with IV pentobarbital, and an abdominal radiograph was obtained. The degree and extent of bowel filling were subjectively evaluated on the MR images and correlated with the radiograph to ensure that the signal void produced was due to PFC and not air.

**Human Study**

Since PFOB is approved for oral use as an investigational drug, two volunteers were studied after appropriate consent. After control MR scans of the abdomen were made, they were given 7 ml/kg (approximately 500 ml) of PFOB orally. The first volunteer was given a bolus of 5 ml/kg at 30 min and a second bolus of 2 ml/kg 5 min before another MR scan. The second volunteer slowly drank 5 ml/kg from 30 to 15 min before scan time followed by a 2 ml/kg bolus 10 min later.

Imaging was performed in the coronal plane with a partial-saturation sequence TR = 600 msec and TE = 25 msec, followed by an axial spin-echo series with TR = 2 sec and TE = 20 and 70 msec. The scans obtained before and after PFOB ingestion were subjectively compared by two observers for bowel recognition and ability to delineate the margin of normal structures such as the pancreas.

To assess safety at this dose level, we obtained hematocrit, RBC count, WBC count, platelet count, liver function tests, and measurements of blood glucose, blood urea nitrogen, creatinine, sodium, and potassium before and two days after PFOB ingestion. All symptoms experienced by the two volunteers acutely and during the next 48 hr were recorded.

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**Fig. 1.—Coronal MR image of the abdomen in a rat.**

A, Before administration of contrast material (TR = 2000, TE = 20 msec), intestinal lumen (arrows) has intermediate signal intensity similar to that of liver (L), and is outlined by high-signal mesenteric fat.

B and C, Coronal images (TR = 2000, TE = 20 msec in B; TR = 2000, TE = 70 msec in C) made 30 min after an oral bolus of 16 ml/kg (5 ml total volume) of perfluorohexylobromide. Signal void in intestinal lumen (arrows) clearly delineates bowel. L = liver.

D, Anteroposterior radiograph shows radiopaque perfluorohexylobromide in distribution seen on MR. Note that a minimal amount of perfluorohexylobromide remains in the stomach (arrow).
Results

Animal Study

No change in bowel signal was observed when the observers compared the two MR scans obtained before and after sham contrast administration in the four control animals studied. In all animals, on both T1- and T2-weighted images, PFOB and PFHB produced signal void in the bowel lumen that was indistinguishable from air. Six of the seven rats given PFC 15 min before scan time, either a single or double dose, had a significant amount of PFC in the stomach. However, 15 min after PFC ingestion, the two rats given 13 or 16 ml/kg as a single dose showed incomplete bowel filling. The single dose given 30 min rather than 15 min before the scan showed more complete bowel filling. However, an insignificant amount of contrast material remained in the stomach. With the single bolus, 16 ml/kg produced more complete filling and distension than 13 ml/kg. The MR scan of one of the two rats given 16 ml/kg 30 min before the scan is shown in Figure 1. The most complete bowel filling, including the stomach, was achieved when PFC was given in two doses of 8 ml/kg each. A typical scan of a rat given 16 ml/kg (5 ml total volume) of PFOB in two doses, 2.5 ml 30 min and 2.5 ml 15 min before scanning, is shown in Figure 2.

Human Study

The first volunteer was given 525 ml of PFOB in two boluses and had no PFOB in the stomach on a scan done 5 min after the second bolus. However, complete filling of the small bowel was achieved. The second volunteer was given a total volume of 504 ml, 370 ml taken gradually over 15 min and 134 ml as a bolus 5 min before the scan, and had a significant amount of PFOB in the stomach and distal small bowel, but little or no PFOB in the proximal small bowel.

In the stomach PFOB allowed the recognition of the gastric wall (Fig. 3). The pancreatic margin, which appeared nodular on pre-PFOB scans, was smooth and well defined after PFOB because of the filling of the gastric antrum and duodenum (Fig. 4). Bowel in the midabdomen (Fig. 5) and pelvis (Fig. 6) was dark on both T1- and T2-weighted images and was easily recognized after PFOB. Bowel motility contributed to the poorly defined bowel margin. The laboratory studies were normal in both volunteers. One subject had an oily sensation in the mouth. Neither volunteer had any gastrointestinal symptoms. PFOB was excreted in liquid form in the stool within 18 hr after ingestion.

Fig. 2.—Axial MR images of a rat at level of left kidney (k) (TR = 2000 msec, TE = 20 msec). A, Preperfluoroctylbromide image shows bowel as intermediate signal (arrow). Black areas represent gas-filled loops (arrowheads). B, After perfluoroctylbromide given 8 ml/kg at 15 and 8 ml/kg 30 min before scan (5 ml total volume), bowel is filled with signal void (arrows).

Fig. 3.—Axial images in a volunteer (TR = 2000, TE = 20 msec). Before (A) and after (B) ingestion of perfluoroctylbromide. Note signal void in gastric fundus and clear visualization of gastric wall (arrow) in B. White signal outlining outer margin of gastric wall (arrowheads) is produced by retroperitoneal fat on these relatively T1-weighted images.
Fig. 4.—Axial images at level of pancreatic head in same volunteer as that in Fig. 3 (TR = 2000, TE = 20 msec).

A, Before perfluorocetylbrromide, anterior margin of pancreas appears nodular and indistinct (arrows).

B, After perfluorocetylbrromide, signal void is present in gastric antrum and duodenum showing pancreas to be normal (arrows).

Fig. 5.—Axial A, B, scans of volunteer at level of aortic bifurcation (TR = 2000, TE = 20 in A; TR = 2000, TE = 70 in B) obtained before perfluorocetylbrromide show bowel as intermediate signal (arrows). Air-filled bowel is dark (arrowhead) and water-filled bowel is bright on long-TE image (B) (curved arrows).

C, D, (TR = 2000, TE = 20 in C, TR = 2000, TE = 70 in D) obtained after ingestion of 525 ml perfluorocetylbrromide, signal void fills bowel (arrows) on both T1-weighted (C) and T2-weighted (D) images, indistinguishable from air (arrowhead).

Fig. 6.—Axial image obtained at level of pelvis of same volunteer as that in Fig. 3 after ingestion of 500 ml of perfluorocetylbrromide. Signal void is present in small bowel (arrows).
Discussion

The results of these studies in rats and in man suggest that PFCs have potential for use as oral MR contrast agents. Lacking hydrogen, they produced a signal void in the bowel lumen. The decrease in signal intensity caused by PFC is more advantageous than the increase in signal produced by paramagnetic solutions, since bowel can be better distinguished from adjacent normal or diseased structures. More importantly, PFCs darken the bowel lumen on T2-weighted images, while paramagnetic solutions at concentrations below peak enhancement have little effect on T2 [1, 2]. Recently, magnetite has been shown to decrease signal in the stomach and bowel on both T1- and T2-weighted images owing to T2 shortening [5]. Paramagnetic solutions increase signal in the stomach and duodenum, but because of dilution this effect is lost as the solutions traverse the bowel [1]. Since magnetite is administered as a suspension of magnetite albumin, it would be expected that its concentration would vary with bowel content, possibly affecting the resultant signal. PFC in rats and PFOB in man produced signal void from stomach to colon because PFCs are immiscible in water. Therefore, their effect on the MR signal is independent of bowel content.

The faster transit time of PFC as compared with Hypaque (Winthrop-Breon, New York, NY) or barium [4] permitted almost complete filling of the small bowel in the two volunteers studied within 30 min. For CT with Hypaque, 90 min are required to opacify the bowel. The optimal human dose of PFC has not yet been established. While 1000 to 1500 ml of Hypaque solution are customarily used for CT, 500 ml of PFOB produced significant small-bowel filling. Smaller volumes of PFC may be sufficient for MR imaging.

PFOB is inert and nontoxic [3, 4, 6, 7]. Greater than 95% of the oral dose is excreted through the gastrointestinal tract within 24 hr [3]. In dogs given 32 g/kg (16 ml/kg) orally, absorption occurs yielding a detectable level of PFOB in the plasma, liver, spleen, and fat [6, 7]. The highest plasma level reported is 0.8 μg/ml. PFOB plasma levels decreased with a 1-day half-life [6]. Fat showed the highest PFOB concentration (20 μg/g). PFOB concentration in fat decreased with a 9.8-day half-life [6, 7]. Similar tissue distribution patterns were observed when PFHB was administered to dogs at a dose of 16 ml/kg. However, the absorbed PFHB was eliminated with a much shorter half-life (hours) than PFOB (days) because of its higher vapor pressure [7].

When PFOB or PFHB were given orally to dogs and rats at 16 ml/kg (32 g/kg), there was no detectable hematologic, hepatic, or renal toxicity [4]. No LD₉₀ could be determined since volumes in excess of 64 ml/kg (124 g/kg), which had no mortality, were lost through the rectum [3, 4].

PFOB has been given orally as a radiographic contrast material to approximately 30 human subjects at a dose of 2 to 6.7 ml/kg (Long DM, unpublished data). Extensive laboratory tests obtained before and at various time intervals after administration showed no change. Minor complaints of an oily sensation in the mouth were reported by one of the 30 subjects. PFHB is not yet available for human use. In this study, one of the two patients complained of the oily sensation. Neither subject had any adverse effects.

REFERENCES