Perfluorooctylbromide as a Contrast Agent for CT and Sonography: Preliminary Clinical Results

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OBJECTIVE. Perflubron emulsion is a bromine-based particulate contrast agent that is taken up selectively by the liver and spleen after IV injection. It does not leave the vascular space and also persists in the blood for a longer period than iodinated contrast agents do. We performed a preliminary study to determine the value of the IV perflubron emulsion as a contrast material for CT and sonography.

SUBJECTS AND METHODS. To determine the safety and dose response of perflubron emulsion as an IV contrast agent for CT and sonography, 18 cancer patients, 14 of whom had hepatic metastases, were given 0.5–3.0 ml/kg of the emulsion. Sonography and CT of the liver and spleen were performed before and immediately after infusion and then again at 24 hr.

RESULTS. A persistent increase in the density of blood, liver, and spleen was observed, where maximal enhancements of 55, 39, and 317 H, respectively, were achieved. Tumor conspicuity increased as metastases enhanced minimally (7 H or less). Peak enhancement of the liver and spleen was delayed to 24 hr with higher doses of perflubron; however, the immediate postinfusion scan allowed the distinction of vessels from hepatic lesions. Sonographically, an increase in tumor echogenicity relative to liver was observed in nine of the 14 subjects, allowing the detection of additional metastases in two. Splenic echogenicity in the near field increased relative to kidney; however, attenuation increased markedly at the time of peak concentration, limiting beam penetration. Similar but milder changes were observed in the liver. Adverse effects occurred in 14 of the subjects; these included lower back pain in six, delayed fever in eight, and malaise in three.

CONCLUSION. Perflubron emulsion produced prolonged enhancement of blood, liver, and spleen and increased the conspicuity of liver metastases. However, the side effects encountered could limit its use to a selected population of patients.

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The limitations of water-soluble contrast-enhanced CT in the detection of hepatic metastases are well recognized [1, 2]. CT portography has emerged as the new gold standard for detection of hepatic lesions [3, 4]; however, this technique has limitations [5, 6], is invasive, and does not serve as a screening tool. A number of hepatotropic contrast agents are being developed to improve the accuracy of detecting focal hepatic lesions with CT. These include ethiodol oil emulsion (EOE)-13, perflubron emulsion (perflubron is the new generic name assigned to perfluorooctylbromide), liposomes containing water-soluble iodinated contrast agents, and polyiodinated triglycerides [7–12]. EOE-13 has been studied extensively in clinical trials, but has not been made available commercially. Polyiodinated triglycerides and liposomes are currently being studied in animals.

Perflubron is a brominated fluorocarbon that is radiopaque. When emulsified with egg-yolk phospholipids, perflubron is stable and injectable IV. The pharmacokinetics and potential applications of this agent in diagnostic imaging have been recently reviewed in detail [13, 14]. Unlike water-soluble contrast media, the emulsion does not diffuse into the interstitial space, is not filtered by the kidneys,

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and produces prolonged blood-pool enhancement [10]. It is the ability to uniquely enhance the blood pool that distinguishes this agent from other agents that only enhance the liver and spleen [14, 15]. The emulsion particles are slowly taken up by the liver and spleen, enhancing these organs [10]. Tissue enhancement on CT after infusion of perflubron emulsion was observed in cancer patients where blood opacification and prolonged liver and spleen enhancement reportedly were shown [16]. Although animal testing of perflubron emulsion had not shown any adverse effects at the expected clinical doses [13], lower back pain and fever were detected in five of 30 human subjects [16].

We report the results of a preliminary clinical study with perflubron emulsion, the aim of which was to determine the tolerance and the dose response in cancer patients when imaging the vascular space, the liver, and the spleen with CT and sonography.

Subjects and Methods

Cancer patients with histologically proved malignant tumors and distant spread were included in the study. Subjects with severe cardiac, renal, hepatic, or pulmonary insufficiency were excluded. Informed consent was obtained in accordance with the regulations of the hospital's ethics committee. Patients were admitted to the hospital and stayed for 24 hr after the end of infusion. Blood was taken for hematologic and biochemical analysis before, 24 hr after, and 7 days after administration of perflubron. The analysis included a blood cell count including differential leukocyte, platelet, and reticulocyte counts; prothrombin and partial thromboplastin times; and liver function tests, which included SGOT, LDH, γ-glutamyl transferase, bilirubin, and alkaline phosphatase; and measurement of electrolytes, blood urea, creatinine, cholesterol, calcium, phosphate, and uric acid. Vital signs were recorded during the infusion and for 12 hr after the end of infusion. Acute and delayed symptoms were elicited by direct questioning at the time of the 24-hr and 7-day follow-ups.

Eighteen patients, including 14 men and four women 20–79 years old, were enrolled in the study. Fourteen had hepatic metastases. The primary tumors were colorectal (13 patients); lung (two patients); and breast, stomach, and lymphoma (one patient each).

Perflubron emulsion was supplied by Fluoromed Pharmaceuticals, which has since become part of Alliance Pharmaceuticals Corp. (San Diego, CA), as a 100% w/v emulsion (1.0 ml contains 1.0 g of perflubron). The agent was infused at 3.0 ml/min. The total volume infused ranged from 30 to 200 ml and the infusion lasted from 10 to 90 min. The starting dose was 0.5 g (ml)/kg, increasing by 0.5 g (ml)/kg increments for each three consecutive subjects until a maximum dose of 3.0 g (ml)/kg was reached. Two batches were used, one for the first six subjects and the second for the remainder.

CT scans of the liver were obtained immediately before, immediately after, and 24 hr after the infusion. Scans were obtained in contiguous 8-mm sections through the liver and spleen. They were obtained on a Siemens Somatom DRH scanner by using the available 96 kV rather than the 125 kV because bromine has a lower K edge than iodine does. Oral contrast medium was not used to better assess tissue enhancement and decrease the likelihood of streak artifacts from the stomach.

CT numbers in Hounsfield units of liver, liver metastases, spleen, and aorta were measured at the same anatomic levels on the three scans obtained before and at two intervals after infusion to ensure comparability. Because the presence of the contrast medium in the vascular space and in the liver and spleen could be readily identified on the CT scans, blinded comparison of scans was not feasible. The unenhanced and enhanced scans were compared subjectively to assess the visual enhancement of the liver parenchyma and intrahepatic vessels and the number, size, and conspicuity of the metastases seen on sections at comparable levels. This was done by three radiologists independently, and then a final consensus was reached. No comparative studies were performed with IV iodinated contrast media.

Sonography of the liver and spleen was performed with a Toshiba SSA-90A unit equipped with a 3.75-MHz phased-array transducer. The sonograms were obtained immediately after the CT scans. A postprocessing technique was used to emphasize differences in low-level echoes. Care was taken to obtain sonographic sections in the same plane at each examination by using the same gain settings. The sonograms were subjectively evaluated by three reviewers independently and a consensus reached thereafter. The following variables were assessed: hepatic and splenic echogenicity in comparison with the adjacent kidney, hepatic and splenic attenuation, and the echogenicity of the center and rim of two separate hepatic tumors compared with normal adjacent liver.

In one subject given a 3.0 g/kg infusion, the change in tissue enhancement on CT could not be ascertained because significant streak artifacts affected the baseline values. This subject was excluded from the analysis.

Results

CT

Vascular enhancement was consistently achieved at doses greater than 1.5 g/kg (Fig. 1). A typical example at 3.0 g/kg is shown in Figure 2. At lower doses, vascular enhancement was minimal in three of nine subjects. Blood enhancement returned to baseline level at 24 hr in all but two subjects given the higher doses. Enhancement of the liver and spleen was observed immediately after administration of the perflubron emulsion in all subjects (Fig. 1), except for one patient with extensive hepatic metastases and moderate hepatic insufficiency who was given 1.5 g/kg. Peak enhancement of the liver occurred immediately after infusion at doses of 0.5–1.5 g/kg and at 24 hr at the higher doses. Peak splenic enhancement was considerably greater than liver enhancement at comparable dose levels (Fig. 1) and occurred immediately after infusion at doses less than 2.0 g/kg and 24 hr after infusion at doses of 2.5 and 3.0 g/kg.

Because tumor enhancement was minimal, it could not be detected subjectively. Measurement of tumor density showed that tumor enhancement never exceeded 7 H on the immediate postinfusion scan. Liver-to-tumor and blood-to-tumor contrast increased appreciably after infusion (Figs. 3 and 4). Although contrast between liver and metastases increased further at 24 hr at doses greater than 1.5 g/kg, the persistent and marked increase in blood-to-tumor contrast increased tumor conspicuity on the immediate rather than the delayed scan in all but one case (Fig. 4). Of the 14 patients with intrahepatic metastases, visualization of tumors was significantly improved in eight cases; in five of these cases, additional tumors not seen on the unenhanced scan were found. In no case was visualization of tumors impaired after perflubron emulsion. The most dramatic improvement in tumor visualization was achieved when tumors were isodense with liver before contrast administration or when tumors were located close to the dome of the

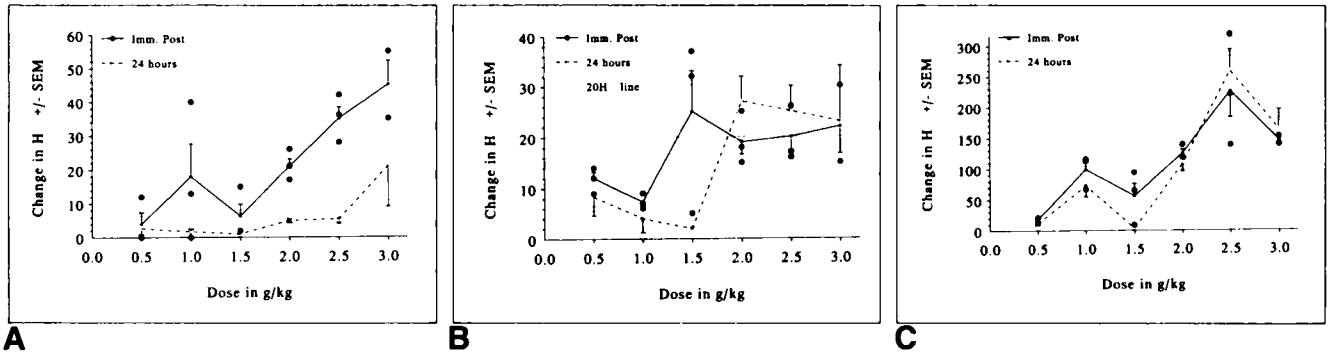

Fig. 1.—CT number (mean ± SEM) of aorta, liver, and spleen relative to baseline for each subject as a function of perflubron dose and time after infusion. Note that at 24 hr, one subject is in the 1.5 g/kg group and two subjects are in the 3 g/kg group. Imm. Post = immediately postinfusion.

***A*, Enhancement of aorta was significant at both time points after infusion of 2.0 and 2.5 g/kg doses. Clear dose response is seen after infusion of 1.0 g/kg emulsion.**

***B*, Enhancement of liver is significant immediately after infusion of 0.5, 1.0, 2.0, and 2.5 g/kg doses and at 24 hr after infusion of 2.0 and 2.5 g/kg doses.**

***C*, Enhancement of spleen is significant immediately after infusion of 0.5, 1.0, 2.0, 2.5, and 3.0 g/kg doses and at 24 hr after infusion of 0.5, 2.0, and 2.5 g/kg.**

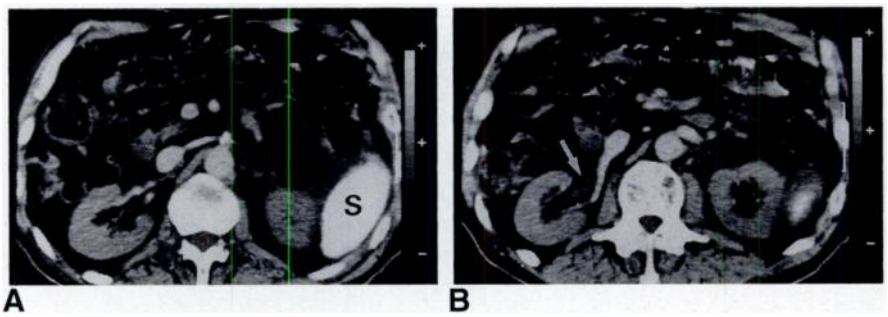

Fig. 2.—*A* and *B*, CT scans obtained at level of left (*A*) and right (*B*) renal veins 1 hr after infusion of 3.0 g/kg dose of perflubron. Blood enhanced by 55 H in this subject, allowing aorta, inferior vena cava, renal veins, and mesenteric vessels to become clearly visible. Water density of renal pelvis (*arrow, B*), indicates absence of urinary excretion. S = spleen.

diaphragm or the inferior angle of the liver, where CT findings are at times compromised (Fig. 5). Tumor rim enhancement was mild and was detected in two of the 14 subjects (Figs. 4 and 5).

Sonography

The effect of perflubron emulsion on sonograms of the liver, spleen, and tumor was dependent on the dose given and the time delay between infusion and imaging. Alterations in tumor echogenicity relative to liver were observed in 10 of the 14 subjects with hepatic metastases. The degree of echogenic enhancement of tumors relative to liver was marked in one subject, moderate in two, and mild in seven. Tumor echogenicity diminished relative to liver in one subject. The nine subjects with increased tumor echogenicity had the lower doses, and the subject with the most dramatic increase (Fig. 6) was given 0.5 g/kg (30-ml total dose). The degree of change in tumor echogenicity was greater shortly after infusion in six subjects and after 24 hr in three subjects. Diffuse tumor enhancement occurred in six subjects. Although enhancement of the tumor rim was observed in one subject, tumors in three subjects increased in echogenicity from the center, leaving a hypoechoic rim, thus producing a "target" lesion (Fig. 7). Tumors not seen on the unenhanced examination became visible after contrast administration in two subjects, one who was given 0.5 g/kg and the other who received 1.0 g/kg.

Liver echogenicity relative to kidney was not affected in most cases. Echogenicity increased mainly in the near field in six patients, one who was given 1.5 g/kg and the other five who received either given 2.5 or 3.0 g/kg. Echogenicity

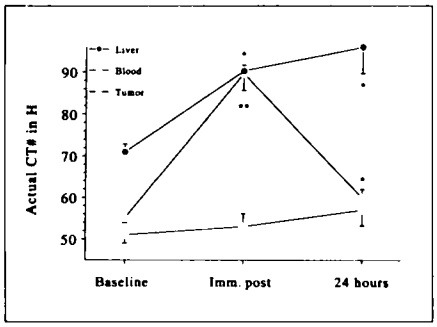

Fig. 3.—Mean ± SEM of actual CT numbers of liver, aorta, and tumor for group given 2.5 g/kg dose of perflubron. Liver density increased significantly relative to tumor after contrast administration. Liver values measured immediately after infusion (Imm. post) were not significantly different from those measured after 24 hr. More importantly, blood, which was not statistically different from tumor at baseline, enhanced markedly to become isodense with liver shortly after infusion. Blood returned to near baseline density at 24 hr, while tumor density remained at baseline values at both time points. * = $p < .05$; ** = $p < .01$ relative to baseline values.

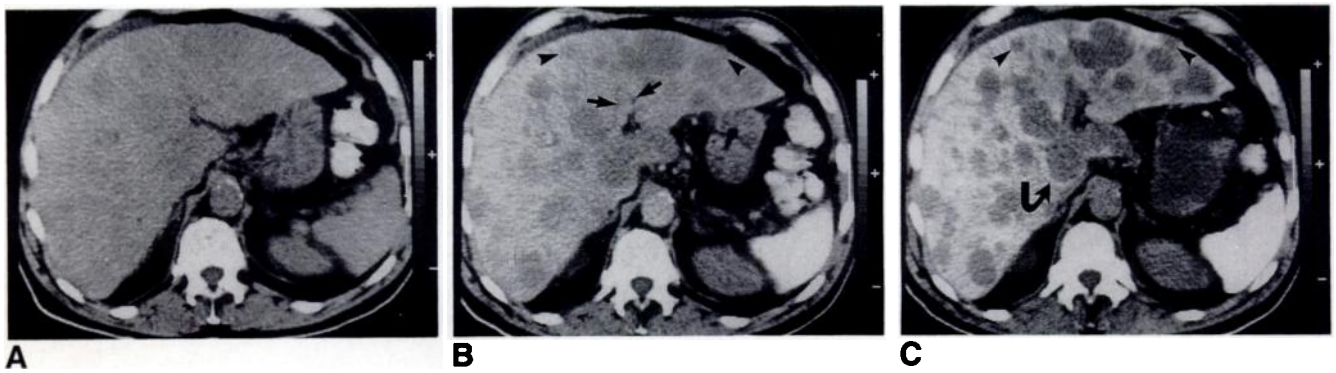

Fig. 4.—*A–C*, CT scans of liver before (*A*), immediately after (*B*), and 24 hr after (*C*) infusion of 2.5 g/kg of perflubron at the same window levels in a subject in whom liver metastases were better seen after 24 hr. Aorta and portal vein enhance on immediate scan (*arrows*, *B*). Small tumors too peripheral to be mistaken for veins are seen on early scan (*arrowheads*, *B*), but are better seen 24 hr later (*arrowheads*, *C*). Faint rim of enhancement is seen on 24-hr scan (*arrow*, *C*).

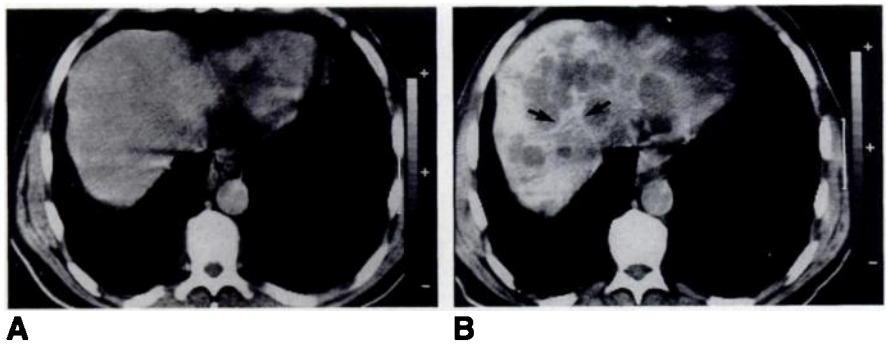

Fig. 5.—Hepatic metastases in same subject as in Fig. 4.
A, Metastases are not visible on unenhanced scan (*A*) because of artifacts from surrounding lung.
B, Lesions are better seen after 24 hr because of increase in liver-to-tumor contrast. Note rim enhancement of tumor (*arrows*).

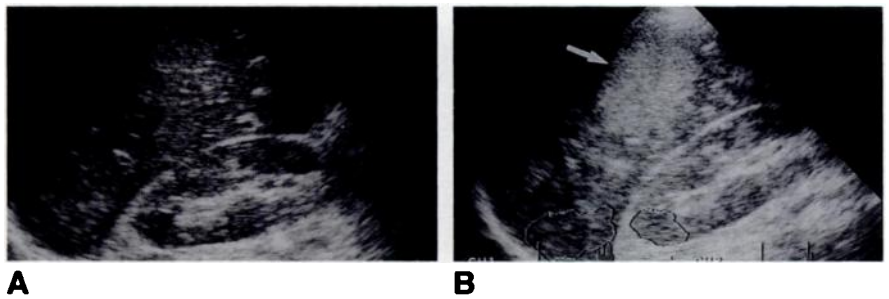

Fig. 6.—*A*, Unenhanced right anterior oblique sonogram of liver and right kidney shows a barely perceptible liver metastasis.
B, Marked enhancement of liver lesion (*arrow*) is detected on sonogram obtained immediately after infusion of 0.5 g/kg (30-ml total dose) of perflubron emulsion.

decreased in one subject who was given 1.5 g/kg. Liver attenuation gradually increased with dose. However, in only two subjects, one who was given 2.5 g/kg and the other who received 3.0 g/kg, was penetration into the far field impaired at 24 hr, which was the time of peak hepatic concentration as determined by CT (Fig. 8).

Echogenicity of the spleen relative to that of the kidney increased at doses greater than 1.0 g/kg. The predominant effect of perflubron on the spleen was a marked increase in attenuation, which prevented the penetration of the beam into the organ at the time of peak concentration. The spleen assumed an appearance similar to a gas-filled viscus. When perflubron concentration in the spleen decreased after 24 hr, as observed on CT after 2.0 g/kg or less, attenuation also diminished, allowing adequate penetration and assessment of the far field.

Side Effects

Side effects were observed in 14 (78%) of 18 subjects and were transient and self-limited. Fever (0.6°C rise above baseline) occurred in eight patients (44%) and reached a maximum of 39.5°C. It began 1 hr after infusion in two cases and 6–13 hr after infusion in the remainder; fever duration ranged from 3 to 12 hr. Two of the three subjects who had fever and malaise for up to 24 hr opted out of the study. The malaise and fever were described as "flulike," and variably included weakness, insomnia, unsteadiness, lightheadedness, facial flushing, and anorexia. One patient had hypotension, drowsiness, and tachycardia 7 hr after infusion. These symptoms responded rapidly to hydrocortisone. This patient had extensive metastatic infiltration of the liver and jaundice, which may have been contributory factors.

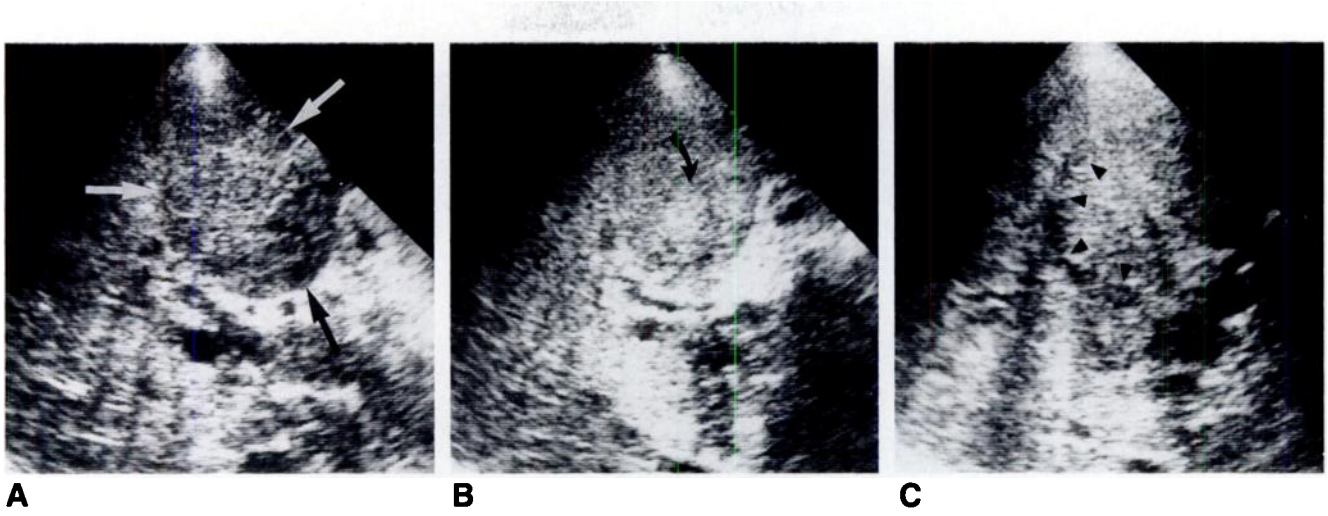

Fig. 7.—*A*, Longitudinal sonogram obtained at level of portal vein before contrast administration shows a large hypoechoic lesion (*arrows*). *B*, Center of lesion is more echogenic on sonogram obtained immediately after infusion (*arrow*). *C*, Echogenic central focus grew in the next 24 hr, leaving a hypoechoic rim (*arrowheads*) and giving lesion a targetlike appearance.

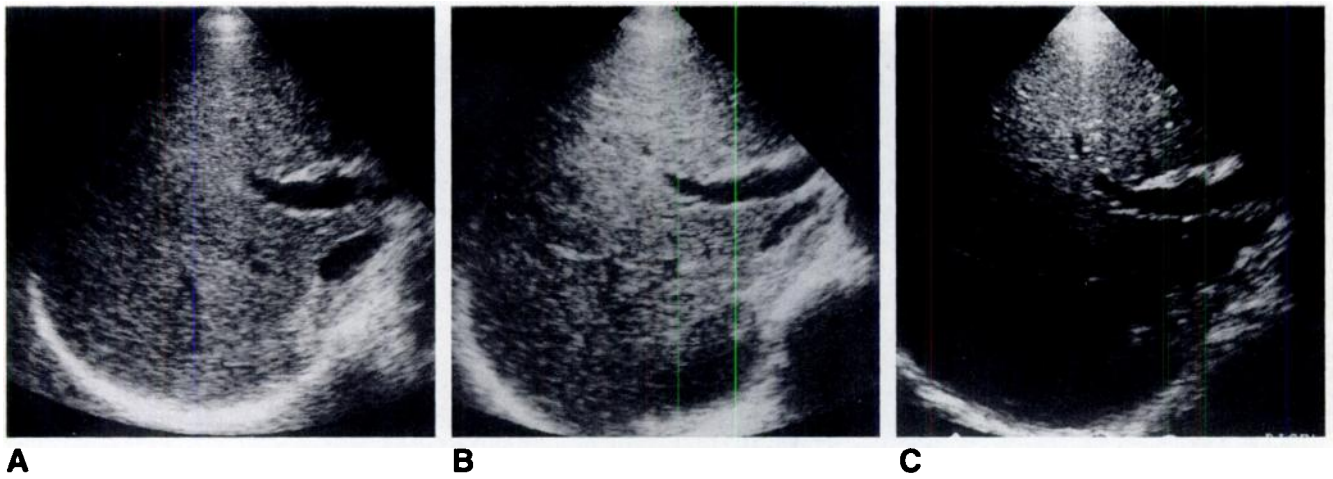

Fig. 8.—*A–C*, Transverse sonograms of liver at level of portal vein obtained at baseline (*A*), shortly after infusion of 3 g/kg perflubron emulsion (*B*), and 24 hr later (*C*) in one of two subjects who had a significant increase in liver attenuation. Although attenuation effects were minimal shortly after infusion, they became more pronounced 24 hr later.

Localized pain was reported in the lumbosacral area (five subjects), sternum (two subjects), and thighs (one subject). The pain started 10–15 min after the infusion began, lasted about 10 min, was not affected by discontinuing the infusion, and was not dose related.

The hematologic and biochemical indexes were not affected by the contrast agent, with the exception of a statistically significant but clinically insignificant decrease in the eosinophil count on the first day after injection ($p = .05$, Wilcoxon rank text). No appreciable difference in side effects was noted between the two batches used.

Discussion

Conservative estimates of the sensitivity of unenhanced CT and bolus-enhanced dynamic CT scanning for detection of liver metastases are 50% and 72.5%, respectively [2, 9]. CT portography, now regarded as the gold standard, has a detection rate of approximately 90% [17] but is invasive, has limitations [5, 6], does not allow adequate assessment of the spleen, and combines the side effects of both angiography and iodinated contrast administration. EOE-13, an emulsion of Lipiodol, has been shown in human trials to increase the sensitivity of hepatic CT scanning for focal lesions to 93%, if lesions less than 1 cm in diameter are excluded [9]. In patients with splenic lymphoma who were given EOE-13, the detection rate increased from 8% before enhancement to 83% after enhancement [8]. The results in the liver were inferior for lesions less than 0.5 cm in diameter, probably because of confusion with small venous radicles, which are not enhanced by EOE-13. These findings provided the impetus to search for a hepatotropic contrast agent with vascular enhancement. In a direct comparison between EOE-13 and perflubron emulsion that used implanted Vx2 tumors in rabbits, perflubron produced superior liver-to-tumor contrast and positive enhancement of veins. Because vascular

enhancement and tumor rim enhancement did not occur with EOE-13, perflubron emulsion was considered a superior contrast agent in the demonstration of hepatic tumors [15].

It has been suggested that a 20-H liver-to-tumor difference would be required to detect a 1-cm lesion with confidence [2]. In the present study, this degree of enhancement was achieved in eight of the 18 subjects. At 2.5 and 3.0 g/kg infused at 3.0 ml/min and imaged at 96 kV, the liver enhanced by 20–25 H and the blood by 40 H. Because 120–130 kV is typically used in most CT scanners, the degree of enhancement should be less if standard exposures are used. However, Bruneton et al. [16], who followed a CT protocol and infusion rate similar to those used in this study, reported a comparable degree of enhancement at 2.5–3.0 g/kg when the higher kilovoltage was used. Our study supports the conclusion by Bruneton et al. that at an infusion rate of 3.0 ml/min, 2.5–3.0 g/kg of perflubron may be sufficient to image the liver satisfactorily.

Even at the slow infusion rate of 3.0 ml/min and the long infusion time lasting an average of 1 hr, the study shows the potential value of this agent in the examination of blood vessels. Blood-pool enhancement was consistently observed at the higher doses (Fig. 1A). It remained noticeably above baseline 24 hr later in only two subjects at the high doses. It is suspected that the blood half-life in human subjects is shorter than the 8 hr determined in rats [13] because an appreciable decrease in aortic density was noted during the 12–15 min period of CT scanning. This may be in part due to the slow infusion rate used in this study.

The CT scan obtained immediately after infusion combines blood-pool and Kupffer cell enhancement and appears to be the optimal time to scan the liver with this agent. Delayed scanning can be done in cases of diagnostic difficulty. Most patients in this series had colorectal carcinoma, a typically hypovascular tumor, and none had a typically hypervascular tumor. It remains to be seen whether such metastases would retain this low degree of enhancement shortly after infusion. Adequate splenic enhancement was achieved at a dose of 1.0 g/kg or greater. The advantage of specific splenic tissue enhancement for the detection of intrasplenic lymphoma has been described with EOE-13 [8].

The emulsion particles, when made stationary in tumors, liver, and spleen, increase scattering of the ultrasound beam. Although this increases the backscatter to effect greater echogenicity, it also increases beam attenuation. The increased attenuation was most noticeable in the liver after 24 hr in two of the six subjects given 2.5 and 3.0 g/kg and in the spleen immediately after infusion in most subjects. These time points correlated with peak tissue enhancement as observed by CT and therefore with peak concentration. These observations are in direct agreement with those of Taylor et al. [18], who reported that the increase in the fat content of the liver had a more direct effect on liver attenuation than on echogenicity. Although attenuation may be directly related to tissue concentration of perflubron, tissue echogenicity is more complex. Perflubron in the same subject had an opposite effect on sonography and CT. Although the tumor became more echogenic than did the liver on sonography, the liver became brighter than tumor on CT, indicating its greater perflubron content. As it is known that perflubron accumulates in tumor macrophages [19], the discrepancy between CT and sonography is most likely due to the more optimally spaced macrophages in the tumor than to the Kupffer cells in the liver, collectively offering more effective and more numerous interfaces.

Because tumor enhancement relative to liver was better seen at lower doses (<2.5 g/kg), this study suggests that hepatic sonography for tumor detection may be most optimal at doses less than 2.5 g/kg. In all but two cases in this series, the metastases were echogenic and were well seen before contrast material was infused. As the predominant effect of perflubron was to increase tumor echogenicity, the benefit of such an agent was appreciated only in the two cases with nonechogenic lesions in whom additional tumors became apparent after infusion. It is also possible that the increase in tumor echogenicity that would be expected at higher doses was masked by the concomitant increase in liver echogenicity.

The results of this study are in general agreement with those reported for another fluorocarbon emulsion, Fluosol, which is five times less concentrated than perflubron emulsion (1.0 ml of emulsion contains 0.2 g of fluorocarbon) [20]. The major difference between the two studies is that hepatic and splenic attenuation values were not reported with Fluosol. We believe this discrepancy occurred because scanning was not performed immediately after Fluosol infusion, precluding the assessment of splenic attenuation, which was most noticeable shortly after perflubron infusion; also, the Fluosol dose did not exceed 2.4 g/kg, beyond which liver attenuation was most affected. Further, the previous study allowed optimization of the time-gain curve for each scan, which obscured the change in attenuation.

The two main side effects detected in our study, lower back pain and flulike symptoms, were similar to those reported by Bruneton et al. [16]; however, the incidence of these side effects was greater in our study. Similar side effects and frequency have been reported with many other particulate agents, including parenteral fat emulsions [21], Fluosol [22], EOE-13 [7], and liposomes [23]. The flulike syndrome is thought to be a nonspecific inflammatory reaction caused by activation of macrophages when exposed to a particulate load [24]. The cyclooxygenase enzyme required for the production and release of active substances expressed by activated macrophages is effectively blocked by steroidal and nonsteroidal antiinflammatory agents [7]. Indeed, when subjects were given steroids before EOE-13 administration, the frequency of fever decreased from 85% to 14% [25].

Although the potential contribution of this agent for CT scanning and sonography for the detection of focal lesions in the liver and spleen is clear even with the limited data presented here, its side-effect profile should be reassessed in human subjects after prophylaxis with antiinflammatory agents. Should prophylaxis prove effective, the safety and efficacy of perflubron emulsion should be compared with that of CT portography, the technique it is likely to replace.

The findings in the 14 patients with hepatic metastases showed the potential of perflubron emulsion as a contrast agent for CT. This agent was effective because it

simultaneously enhanced hepatic vessels and liver without enhancing tumors, eliminating the confusion between small veins and tumors. It appears from this study that when perflubron is infused at 3.0 ml/min, the optimal dose for CT is 2.5–3.0 g/kg. On the other hand, the optimal dose for the sonographic detection of liver tumors is not clear from this study but appears to be less than 2.5 g/kg. Although the side effects encountered were not accompanied by significant changes in the hematologic or biochemical indexes, the side-effect profile needs to be ameliorated by further refinement of the emulsion or by proper prophylaxis.

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