PRELIMINARY NOTE

The Importance of Delayed Imaging in the Study of Hepatoma with a New Hepatobiliary Agent

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Concentration of Tc-99m(Sn)-N-pyridoxyl-5-methyltryptophan (Tc-99m PMT), a biliary agent, in hepatic tumors was studied with delayed hepatobiliary imaging in 23 patients with histologically verified hepatocellular carcinomas. All 23 showed filling defects on liver images obtained with Tc-99m tin colloid. In the images taken 5 hr after Tc-99m PMT injection, ten cases showed increased uptake in the carcinoma, six nearly normal uptake, and seven decreased uptake. In those showing the increased uptake of Tc-99m PMT in the tumor, the ratio of the radioactivity in the lesion to that in the adjacent liver parenchyma (T/L ratio) increased progressively with time for 5 hr after injection. These results indicate that delayed Tc-99m PMT images, obtained 5 hr after injection, are useful in assessment of uptake of the radioactivity by hepatocellular carcinoma.

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In the nuclear medical diagnosis of hepatocellular carcinoma, it is advantageous if a radiopharmaceutical could be specifically concentrated by the tumor and thus enhance visualization of the lesions. Several reports have demonstrated that some hepatomas were positively visualized by radiopharmaceuticals such as I-131 rose bengal and Tc-99m-labeled biliary agents (*1–7*). The positive cases in the literatures, however, were remarkably rare (*6–8*), and therefore these agents have not been widely used for the diagnosis of hepatocellular carcinoma.

We have conducted a study to ascertain whether Tc-99m(Sn)-N-pyridoxyl-5-methyltryptophan* (Tc-99m PMT), a recently developed biliary agent (*9*), would be taken up by hepatocellular carcinomas. As a preliminary study, the uptake of Tc-99m PMT by the tumor was studied with the images obtained at 2 and 5 hr after the administration of the agent. The purpose of this paper is to describe the significance of delayed images in assessing the degree of Tc-99m PMT uptake in hepatomas.

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MATERIALS AND METHODS

From December 1982 to August 1983, Tc-99m PMT studies were performed in 69 patients in our hospital. Twenty-three of them were diagnosed histologically as hepatocellular carcinoma, and showed filling defects on Tc-99m tin colloid liver images obtained 3 days after the Tc-99m PMT study. Results of the Tc-99m PMT studies were analyzed in these 23 patients.

Hepatobiliary images were obtained in anterior, right lateral, and posterior views with a gamma camera equipped with low-energy, high-resolution, parallel-hole collimeter at 5 and 60 min after i.v. injection of Tc-99m PMT (5–15 mCi). Delayed images were made at 2 and 5 hr after injection. Individual images consisting of 400–600k counts were recorded on Polaroid film. The required data acquisition time to yield a clear liver image was less than 10 min at 5 hr after injection of Tc-99m PMT, despite the decrease of radioactivity concentration in normal liver tissue to a low level at this time. In some cases, a digital image was recorded in 64 × 64 matrix for 150 sec, and stored on the disk of a computerized image processor. Rectangular regions of interest (ROI) with equivalent area were made within the tumor region and the adjacent normal liver parenchyma on each digital image. The ratios between counts registered

TABLE 1. RESULTS ON Tc-99m PMT UPTAKE* IN LESION EXAMINED AT VARIOUS TIMES AFTER INJECTION

Case no.	Time after injection			
	5 min	1 hr	2 hr	5 hr
1	−	±		+
2	−	−	+	+
3	−	±	+	+
4	−	±	+	+
5	−	−		−
6	−	−		±
7	−	−		±
8	−	±		+
9	−	−	+	+
10	−	−	±	+
11	±	+	+	+
12	−	±		±
13	−	−		−
14	−	−		−
15	−	−	−	−
16	−	−	±	±
17	−	−	±	±
18	−	−	−	−
19	−	−	−	−
20	−	−	−	−
21	−	−	±	+
22	−	±	±	±
23	−	±	+	+
Totals	+ 0	1	6	10
	± 1	7	5	6
	− 22	15	4	7

* + = increased uptake; ± = equilibrated uptake; − = decreased uptake.

in the two ROIs (T/L ratios) were then calculated. The location of the tumor in the liver was routinely mapped by colloid liver studies as well as selective arteriography, and in occasional cases Ga-67 citrate imaging was also used.

The Tc-99m PMT uptake by hepatic tumors was evaluated using the radioactivity in the area corresponding to the location of the defect on the colloid liver image. The degree of Tc-99m PMT uptake in the lesions was visually classified into three grades as follows: + = increased uptake [greater radioactivity in the neoplastic lesion compared with that in the adjacent normal liver tissue]; ± = equilibrated uptake [radioactivity comparable in the lesion and the normal liver]; and − = decreased uptake [lesion radioactivity lower than in the adjacent liver tissue] (−).

RESULTS

Table 1 shows the results of Tc-99m PMT studies performed at 5 min and at 1, 2, and 5 hr after i.v. injection of Tc-99m PMT in 23 cases of hepatoma. Two-hour images were obtained in 15 of 23 cases. As summarized in the table, images obtained at 5 min following injection revealed 22 cases (96%) of lower radioactivity distribution in the tumor compared with that in the nonneoplastic region of liver, and only one case showing equilibrated uptake. At 60 min after injection, equilibrated Tc-99m PMT uptake was seen in seven patients (30%), with increased uptake in only one (4%) of the 23. In contrast, a delayed imaging study at 2 hr after injection showed six cases (40%) of increased uptake among 15 cases, and ten cases (43%) among the 23 at 5 hr. Thus Tc-99m PMT uptake by hepatocellular carcinomas became distinct in delayed images (Table 1).

The changes of T/L ratio with time in 15 patients examined by Tc-99m PMT at 2 and 5 hr after injection are shown in Table 2. In all eight patients whose 5-hr images were assigned as (+), the T/L ratios were smaller than unity at 5 min, whereas they increased steadily for 5 hr and exceeded unity at 5 hr after injection. The increases in T/L ratio between each time point (5 min, 1 hr, 2 hr, and 5 hr) in these cases were statistically significant by Student's t-test for paired data (Table 2).

Typical Tc-99m PMT images obtained in two cases of hepatoma are shown in Figs. 1 and 2. In these cases, radioactivity concentration in the lesions at 5 min was lower than in the adjacent liver. In 1-hr images, however, radioactivity concentration in the lesion appeared to be nearly equivalent to that in the surrounding area, and the lesions were clearly visualized on delayed images, especially those taken at 5 hr after injection.

DISCUSSION

Gallium-67 citrate is widely used for the positive visualization of the tumor in the diagnosis of hepatoma (*10,11*). The specificity of this agent for primary malignant tumors, however, is not satisfactorily high, and hence this agent is not suitable for differentiating hepatoma from either liver abcess or a metastasis taking up gallium.

Some evidence of bile secretion is often histologically demonstrable in primary hepatocarcinoma tissues, and the hepatoma cells frequently show some resemblance to hepatocytes (*12,13*). It is natural to speculate that some bile-producing hepatoma cells might retain the hepatocytic function of taking up a biliary agent from blood, and several cases of hepatoma were found to concentrate biliary agents (*1–5*). Utz et al. reported a case of hepatoma in which Tc-99m pyridoxylidene glutamate was concentrated in the lesion, and they proposed a possible role of biliary imaging in the characterization of the focal defects seen on colloid liver studies (*4*).

Some investigators, however, reported that the frequency of the positive visualization of the masses was disappointingly low in hepatoma (*6–8*). Using Tc-99m

TABLE 2. RATIOS FOR TUMOR TO NORMAL LIVER AT VARIOUS TIMES AFTER Tc-99m PMT INJECTION

Type of Tc-99m PMT uptake in lesion	Case no.	Time after injection			
		5 min	1 hr	2 hr	5 hr
	2	0.16	0.90	1.64	2.19
	3	0.70	0.97	1.20	1.34
(+)	4	0.74	1.11	1.36	1.49
n = 8	9	0.64	0.67	1.22	1.49
	10	0.21	0.60	1.05	1.63
	11	0.97	1.91	3.79	6.40
	21	0.22	0.55	0.99	2.31
	23	0.87	0.98	1.95	2.54
	16	0.24	0.88	1.04	1.05
(±)	17	0.60	0.78	0.95	0.98
n = 3	22	0.80	0.96	1.03	0.95
	15	0.91	0.85	0.77	0.60
(−)	18	0.78	0.88	0.79	0.76
n = 4	19	0.20	0.27	0.34	0.44
	20	0.27	0.71	0.89	0.75

HIDA, uptake in the lesion was seen in only three (4%) of 80 cases of hepatocellular carcinomas examined by Yeh et al. (*6*), and in only one of 12 cases studied by Yasunaga et al. (*7*). Recently, Savitch et al. applied Tc-99m DISIDA to the study of 30 patients with defects on Tc-99m tin colloid liver images, and they reported no "complete filling in" of the defects, and "partial filling in" in only 11 (36.7%) of these patients (*8*). The degree of Tc-99m DISIDA uptake by the tumor characterized by "complete filling in" in the report seems to correspond to either the increased or the equilibrated uptake by our criteria. Thus this type of biliary agent has not been widely used in characterizing localized intrahepatic lesions. In investigations reported thus far using Tc-99m HIDA or Tc-99m DISIDA, however, hepatobiliary studies have not been performed later than 1 hour after the tracer injection.

Our current investigation was initiated to reveal the applicability of a recently introduced biliary agent, Tc-99m PMT, to the diagnosis of human hepatocellular carcinoma. This radiopharmaceutical has been reported to show the fastest blood clearance and hepatobiliary transit among various biliary agents tested so far (*9*).

In the evaluation of Tc-99m PMT uptake by hepatoma, we used delayed imaging after the administration of the tracer to take advantage of the difference in clearances from normal and tumoral tissue, and thus found that the hepatic tumors were positively visualized on the delayed images in about 40% of the cases, with a progressive increase in T/L ratio with time over 5-hr period after injection. These results clearly indicate the usefulness of delayed imaging with Tc-99m PMT in the evaluation of uptake of the tracer by the tumors.

To estimate intrahepatic accumulation of radioactivity

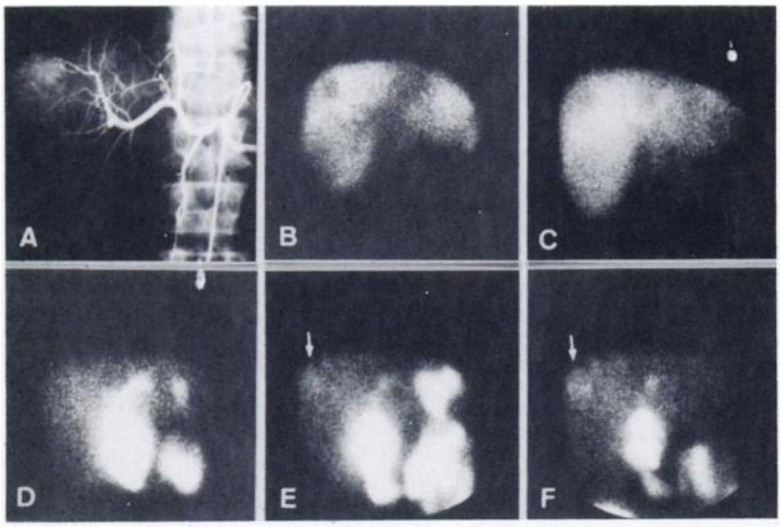

FIG. 1. Hepatocellular carcinoma in 72-yr-old man (Case 4). Lesion is shown as hypervascular tumor in upper portion of right hepatic lobe by selective hepatic arteriogram (A), and as filling defect in image with Tc-99m tin colloid (B). With Tc-99m PMT, lesion density is less than in normal liver at 5 min after injection (C), nearly normal at 1 hr (D), and above normal (arrows) at 2 hr (E) and 5 hr (F).

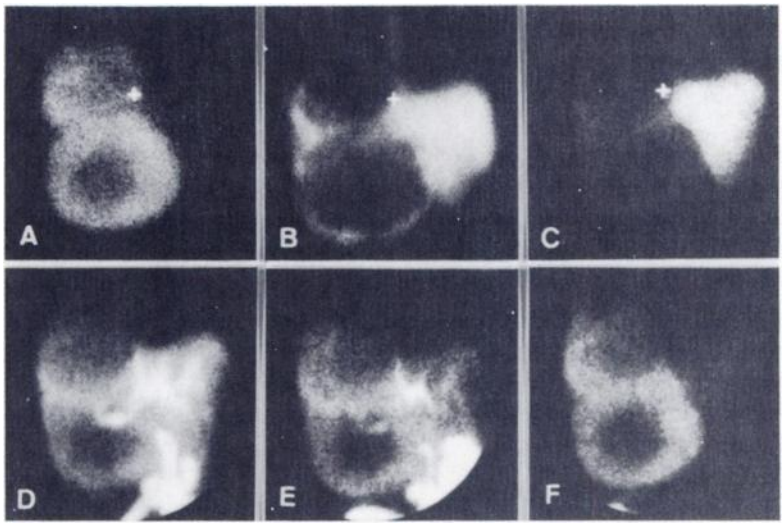

FIG. 2. Hepatocellular carcinoma in 63-yr-old woman (Case 21). Two large tumors give intense Ga-67 citrate uptake (A), and show as filling defects occupying almost all of right hepatic lobe on colloid liver scan (B), and also on Tc-99m PMT image made 5 min after injection (C). Radioactivity in lesions appears more nearly equal to that in left hepatic lobe on Tc-99m PMT images made at both 1 hr (D) and 2 hr (E). Tumors are clearly delineated on 5-hr image (F).

after injection of Tc-99m PMT, however, the following should be noted; first, retention of the radioactivity by segmental biliary obstruction and dilatation. Intrahepatic pooling of tracer was previously confirmed in cases of intrahepatic lithiasis, using Tc-99m PG (*14*). Primary and secondary malignant hepatic tumors can also produce segmental obstruction of bile ducts (*15–18*). Second, Tc-99m PMT concentration occurs in benign and malignant hepatic tumors other than hepatocellular carcinoma. A few cases of benign hepatic tumors—such as focal nodular hyperplasia (*19*) and liver-cell adenoma (*20*),—and a single case of liver metastasis from breast carcinoma (*21*)—were reported to concentrate biliary agents in the hepatic lesions. In addition, uptake of Se-75 methionine was shown in the region of filling defects ("pseudotumors") seen on Tc-99m colloid scintigrams in patients with acute hepatitis (*22–23*). A liver biopsy specimen obtained from the "pseudotumor" showed marked swelling of hepatocytes, bile stasis, and the diminution of the number of Kupffer cells (*23*). Tc-99m PMT could also accumulate in the region of a "pseudotumor." Third, the appearance of overlapping radioactivity occurs in the gallbladder and/or bowel. In the present study, fortunately, no such interference was observed in all 23 cases. In most cases, radioactivity in the gallbladder was minimal on 5-hr images except in one case, which showed marked tracer retention in the gallbladder even in a 5-hr image. A subcutaneous injection of ceruletide diethylamine† was necessary for the clear visualization of a lesion close to the gallbladder.

In the 23 cases of hepatoma, 14 were histologically confirmed by surgery, six by biopsy, and three by necropsy. The locations of the hepatic tumors were determined by both selective celiac arteriography and Tc-99m tin colloid liver image in 19 cases, and by both Ga-67 citrate image and colloid liver image in the remaining four. In all positive cases in this study, the location of accumulated Tc-99m PMT seen on images coincided with the location of the tumor demonstrated by the above methods. Thus all these positive scintigrams were ascribed to the retention of Tc-99m PMT in the tumor per se.

On the basis of the results presented above, we now believe that the 5-hr image after injection of the hepatobiliary radiopharmaceutical is very useful for the characterization of the nature of mass lesions in liver that are found by examinations such as colloid liver study and ultrasonic echography. In order to clarify the significance of delayed imaging with Tc-99m PMT in the diagnosis of hepatoma, however, the frequency of accumulation of the radiopharmaceutical in various benign and malignant hepatic lesions other than hepatocellular carcinoma should be determined. It would also be important to clarify whether the histologic types of hepatoma are related to uptake of this agent, and whether Tc-99m PMT is the most suitable agent for the delayed positive visualization of hepatomas.

FOOTNOTES

* Manufactured by Nihon Medi-Physics, Co., Ltd., Takarazuka, Japan.

† Manufactured by Kyowa Hakko Kogyo, Co., Ltd., Tokyo, Japan.

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