HEPATOBILIARY SCINTIGRAPHY AND FUNCTION TEST WITH 99MTC-N-PYRIDOXYL-5-METHYLTRYPTOPHAN (99MTC-PMT)

SUGIMURA, KAZURO

(Citation)
The Kobe journal of the medical sciences,31(2):85-94

(Issue Date)
1985-04

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100488759

Kobe J. Med. Sci. 31, 85/94, April 1985

HEPATOBILIARY SCINTIGRAPHY AND FUNCTION TEST WITH ^{99M}TC-N-PYRIDOXYL-5-METHYLTRYPTOPHAN (^{99M}TC-PMT)

KAZURO SUGIMURA, SHOJI NISHIYAMA, AND ISAMU NARABAYASHI

Department of Radiology
Kobe University School of Medicine

INDEXING WORDS

liver; hepatobiliary scintigraphy; liver function

SYNOPSIS

The authors studied the effectiveness of ^{99m}Tc-N-pyridoxyl-5-methyltryptophan (^{99m}Tc-PMT) for dynamic imaging and function on 40 patients with various hepatobiliary diseases and on healthy individuals.

In healthy subjects, ^{99m}Tc-PMT is rapidly removed from the blood by the parenchymal cells of the liver and is excreted through the biliary system. The imaging of the liver, bile ducts, gallbladder and intestines with ^{99m}Tc-PMT was satisfactory. There was no renal visualization. In the case of serial images of healthy individuals, the gallbladder, intrahepatic bile duct and small intestine were visualized after 18.8 ± 7.2, 8.8 ± 1.4, and 16.7 ± 6.3 min, respectively; the mean peak time on the hepatogram was 8.0 ± 5.3 min. The bile ducts of patients with liver disorders were visualized later than those of healthy individuals. Particularly in the case of severe liver parenchymal diseases, the appearance time for the bile duct was significantly delayed. However, the delays in appearance time did not correlate well with low scores on the liver function test.

Received for publication : March 8, 1985
Authors' names in Japanese : 杉村和朗　西山章次
楢林　勇

At 70 min after the intravenous administration of ^{99m}Tc-PMT, 2.5 ± 1.5% of the injected dose was excreted into the urine of the healthy individuals. The urinary excretion of ^{99m}Tc-PMT by the patients with hepatobiliary diseases showed no increase, and it was not entirely related to the results of the serum function tests. However, a larger amount of ^{99m}Tc-PMT was retained in the blood of the patients with hepatobiliary diseases. The blood retention values at 20 min after injection into those with liver cirrhosis and hepatoma were significantly delayed.

INTRODUCTION

As radioactive agents for diagnosing the liver and biliary tract system, I-131 labelled compound, I-123 labelled compound and Tc-99m labelled compound have been used in various ways since the use of I-131 Rose Bengal by Taplin[10] et al. in 1955.

Of the 2 systems of Tc-99m labelled compounds,[2, 7, 9, 11] Tc-99m-pyridoxylideneglutamate (PG) and Tc-99m-(2.6 dimethyl phenylcarbamoyl methyl)-iminodiacetic acid (HIDA), the authors used Tc-99m-N-pyridoxyl-5-methyltryptophan[6] (Tc-99m-PMT), which is a derivative of the former; we examined the differences between them in various kinds of diseases of the hepatobiliary system and the relations with liver functions.

MATERIALS AND METHODS

Tc-99m-PMT provided by Japan Mediphysics Co. was used. In Fig. 1 the structural formula of N-pyridoxyl-5-methyltriptophan is shown. The labelling rate of Tc-99m-PMT was thought to be close to 100% in our study. In the 40 cases in this study, no side effects were recognized. The subjects were 40 persons who had been examined by means of hepatobiliary scintigraphy using Tc-99m-PMT between January and May 1982 at Kobe University Hospital. Twenty-eight subjects were studied by disease, consisting of 6 patients with cholelithiasis, 8 with chronic liver cirrhosis, 6 with hepatoma, and 6 healthy persons without any history of hepatobiliary disease who were studied as controls.

In order to examine the subjects under the same conditions, they fasted from breakfast until the tests started at around noon.

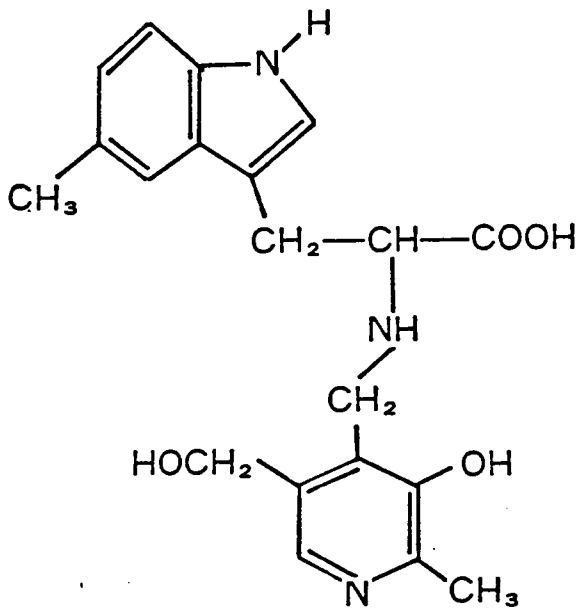

Fig. 1 Postulated chemical structure of N-pyridoxyl-5-methyl-tryptophan.

In a supine position 3.75mCi of Tc-99m-PMT was administered with the patients in a supine position. Pictures were taken every 150 sec by scinticamera and the data was input into a nuclear medical data processor for 60 min. Two ml of blood was collected 5 min and 20 min after administration. From the radioactivity, total dose and body weight the blood retention rate was calculated. Total urine was collected, and the radioactivity in 1ml of the urine was determined. The blood retention rate and the urinary excretion rate were also calculated as percentages.

RESULTS

Time of appearance of the gallbladder, choledochus and small intestine and peak hepatogram time

The time of appearance was determined by scintigram and the mean values S.D. are shown in Table 1. The 4 cases in which the gallbladder did not appear were all cases of cholelithiasis. The

appearance time of the gallbladder was the shortest in the normal cases at 18.8 ± 7.2 min, followed by 20.4 ± 8.3 min in hepatoma, 23.8 ± 18.4 min in chronic hepatitis and 27.5 ± 7.1 min in liver cirrhosis groups. But in gallbladder appearance time, no statistically significant difference was recognized between any of those groups and the normal group. The appearance time of the choledochus in normal cases was the quickest at 8.8 ± 1.4 min, followed by 11.7 ± 4.4 min in cholelithiasis cases. In chronic hepatitis and liver cirrhosis, the time of appearance was delayed significantly in comparison with the normal group. The appearance time of the small intestine was 16.7 ± 6.3 min in the group of normal cases, 20.4 ± 7.8 min in cholelithiasis, 21.3 ± 1.8 min in liver cirrhosis, 25.0 ± 23.1 min in hepatoma and 25.3 ± 9.0 min in chronic hepatitis. The appearance time in all the diseased groups was delayed in comparison with the normal group, but no statistically significant difference was recognized. The peak time was 8.4 ± 5.3 min in normal cases, 12.5 ± 1.8 min in hepatoma, 13.8 ± 4.1 min in chronic hepatitis and 16.3 ± 9.6 min in liver cirrhosis groups. The latest peak time was that of Case 26 (liver cirrhosis) where appearance occurred at 23 min. A significant difference was recognized between the normal group and those with chronic hepatitis, and between the normal and hepatoma groups.

Urinary excretion and blood retention rates

The urinary excretion rate of each group is shown in Table 2. The rate was 2.5 ± 1.5% in the normal cases, 3.4 ± 1.0% in cholelithiasis, 3.9 ± 1.9% in chronic hepatitis, 4.7 ± 1.4% in liver cirrhosis and 6.0 ± 4.0% in hepatoma cases, showing an increasing tendency. The highest rate of 11.9% was registered for Case 1 (hepatoma). No statistically significant difference was found between the urinary excretion rate of the normal group and any of the diseased groups.

Blood retention rates are shown in Table 2. The 20 min blood retention rate was 9.5 ± 3.2% in the normal cases, 13.5 ± 4.9% in cholelithiasis, 17.7 ± 11.7% in chronic hepatitis, 24.6 ± 13.1% in hepatoma, and 28.9 ± 16.0% in liver cirrhosis significant difference was found between the normal control group and those with hepatoma and liver cirrhosis.

Table 1 Appearance time of gallbladder and common bile duct, and peak time of radioactivity in the liver after ^{99m}Tc-PMT injection.

	No. of cases	Gallbladder	Bile duct	Intestine	Peak time
Controls	6	18.8± 7.2	8.8± 1.4	16.7± 6.3	8.0± 2.0
Chronic hepatitis	8	23.8±18.4	12.5± 3.8	25.3± 9.0	13.8± 4.1
Cholelithiasis	6	(-)	11.7± 4.4	20.4± 7.8	11.8± 5.3
Hepatoma	6	20.4± 8.3	13.8± 6.5	25.0±23.1	12.5± 1.8
Liver cirrhosis	2	27.5± 7.1	18.8± 8.8	21.3± 1.8	16.3± 9.6

Table 2 Urinary excretion % of dose at 70 min after the intravenous administration of ^{99m}Tc-PMT, and blood retention values of ^{99m}Tc-PMT.

	No. of cases	Urinary excretion for 70 min % dose	Blood RI level (% dose)
			20 min
Controls	6	2.5± 1.5	9.5± 3.2
Chronic hepatitis	8	3.9± 1.9	17.7±11.7
Cholelithiasis	5	3.4± 1.0	13.5± 4.9
Hepatoma	6	6.0± 4.0	24.6±13.1
Liver cirrhosis	2	4.7± 1.4	28.9±16.0

Correlation between activity of Tc-99m-PMT and biochemical examination of the liver

We correlated the appearance time of the gallbladder and choledochus, the peak time of the hepatogram, urinary excretion rate, 20 min blood retention rate value and GOT, GPT, γ-GTP, T-Bil, D-Bil, ALP; the correlation coefficients are shown in Table 3.

Significant correlations were observed, between the time of appearance of the choledochus and each function of the liver, such as $r=0.43$ ($P<0.01$) in γ-GTP, $r=0.42$ ($P<0.02$) in D-Bil and $r=0.49$ ($P<0.01$) in ALP, but no significant correlation was found with the

other functions of the liver. Correlation was observed between the peak time and liver function test except for one weak correlation, r=0.35 (P<0.05) in GOT. For the urinary excretion rate and GOT and GPT, respective correlations of r=0.50 (P<0.01) and r=0.51 (P<0.01) were found. Many good correlations were found between the 20-min value for the blood retention rate and the serological liver examination, such as r=0.70 (P<0.001) with GOT, r=0.43 (P<0.02) with GPT, r=0.47 (P<0.01) with γ-GTP, r=0.84 (P<0.001) with T-Bil and r=0.77 (P<0.001) with D-Bil.

Table 3 The relationship between appearance time of gallbladder and bile duct, peak time of radioactivity in the liver, urinary excretion dose, blood retention values and liver function in 39 cases.

	Appearance time (min)		Peak time min	Urinary excretion % dose	Blood RI level (% dose)
	Gallbladder	Bile duct			20 min
GOT (IU/ℓ)	-0.03	0.07	0.35	0.50	0.70
GPT (IU/ℓ)	-0.15	0.01	0.22	0.51	0.43
γ-GTP(IU/ℓ)	0.09	0.43	0.14	0.17	0.47
Bil-T (mg/dl)	-0.19	0.30	-0.02	0.39	0.84
Bil-D (mg/dl)	-0.11	0.42	0.00	0.33	0.77
ALP (IU/ℓ)	0.16	0.49	0.28	-0.10	0.26

DISCUSSION

The appearance times of the gallbladder, choledochus and small intestine in hepatobiliary scintigraphy with the use of Tc-99m-PMT reflect the functions of the liver and biliary tract, and are useful as clinical indexes.[6, 9]

The gallbladder appearance time has been reported as 14.0 ± 3.4 min for Tc-99m-PI,[4] 15 min to 30 min for Tc-99m-HIDA,[7] and 15 min to 30 min for Tc-99m-E-HIDA,[8] representing no great difference from the 18.8 ± 7.2 min for Tc-99m-PMT. It was reported that biliary duct times were 12.1 ± 1.5 min for Tc-99m-PI, up to 15 min for Tc-99m-HIDA and about 10 min for Tc-99m-E-HIDA. Tc-99m-PMT's appearance time was 8.8 ± 1.4 min so

the biliary duct may appear slightly earlier than with the other agents. But, as no identical comparisons have been made, this may be said to be open to further discussion. The appearance time of the small intestine has been reported to be 10 to 90 min with Tc-99m-PI, up to 60 min with Tc-99m-HIDA and up to 20 min with Tc-99m-E-HIDA. The time was 16.7 ± 6.3 min with Tc-99m-PMT, but the differences between the agents cannot be usefully discussed on account of the wide gap in intestine appearance times among individuals.

In view of the above, it suspects that Tc-99m-PMT has high transmission speed, just like other Tc-99m labelled hepatobiliary agents. In our study, the biliary tract appearance time was delayed significantly in chronic hepatitis and liver cirrhosis, but in the liver function tests, only weak correlations such as $P<0.01$-0.02 were recognized between γ-GTP, D-Bil and ALP. The time of appearance of the agent in the biliary tract may not have correlated well with each inspection value because many stages occur between liver uptake and excretion in the bile. Also, in the gallbladder and small intestine appearance times no correlation was observed with any of the liver function data or clinical comparisons.

The agent Tc-99m-PMT with its peak time of 8.0 ± 2.0 min may be said to have one of the fastest peak times; the other peak times are Tc-99m-PI with 11.0 ± 1.0 min, Tc-99m-HIDA with 16.0 ± 4.0 min, 20.0 ± 2.0 min with Tc-99m(P-Butyl)-IDA[5] and Tc-99m-E-HIDA with 10.3 ± 1.3 min.

Comparing normal cases and diseased cases, a significant delay in peak time was recognized in chronic hepatitis and hepatoma, but no significant difference was found for the other diseases.

No significant correlation was found between the liver function test and the peak time, except for a weak correlation with GOT ($P<0.05$). This may be considered a remarkable difference when compared in comparison with the fact that between the GOT, D-Bil and γ-GTP, and the 5-min and 20-min values a good correlation was shown by the blood collection method, which allows the hepatic uptake to be most accurately determined. In this record, it was reported that with Tc-99m-E-HIDA, a good correlation was shown between T-Bil and the peak time, and it is possible that the

activity of Tc-99m-PMT is different from that of Tc-99m-E-HIDA. So this may be judged an interesting problem.

In our observations on Tc-99m-PMT the latest peak time was 23 min and it is possible by a 60 min determination to draw a hepatic excretion curve even in the case of serious hepatic dysfunction.

In normal cases, urinary excretion rates have been reported: Tc-99m-PI-11.2 ± 1.2% in 90 min, Tc-99m-HIDA-14.2 ± 1.8% in 90 min,[1)] Tc-99m-E-HIDA-7.5 ± 0.9% in 24 hr while Tc-99m-PMT in the 6 normal cases which we observed in the present study, was 2.5 ± 1.5%. As the times of determination were dissimilar, the figures cannot readily be compared, but among Tc-99m labelled agents, together with Tc-99m-(P-Butyl)-IDA, Tc-99m-PMT was scarcely excreted in the urine, and its rate of urinary excretion was similar to those of I-131-BSP[3)] (about 2%) and I-131-Rose Bengal.

In the use of Tc-99m-PMT, no significant increase in the urinary excretion rate was found between the diseased group and normal group. The highest urinary excretion rate in the present study was only 11.9%. On the other hand, when we used Tc-99m-E-HIDA, whose urinary excretion rate is said to be very low, the 24-hour value was 1.5-3.1mg/dl in total bilirubin, displaying a significant increase in comparison with the 7.5 ± 0.9% seen in normal cases. It was reported to be 82.0% in pancreatic cancer case when the bilirubin value was 22.3mg/dl. Also with Tc-99m-(P-Butyl), the 24-hour mean urinary excretion rate in 5 cases of liver cirrhosis was 14.8%, and the highest was registered with cholelithiasis at 52.2%. In comparison with those agents Tc-99m-PMT is low in urine excretion among the Tc-99m labelled hepatobiliary agents, and it may be said not to cause any noticeable increase in urinary excretion due to liver dysfunction.

Concerning the high correlation between bilirubin value and blood retention rate, it is thought, as reported by Kitani[11)] et al., BSP with Tc-99m-HIDA, to be attributable to the competition taking place between Tc-99m-PMT and bilirubin in the process of excretion. At present we do not yet know the details of the process of hepatic uptake and bile excretion in Tc-99m labelled hepatobiliary agents. However, with respect to maintaining a satisfactory correlation with some liver function tests which reflect hepatic cell impairment, this agent is useful for diagnosing hepatic cell impairment. If its activity is further clarified, it will become possible to estimate the site of the impair-

ments of the hepatic cells, and there will be the possibility of it serving as a load test like BSP or ICG.

We concluded that 1) if we look at image changes over the course of time with chronic hepatitis and liver cirrhosis, the appearance time of the biliary tract was statistically delayed, 2) the amount of urine excreted in 70 min in all diseased groups represented no significant increase in comparison with normal cases (2.5 ± 1.5%), 3) an above normal increase was observed in the blood retention rates in all the diseased groups and relatively high correlations were shown between GOT and 20-min value (r=0.70), between T-Bil and 20-min value (r=0.84), and between D-Bil and 20-min value (r=0.74), 4) no correlation was found between the various kind of biochemical test values and the appearance time (liver, bile, intestines), urinary excretion rate and hepatic peak time.

REFERENCES

1. Aburano, T., Kuwajima, A., Ohara, K., Nikaku, R., Tonami, N., Hisada, K., and Ito K.: Jap. J. Nucl. Med. 1978. 15. 689/695. A clinical evaluation of ^{99m}Tc-HIDA hepatobiliary scintigraphy.
2. Baker, R.J., Bellen, J.C., and Ronai, P.M.: J. Nucl. Med. 1975. 16. 720/727. ^{99m}Tc-pyridoxylideneglutamate: A new hepatobiliary radiopharmaceutical. I. Experimental aspects.
3. Freeman, L.M., Kay, C.J., and Derman, A.: J. Nucl. Med. 1968. 9. 227/232. Renal excretion of radioiodinated rose bengal - A pitfall in the interpretation of rose bengal abdominal scans.
4. Ito, K.: Nip. Acta Radiol. 1979. 39. 132/143. ^{99m}Tc-(Sn)-Pyridoxylideneisoleucine hepatobiliary scintigraphy in diffuse liver disease.
5. Kawaguchi, S., Iio, M., Chiba, K., Yamada, H., Murata, K., Noguchi, M., Ohtake, E., and Toyama, H.: Jap. J. Nucl. Med. 1980. 17. 943/950. An clinical evaluation of ^{99m}Tc-(P-Butyl) IDA.
6. Kato-Azuma, M.: J. Nucl. Med. 1982. 23. 517/524. ^{99m}Tc-(Sn)-N-Pyridoxylaminates: A new series of hepatobiliary imaging agents.
7. Rosenthall, L., Shaffer, E.A., Lisbona, R., and Pare, P.:

Radiol. 1978. 126. 467/474. Diagnosis of hepatobiliary disease by ^{99m}Tc-HIDA cholescintigraphy.

8. Senda, K., Sasaki, T., Mishima, A., Kobayashi, H., Matsubara, K., Arai, O., Mashimo, S., Ishiguchi, T., Ohno, A., Ohga, T., and Kodama, I.: Jap. J. Nucl. Med. 1980. 17. 187/197. An evaluation of ^{99m}Tc-Diethyl-IDA hepatobiliary scintigraphy.
9. Sugimura, K., Narabayashi, I., Nabeshima, K., Ishido, N., Hashimoto, K., Yamasaki, K., Hamada, T., Sugimura, C., Suematsu, T., Inoue, Y., Matsuo, M., Nishiyama, S., and Kimura, S.: Nip. Acta Radiol. 1983. 43. 1205/1213. Hepatobiliary scintigraphy and function test with ^{99m}Tc-N-pyridoxyl-5-methyltryptophan.
10. Taplin, G.V., Meredith, O.M.Jr., and Kade, H.: J. Lab. and Clin. Med. 1955. 45. 665/678. The radioactive (^{131}I-tagged) rose bengal uptake excretion test for liver function using external gamma-ray scintillation counting techniques.
11. Winstow, B.W., Subramanian, G., Heertum, R.L.V., Henderson, R.W., Gagne, G.M., Hall R.C., and McAfee, J.G.: J. Nucl. Med. 1977. 18. 455/461. An evaluation of ^{99m}Tc-labeled hepatobiliary agents.