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Abstract

The reduced hepatic blood flow calculated from hepatic scintigram with 198Au colloid was elucidated as the primary responsible factor for postoperative hepatic insufficiency. However 198Au colloid is no longer in use because of the high levels of radiation. Although 99mTc-phytate behaves similarly to 198Au on imaging, there were discrepancies between the hepatic blood flow index (KL) value and the severity of cirrhosis determined by laboratory data or by histology. In the measurement of hepatic blood flow using a radioactive colloid, factors like organ distribution, stability and uniformity of the colloid particles influence the values. In the present study, a 111In colloid was prepared and administered to rats to investigate the usefulness: as much as 95.4 (0.8) [Mean (+/- SD)]% of the colloid accumulated in the liver at pH 6.8. The distribution of particle diameter was within a relatively narrow range with the peak at 0.2 to 0.4 microns. Moreover, the KL values were not affected by condition of the reticuloendothelial system. The values showed a significant correlation with the measurements of the hepatic tissue blood flow obtained by the hydrogen gas clearance method (gamma = 0.83, $P < 0.001$). Thus, the 111In colloid can be clinically used as a substitute for 198Au colloid in the preoperative examination for estimation of the limit of resection.

KEYWORDS: 111in colloid, hepatic functional reserve, hepatic blood flow

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Measurement of Hepatic Blood Flow Using ^{111}In Colloid

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The reduced hepatic blood flow calculated from hepatic scintigram with ^{198}Au colloid was elucidated as the primary responsible factor for postoperative hepatic insufficiency. However ^{198}Au colloid is no longer in use because of the high levels of radiation. Although ^{99m}Tc-phytate behaves similarly to ^{198}Au on imaging, there were discrepancies between the hepatic blood flow index (K_L) value and the severity of cirrhosis determined by laboratory data or by histology. In the measurement of hepatic blood flow using a radioactive colloid, factors like organ distribution, stability and uniformity of the colloid particles influence the values. In the present study, a ^{111}In colloid was prepared and administered to rats to investigate the usefulness: as much as 95.4 (0.8) [Mean ($\pm$SD)] % of the colloid accumulated in the liver at pH 6.8. The distribution of particle diameter was within a relatively narrow range with the peak at 0.2 to 0.4 μm. Moreover, the K_L values were not affected by condition of the reticuloendothelial system. The values showed a significant correlation with the measurements of the hepatic tissue blood flow obtained by the hydrogen gas clearance method ($\gamma = 0.83$, $P < 0.001$). Thus, the ^{111}In colloid can be clinically used as a substitute for ^{198}Au colloid in the preoperative examination for estimation of the limit of resection.

Key words: ^{111}In colloid, hepatic functional reserve, hepatic blood flow

In Japan, more than 80% of the cases of hepatocellular carcinoma are complicated with cirrhosis, and therefore hepatic functional reserve should be estimated as accurately as possible before operation. The effective hepatic blood flow index (K_L) has been estimated by Mimura *et al.* (1) and Tsumura (2) using ^{198}Au colloid, and it was reported to be useful for evaluation of the pre- and postoperative hepatic functional reserve. Because of its clinical use, the mortality due to postoperative hepatic insufficiency decreased markedly. ^{99m}Tc phytate was used because it was impossible to obtain ^{198}Au colloid, but in many cases there were discrepancies between the results of the preoperative evaluation by ^{99m}Tc phytate and the severity of cirrhosis determined by biochemical data or histology. The index estimated by the ^{99m}Tc phytate was not as reliable as the index estimated by ^{198}Au colloid. The reason for this may be that ^{99m}Tc phytate forms a colloid only after injection, and there are some variables in the formation of the colloid or regarding particle size.

Thus it became necessary to select a nuclide with a high accumulation in the liver and good stability. Based on the fact that In^{+3} can be converted into $In(OH)^{+2}$, $In(OH)_2^{+1}$, $In(OH)_3$, or $In(OH)_4^{-1}$ depending on the pH, and that nearly 100% of the atoms are present in the colloidal state in the form of $In(OH)_3$ in the pH range of 6 to 7 while atoms in other forms account for only a small portion (3). The colloid from $^{111}InCl_3$ (Japan Mediphysics Co., Tokyo, Japan) was prepared and an experimental investigation was performed in rats to evaluate its clinical usefulness.

Materials and Methods

Preparation of ^{111}In colloid. After a $^{111}InCl_3$ solution was mixed with 0.01 N NaOH solution, 0.1 M phosphate buffer (containing 10% mannitol as a stabilizer) of various pH was added. The solution was then rested to allow stabilization. The pH of the solution thus prepared was measured with a pH/ionmeter model 720 (Iwaki Glass, Tokyo, Japan).

The ^{111}In colloidal solution at the dose of 185×10^4 Bq was injected in the caudal vein of five Wistar male rats

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at the respective pH values (weighing 250 to 300g) anesthetized with pentobarbital intraperitoneally. One hour after injection, the rats were killed by exsanguination, and the liver, spleen, lungs, kidneys and blood were subjected to counting with a radioisotope calibrator CRC30 (Capintec Co., NJ, USA) to estimate the accumulation in each organ. The blood weight was assumed to account for 8% of the body weight of the rats.

Nuclipore membranes (Nomura Micro Science Co., Tokyo, Japan) with pore sizes of 0.08, 0.1, 0.2, 0.4 and 0.6μm were used for measuring of the distribution of the diameter of ^{111}In colloid particles.

Calculation of the value of hepatic blood flow index (K_L). Data were collected by a scintillation camera with a collimator for moderate energy (250 KeV) connected with an on-line minicomputer for processing of nucleomedical data (Shimazu Scintipac 1200, Shimazu Co., Tokyo, Japan). A region of interest (ROI) was fixed on the liver scintigram, the hepatic accumulation curve was drawn, and the K_L was then calculated (4). The ^{111}In colloidal solution was injected intravenously in those five rats at an increasing dose of 50, 100, 200, 400 and 800μCi, and the change of K_L was examined.

Activation and suppression of the reticuloendothelial system. Zymosan A (Sigma, St. Luis, MO, USA) 40mg/kg was injected intravenously 3 days before the measurement of K_L to stimulate the reticuloendothelial function according to the method of Kawaguchi *et al.* (5). On the other hand, the suppression of the reticuloendothelial function was obtained by intravenous injection of 500mg/kg of silica 2 days before the measurement of K_L according to the method of Nash *et al.* (6).

Measurement of hepatic blood flow with the hydrogen gas clearance method. The hepatic tissue blood flow was measured using the hydrogen gas clearance method. The hepatic tissue blood flow was calculated with the initial slope method from the clearance curves recorded with a PHG 200 (Medical System Co., Tokyo, Japan). For this, a needle-type platinum electrode was inserted into the hepatic parenchyma.

Results

Changes in hepatic accumulation with pH. The mean percentage (SD) of hepatic accumulation at pH 5.5, 6.0, 6.5, 6.8, 7.0, and 7.5 was 80.6 (2.4)%, 82.6 (2.2)%, 90.7 (1.0)%, 95.4 (0.8)%, 94.1 (0.5)%, and 87.4 (2.0)%, respectively (Fig. 1).

Distribution of the diameter of ^{111}In colloid particles at pH 6.8. Measurement of the diameter of the particles performed by Nuclipore membranes showed that more than 90% of particles had diameters between 0.08μm and 0.6μm (Table 1).

Organ distribution of ^{111}In colloid. The ^{111}In colloid accmulated 95.4 (0.8)% in the liver, 1.1 (0.6)% in the spleen, 0.6 (0.3)% in the lungs, 0.4 (0.1)% in the kidneys and 0.9 (0.2)% in the blood. The accumulation rates are shown in Fig. 2.

Changes of the K_L according to dose. Mean (SD) K_L at a dose of 50μCi, 100μCi, 200μCi, 400μCi, 800μCi was 881 (63), 892 (50), 885 (33), 904 (59), and uncountable, respectively. The count at 800 μCi was so high, it became impossible to measure by computer (Fig. 3).

Influence of the reticuloendothelial system on K_L. K_L values before and after stimulation with Zymosan A were 889 (62) and 877 (73), respectively. At

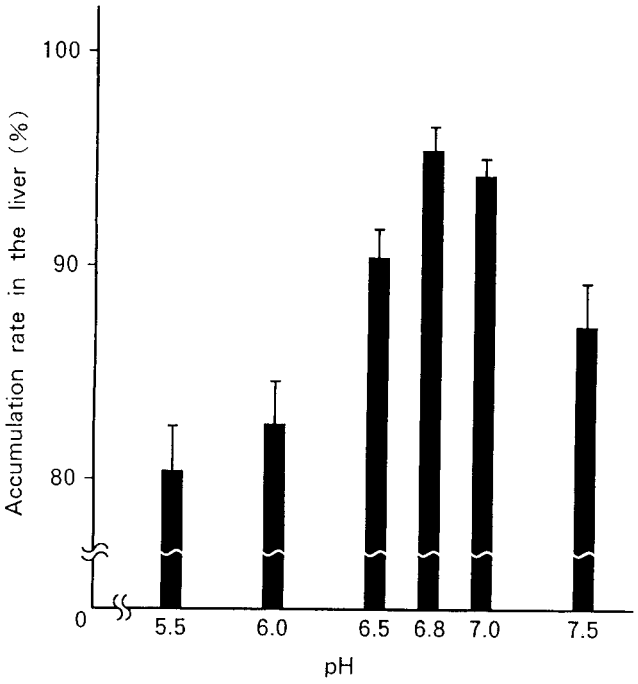

Fig. 1 Changes in hepatic accumulation rate by the pH examined in 5 rats. The highest accumulation in the liver was obtained at pH 6.8.

Table I Distribution of the diameter of ^{111}In colloid particle at pH 6.8

	The diameter of ^{111}In colloid particle (μm)					
	< 0.08	$0.08 \leqq < 0.1$	$0.1 \leqq < 0.2$	$0.2 \leqq < 0.4$	$0.4 \leqq < 0.6$	$0.6 \leqq$
Mean percent (SD)	5.3 (0.9)	6.9 (3.7)	13.3 (7.7)	63.5 (10.1)	7.2 (5.7)	3.7 (2.6)

Five rats were used to determine the diameter of ^{111}In colloid particle.

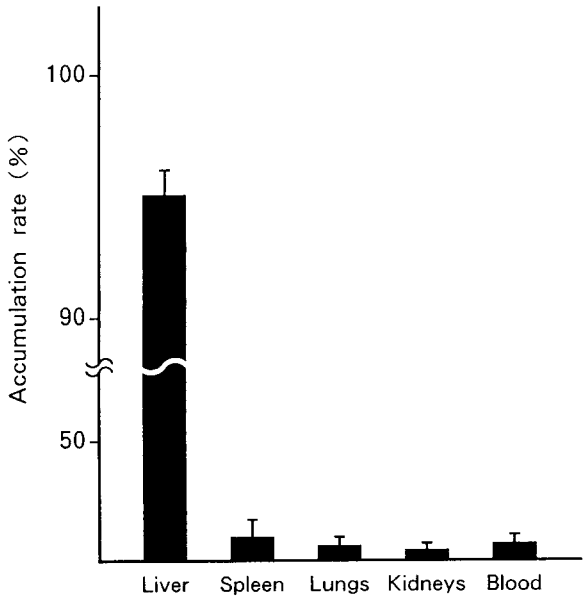

Fig. 2 Organ distribution of ^{111}In colloid examined in 5 rats. More than 95% of ^{111}In colloid accumulated in the liver.

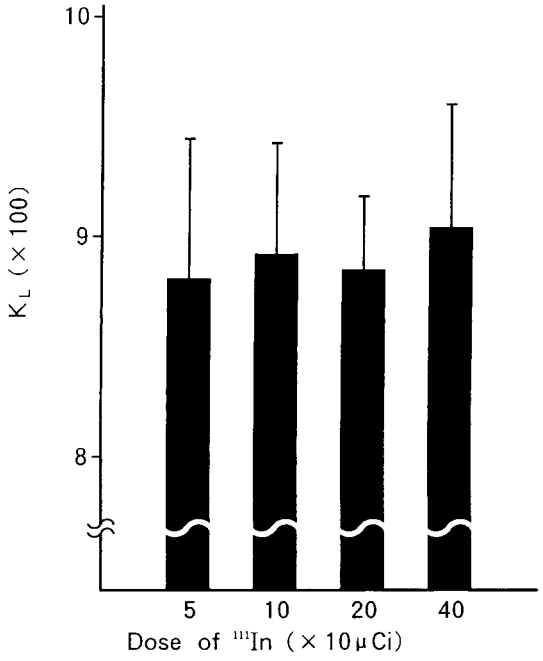

Fig. 3 Changes of the K_L value according to the administered dose examined in 3 rats. K_L values for each dose were similar.

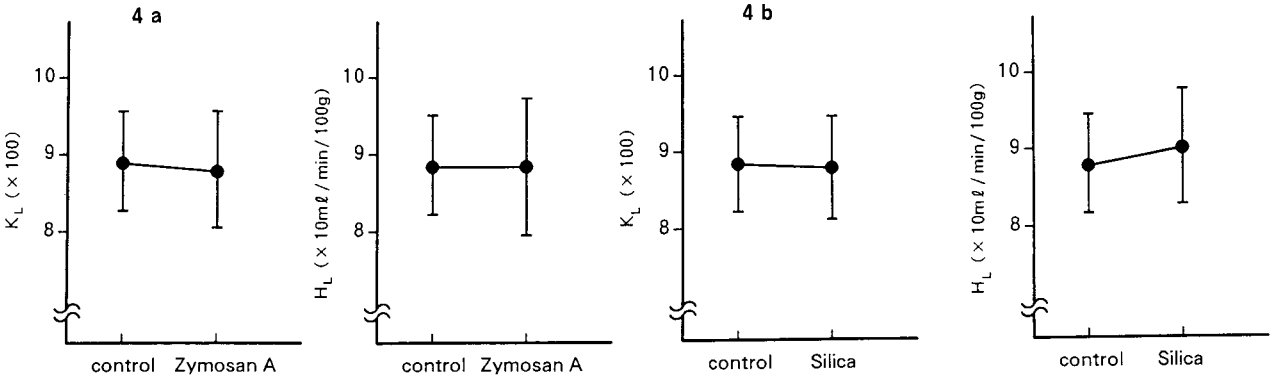

Fig. 4 Influence of stimulation or suppression of the reticuloendothelial system on the K_L values. (**a**) K_L values before and after stimulation with Zymosan A did not change. Control rats ($n = 8$); Rats treated with zymosan A ($n = 6$). (**b**) K_L values before and after suppression with silica did not change. Control rats ($n = 8$); Rats treated with silica ($n = 5$).

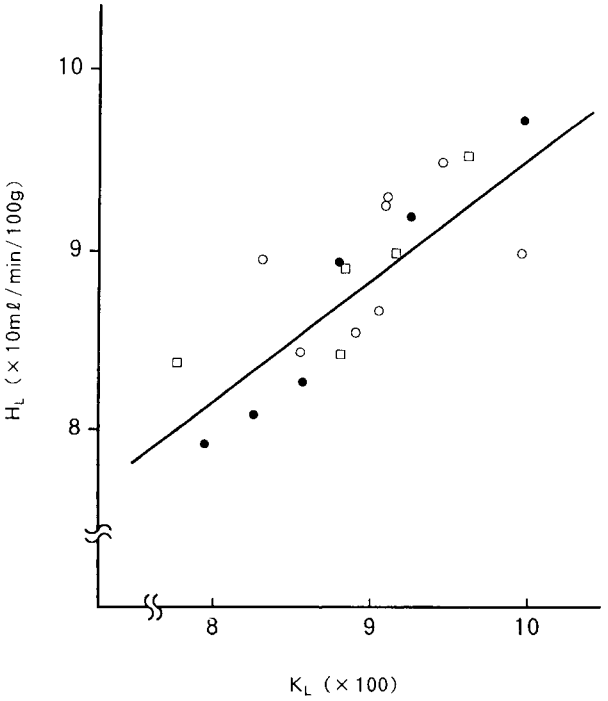

Fig. 5 Correlation of K_L value and hepatic tissue blood flow (H_L) measured by hydrogen gas clearance method. The K_L values correlated significantly well ($Y = 0.0923X + 7$, $\gamma = 0.83$, $P < 0.001$) with the H_L values. ○ (n = 8): Without treatment, ● (n = 6): With Zymosan A treatment, □ (n = 5): With silica treatment.

the same time, by the hydrogen gas clearance method k_L remained unchanged before and after the stimulation with Zymosan A (Fig. 4a).

K_L values before and after suppression with silica were 889 (62) and 881 (67), respectively. At the same time, the values of hepatic tissue blood flow measured by the hydrogen gas clearance method remained unchanged before and after the suppression with silica (Fig. 4b).

Correlation between K_L and heaptic tissue blood flow measured by hydrogen gas clearance method (H_L). K_L correlated significantly ($\gamma = 0.83$, $P < 0.001$) with the values of H_L (Fig. 5).

Discussion

^{198}Au colloid has long been used for measurement of hepatic blood flow due to its high uniformity and specificity, and since it is not taken up by the spleen (7). However, this colloid was eventually prohibited because the raido activity was too high.

^{198}Au was replaced by ^{99m}Tc-Sn colloid and ^{99m}Tc phytate, which are now frequently used for hepatic scintigraphy. Although ^{99m}Tc-Sn colloid is presented as colloidal form at the time of administration, it also tends to concentrate in the spleen because of the large diameter of the particles, and it accumulates gradually in the lungs as aggregation progresses. Thus the particle diameter and the stability of ^{99m}Tc-Sn colloid are not suitable for the estimation of hepatic blood flow.

Additionally, it has been reported that K_L values obtained with ^{99m}Tc-Sn colloid did not correlate well with the corresponding values of ^{198}Au colloid (8).

In contrast, ^{99m}Tc phytate hardly concentrates in the spleen, and gives an image similar to that of ^{198}Au colloid. However, we found cases where the values were not reliable to examine the hepatic functional reserve preoperatively, possibly because ^{99m}Tc phytate forms a colloid after administration by chelation with calcium ions, so the precise particle diameter and the rate remaining in the colloid form in the body is not known. Moreover, it has been reported that the characteristics of the colloid particles may vary among individuals, and that the image of the kidney is particularly intense in some cases (9, 10).

According to our experience, the hepatic accumulation curve tended to decrease with time more markedly in normal cases even after correction of the half-life of ^{99m}Tc, and therefore correct clearance values cannot be obtained unless its hepatic metabolic and excretion are taken into account. In summary, ^{99m}Tc phytate is not suitable to estimate the hepatic blood flow because of the unstable characteristics of its colloid.

In this study, a ^{111}In colloid was used for the measurement of the hepatic tissue blood flow. A ^{111}In colloid was prepared according to the method of Komarek (11), and the images were evaluated with a collimator after intravenous injection in the rats. However, it was difficult to obtain images with stable high accumulation in the liver since both bone marrow and heart imaging were labelled too intensely. However, 95% of nuclide could be accumulated in the liver when a preparation obtained simply by mixing the $^{111}InCl_3$ solution with 0.01 N NaOH, and 0.1 M phosphate buffer (PH 6.5) containing 10% mannitol at the volume ratio of 2:5:5 was used.

Stabilizer was not used during the initial steps of the method. Aggregation was observed over time after preparation, and resulted in imaging of the lungs. Then mannitol was employed as a stabilizer.

The particle diameter of the ^{111}In colloid was greater than that of ^{198}Au colloid (0.03 μm) but smaller than that of ^{99m}Tc-Sn colloid (0.7 to 1.0 μm), with a narrower range of distribution. Therefore, stable distribution into the liver was achieved.

The organ distribution of a radioactive colloid may be influenced also by the condition of the reticuloendothelial system. Then the changes in K_L by increasing the dose was studied, but no difference was observed within the range where measurement was possible. This result may be different from that $^{111}InCl_3$ solution containing no carrier, and therefore administration of a considerably large amount of the solution cannot be a burden to the reticuloendothelial system. The K_L values remained unchanged by the addition of an activator or suppressor to the reticuloendothelial system. Furthermore, the K_L values correlated significantly with those values of hepatic blood flow measured by the hydrogen gas clearance method. These results suggest that the clearance of ^{111}In colloid may be a useful index of hepatic blood flow, as long as the administration dose is below the limit of uptake for the reticuloendothelial system.

Recently, a new liver scintigraphy using ^{99m}Tc-DTPA-galactosyl human serum albumin (GSA) has been developed. GSA binds specifically to the asialoglycoprotein receptors on the membrance of hepatocytes. Therefore, liver imaging with ^{99m}Tc-GSA reflects receptor binding activity, and the parameter calculated from the intensity of images is thought to be correlated well with the liver function (12).

Although ^{111}In colloid is promising, further clinical experience is required to elucidate its usefulness.

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