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Assessment of hepatic excretory function in chronic liver disease by hepatobiliary scintigraphy

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Hepatobiliary scintigraphy was performed in 23 normal subjects and 47 patients with chronic liver disease (chronic hepatitis; n=27, liver cirrhosis; n=20) to evaluate its availability as a test of liver function. After intravenous administration of Tc-99m N-pyriodxyl-5-methyl-tryptophan, the data were acquired for 60 min and the time-activity curves of ROIs (the heart and liver) were generated. In two compartment model simulation, the early blood clearance rate (*kl*), late blood clearance rate (*km*), hepatic uptake rate (*ku*), hepatic excretion rate (*ke*), and hepatic excretion T 1/2 were calculated. There was no significant difference in those four *k* values in normal and chronic hepatitis. However, in liver cirrhosis each of them, except *km*, was lower than in normal subjects. The *kl* value correlated closely with the indocyanine green plasma clearance test, whereas the *ke* and T 1/2 values were closely correlated with the level of serum bilirubins. Only hepatobiliary scintigraphy showed the excretory function of the liver quantitatively and the *ke* value was helpful in detecting hepatic excretory dysfunction early in chronic liver disease before serum bilirubins increased.

Key words: Hepatobiliary scintigraphy, Tc-99m PMT, Liver function, Chronic hepatitis, Liver cirrhosis

INTRODUCTION

RADIONUCLIDE STUDIES with radioactive colloid have been applied to evaluate liver function in chronic liver disease.[1–5] The appearance of extrahepatic uptake in Tc-99m colloid scintigraphy such as in the spleen and bone marrow has been interpreted as an indication of poor liver function[1–3] and the usefulness of the colloid extraction rate in the evaluation of diffuse hepatocellular disease has been reported.[4,5] However, the radioactive colloid study does not provide information about hepatic excretory function. Although the main use for hepatobiliary scintigraphy is to rule out acute cholecystitis, it has been applied to the assessment of liver function.[6–9] The liver function test using hepatobiliary scintigraphy may have the advantage of obtaining quantitative information about hepatic uptake and excretion simultaneously as well as blood clearance of radioactive agents. In this study, the availability of hepatobiliary scintigraphy as a liver function test, especially in the assessment of hepatic excretory function, is discussed.

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MATERIALS AND METHODS

Hepatobiliary scintigraphy was performed in 23 normal subjects (normal volunteers and hospital controls) and 47 patients with chronic liver disease in Ehime University Hospital. Normal subjects (5 females and 18 males) with a mean age of 53 yr, ranging 35 to 70 yr, were chosen who had no history of both hepatic or biliary diseases and showed normal liver function in blood tests. Of the 47 patients

with chronic liver disease (14 females and 33 males, mean age: 46 yr; range 16 to 75 yr), there were 27 patients with chronic hepatitis (CH) and 20 patients with liver cirrhosis (LC). The data on blood tests of liver function such as serum total bilirubin (TB), serum direct bilirubin (DB), serum total protein (TP), serum albumin (Alb), serum glutamate oxalacetic transaminase (GOT), serum glutamate pyruvate transaminase (GPT), gamma-glutamyl transpeptidase (γ-GT), alkaline phosphatase (AP), cholinesterase (CE), zinc sulfate turbidity test (ZTT), and indocyanine green (ICG) test were available for each patient and the interval between these tests and hepatobiliary scintigraphy was within two weeks. The diagnosis was established by a histological examination from biopsied specimens in all patients with CH and 7 patients with LC. The remainder with LC were diagnosed clinically.

After at least 4 hours' fasting a patient lay supine under a gamma camera with a large field of view equipped with a low energy, high resolution, parallel hole collimator. Tc-99m N-pyridoxyl-5-methyltryptophan (PMT) characterized by rapid blood clearance, fast hepatobiliary transit, low urinary excretion[10] was injected intravenously at a dose of 185 MBq (5 mCi) and serial images were acquired at 5, 10, 20, 30, 45, 60 min. The data were simultaneously transferred to a computer on a 64×64 matrix every 30 seconds for 60 min.

Two regions of interest (ROI) were created on the computer image, one over the heart and another over the right lobe of the liver. The counts from both ROIs were corrected for physical decay and the time-activity curves were generated. The cardiac time-activity curve was analyzed by nonlinear, unweighted, least squares fitting to obtain the early blood clearance rate (*kl*) and late blood clearance rate (*km*) of the radionuclides by means of the following bi-exponential function:

$$\text{Cardiac counts}(t) = A*\exp(-kl*t)+(B*\exp(-km*t) \quad (1)$$

where A and B are constants. The hepatic time-activity curve was also fitted with the following bi-exponential function to obtain the hepatic uptake rate (*ku*) and hepatic excretion rate (*ke*):

$$\text{Hepatic counts}(t) = C*\exp(-ke*t)-D*\exp(-ku*t) \quad (2)$$

where C and D are constants. The hepatic excretion T 1/2 was acquired from the following equation:

$$\text{T } 1/2 = \frac{0.693}{ke} \quad (3)$$

The statistical difference between the groups was analyzed by Student's t-test for unpaired values.

RESULTS

Five scintigraphic parameters in normal subjects and patients with chronic liver disease are shown in Table 1. No significant differences between normal and CH in *kl*, *km*, *ku*, and *ke* were seen, but between normal and LC, there were statistically significant differences in *kl*, *ku*, *ke*, and T 1/2. The *km* value did not depend on hepatic diseases.

The coefficients of correlation between scintigraphic parameters and the values obtained in liver function blood test are shown in Table 2. The *kl* value showed a good correlation with the *k* value for ICG plasma clearance (k-ICG) (r=0.858). The *km* value showed no significant correlation with any blood test result. The *ku* value showed the same pattern of correlation as that of *kl*, while the T 1/2 value correlated well with the levels of TB (r=0.802) and DB (r=0.768). The *ke* value had a relatively better correlation with k-ICG, DB, and TB (r= 0.670, −0.661, and −0.648, respectively). The plot of *ke* in relation to DB is shown in Fig. 1. The normal range of the level of DB in our institute was from 0.1 to 0.6 mg/dl. All patients remained within the normal DB range except two with the *ke* value greater than 0.02. In the *ke* range from 0.015 to 0.02, about two-thirds of the patients showed an

Table 1 Values for five scintigraphic parameters

	Normal (n=23)	Chronic hepatitis (n=27)	Liver cirrhosis (n=20)
kl (/min)	0.288±0.0413 (mean±s.d.)	0.286±0.0299	0.182±0.0348**
km (/min)	0.0191±0.00456	0.0196±0.00605	0.0171±0.00483
ku (/min)	0.326±0.0708	0.287±0.0710	0.172±0.0505**
ke (/min)	0.0347±0.00520	0.0309±0.00963	0.0167±0.00642**
T 1/2 (min)	20.4±3.27	25.9±13.0*	59.8±58.6**

kl: Early blood clearance rate; *km*: Late blood clearance rate; *ku*: Hepatic uptake rate; *ke*: Hepatic excretion rate; T 1/2: Hepatic excretion T 1/2, *p<0.05, **p<0.01.

Table 2 Coefficients of correlation between scintigraphic parameters and blood tests of liver function

kl		*ku*		*ke*		T 1/2	
test	r	test	r	test	r	test	r
k-ICG	0.858	k-ICG	0.709	k-ICG	0.670	TB	0.802
CE	0.662	CE	0.517	DB	−0.661	DB	0.768
ZTT	−0.505	ZTT	−0.511	TB	−0.648	k-ICG	−0.447
TB	−0.467	DB	−0.497	CE	0.527	CE	−0.408
DB	−0.460	TB	−0.485	ZTT	−0.481	Alb	−0.291
Alb	0.396	Alb	0.377	Alb	0.389	ZTT	0.289
GOT	−0.342	AP	−0.349	GOT	−0.366	GOT	0.273
AP	−0.303	GOT	−0.327	γ-GT	−0.324	AP	0.151
γ-GT	−0.212	γ-GT	−0.225	AP	−0.308	γ-GT	0.135
GPT	0.134	TP	0.125	GPT	0.121	TP	−0.100
TP	0.017	GPT	0.060	TP	0.059	GPT	−0.047

r: Correlation coefficient; k-ICG: *k* value for indocyanine green plasma clearance; TB: Serum total bilirubin; DB: Serum direct bilirubin; TP: Serum total protein; Alb: Serum albumin; CE: Cholinesterase; ZTT: Zinc sulfate turbidity test; GOT: Serum glutamate oxalacetic transaminase; GPT: Serum glutamate pyruvate transaminase; AP: Alkaline phosphatase; γ-GT: Gamma-glutamyl transpeptidase.

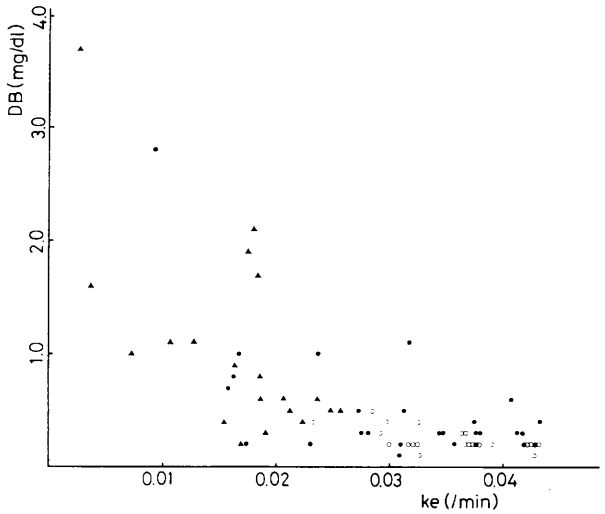

Fig. 1 Plot of hepatic excretion rate (*ke*) versus serum direct bilirubin (DB) in normal subjects (○), patients with chronic hepatitis (●), and patients with liver cirrhosis (▲).

increase in DB. When the *ke* value was decreased to less than 0.015, the level of DB was increased to more than 1.0 mg/d*l* in all patients.

DISCUSSION

Although a number of blood tests have been used to distinguish and assess hepatocellular injury and biliary tract dysfunction or obstruction, there are very few tests which assess hepatic excretory function directly. In hepatocellular diseases, there is usually interference in the three major phases of bilirubin metabolism: hepatic uptake, conjugation, and excretion into bile. Of these steps, excretion is the rate-limiting step and is usually impaired to the greatest extent. Therefore, to assess excretory function of the liver is very important and useful in the management of a patient with hepatitis or liver cirrhosis.

The *kl* value obtained from the time-activity curve of the ROI over the heart correlated well with the value for k-ICG. These two values corresponded to the rate of blood clearance of each agent. The values for *ku* and *ke* were calculated by the analysis of the hepatogram obtained from the ROI over the right lobe. The *ku* value represented the accumulation rate for PMT which was extracted from the circulation to the hepatic compartment and *ke* the disappearance rate from the hepatic compartment to the biliary system. Because the amount of PMT administered was a tracer dose foı scintigraphy and low urinary excretion was one of the characteristics of PMT,[10] *ku* was thought to be mainly a reflection of the effective blood flow of the hepatic parenchyma. Therefore, it was not unexpected that the pattern of correlation of *kl* was similar to that of *ku*. The T 1/2 value was a reciprocal of *ke* and showed the best correlation with the level of TB.

The increase in serum bilirubins is considered to be due to interference in the hepatic excretion of bile. However, it would not occur in its early stage. The plot of *ke* versus DB (Fig. 1) shows that the level of DB remains in the normal range unless the *ke* value becomes lower than 0.02. It is possible that the threshold for elevation of the level of DB would be about 0.02 for *ke*. The *ke* value is a sensitive index and is thought to be helpful in the early detection of excretory dysfunction of the liver before an increase in serum bilirubins.

Hepatobiliary scintigraphy has generally been used

as a noninvasive examination procedure for the diagnosis of acute cholecystitis and the assessment of bile passage and detection of obstructive changes in the biliary system including the intrahepatic and extrahepatic ducts. When chronic liver disease is complicated with a biliary obstruction causing an increase in serum bilirubins, hepatobiliary scintigraphy is useful in the differentiation of its causes by reading serial scintigrams. The findings of intrahepatic and/or extrahepatic bile pooling,[11,12] prolonged transit time,[13] segmental narrowing and abrupt cutoff of the common bile duct[12] suggest the presence of biliary obstruction.

This scintigraphic method for the assessment of liver function is noninvasive, relatively simple, and can be performed with ordinary hepatobiliary imaging simultaneously. The *kl* value has exactly the same meaning as the k-ICG value. The values for *ke* and T 1/2 offer quantitative information about the excretory function of the liver. It is important that the excretory function of the liver is assessed quantitatively by an analysis of the hepatogram from hepatobiliary scintigraphy only.

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