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—Original Article—

CONSIDERATION OF HEPATIC FACTOR INFLUENCE ON DRIP INFUSION CHOLANGIOGRAPHY

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Summary

The plasma disappearance rate (K) and transfer rate constants for the two compartmental system of Indocyanine Green (ICG) were calculated in visualized and nonvisualized cases of the biliary tract with hepatobiliary disease using drip infusion cholangiography (DIC). In nonvisualized cases with hepatocellular disrder K and the fractional hepatic removal rate mainly decreased, and in nonvisualized cases with cholelithiasis the fractional biliary secretory rate significantly decreased by DIC-A, utilizing it as a screening test. Three methods (B, C and D) of drip infusion cholangiography were established according to the result of the ICG test. Through DIC-B, -C or -D in addition to DIC-A the visualization of the biliary tract significantly elevated in patients with hepatocellular disorder and cholelithiasis. These results were confirmed using ^{131}I-iodipamide. In some cases the serum transaminase activity elevated, but the elevation was temporary.

Key Words: *drip infusion cholangiography, indocyanine green test, ^{131}I-iodipamide.*

Cholecystocholangiography has been performed for many years. This is one of the most important methods used to diagnose hepatobiliary disease. In patients with hepatobiliary disease the oral administration method and the single intravenous injection method are not sufficient to visualize the gallbladder and the bile duct[1]. For this reason, many modified methods have been reported and the continuous drip infusion method has been developed[2,3].

The contrast medium used in cholecystocholangiography is an organic anion product which is carried from the blood to the liver and excreted from the liver to the bile[4]. The same transport mechanism of other organic anion substances has been utilized in the liver function test as Bromsulfalein (BSP) and Indocyanine Green (ICG).

In this study the relationship between the visualization of the biliary tract by drip infusion cholangiography (DIC) and the result of ICG test were observed in patients with hepatobiliary disease, and the appropriate DIC was determined according to the result of ICG test.

Materials and Methods

Materials: DIC and ICG tests were performed in 198 patients, including 167 with clinically suspected gallstone, 11 with acute hepatitis, 9 with chronic hepatitis and 11 with liver cirrhosis. Patients with hepatocellular disorder were diagnosed by histological findings

Table 1. Methods of infusion cholangiography

Methods	50% iodipamide (ml)	5% glucose solution (ml)	Infusion time (min)	Iodipamide gr/min	Iodipamide gr(Total)
A	40	100	60	0.33	20
B	60	200	90	0.33	30
C	40	300	120	0.16	20
D	60	400	120	0.25	30

DIC-A was examined in all patients basically as a screening test. In patients in whom DIC-A did not serve to visualize the gallbladder DIC-B, -C or -D was performed according to the result of ICG test.

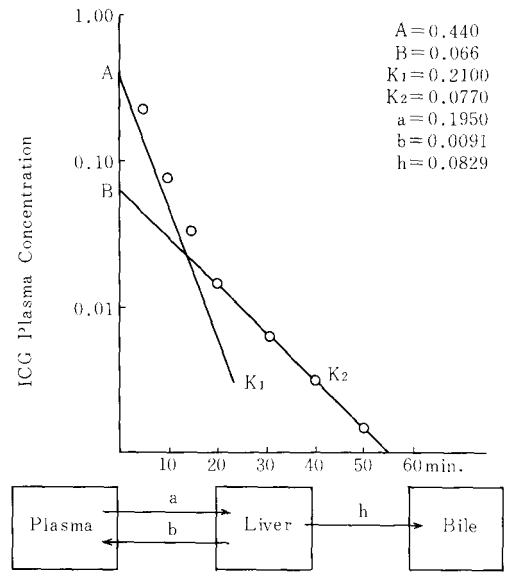
of biopsied specimens in liver tissue.

Methods of DIC: Four methods, A, B, C and D were established for DIC (**Table 1**). Method A (DIC-A), in which 50% meglumine iodipamide* was diluted in 100 ml of 5% glucose and administered by slow intravenous injection during a period of sixty minutes, was utilized basically as a screening test and was performed in all patients. In such a case in which DIC-A did not serve to visualized the gallbladder, DIC-B, -C or -D was performed according to the result of ICG test.

X ray films of the gallbladder and the bile duct were obtained at the end of the infusion and at 30, 60, 90, and 120 minutes after the infusion.

ICG test: The disappearance rate of ICG (K_{ICG}) was calculated from the first linear part of the disappearance curve after a single injection of ICG** 0.5 mg per kg of body weight. Three fractional transfer rates were determined for the two compartmental system of ICG. Transfer rate (a) is the fractional hepatic removal rate, (b) is the fractional hepatic plasma reflux rate and (h) is the fractional biliary secretory rate[5,6] (**Fig. 1**).

Examination using ^{131}I-iodipamide: 250 microcurie of ^{131}I-iodipamide*** mixed with



a: The fractional hepatic removal rate
b: The fractional hepatic reflux rate
h: The fractional biliary excretory rate

Fig. 1. ICG plasma disappearance curve and kinetics model in normal subject.

20 ml of 50% nonradioactive iodipamide was administered by a single injection to 5 cases, including 2 cases of gastric ulcer as control and one each of cholelithiasis, Rotor's type of hyperbilirubinemia and liver cirrhosis. 300 microcurie of ^{131}I-iodipamide mixed with 40 ml of 50% nonradioactive iodipamide and 100 ml of 5% glucose was administered by slow infusion during a period of sixty minutes

* Biligrafin, Nihon Schering KK. Japan.
** Diagnogreen, Daiichi Seiyaku Co., Ltd. Japan.
*** ^{131}I-Biligrafin, Radioisotope Association Japan.

to each one case of gastric ulcer, as control, chronic hepatitis and liver cirrhosis.

The plasma disappearance of ^{131}I-iodipamide were observed through the blood samples obtained at 10, 20, 30, 40, 50, 60, 90 and 120 minutes after the injection. Radioisotope activity of these samples was counted by scintilation counter of Well type. The sagittal linear scanning of the body was examined at 5, 30, 60, 90, 120, 150 and 180 minutes after the injection, and S_1 and S_2 values were measured by the planimeter. S_1 value mainly revealed the accumulation of radioactivity in the liver and the gallbladder, and S_2 value mainly revealed the accumulation in the urinary bladder (**Fig. 2**).

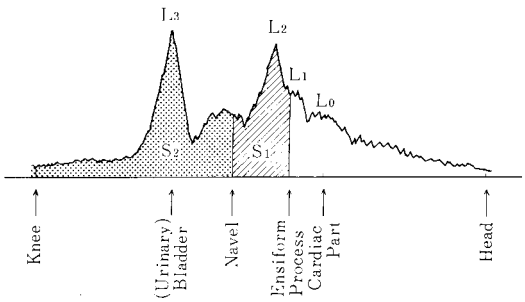


Fig. 2. Linear scanning of ^{131}I-iodipamide in every parts of body.
S_1 and S_2 mean activity levels of radioisotope in the gallbladder and in the urinary bladder. These areas were measured by planimeter.

Results

1. Relationship between the visualization of the gallbladder and the result of ICG test

In cases with cholelithiasis K_{ICG} did not show a significant difference between visualized and nonvisualized cases of the gallbladder. In acute hepatitis and chronic hepatitis K_{ICG} of cases with visualized gallbladder showed a significantly higher value than that of nonvisualized cases.

In cases with cholelithiasis transfer rate (a) and (b) did not show a significant difference between visualized and nonvisualized cases of the gallbladder, whereas transfer rate (h) decreased significantly in nonvisualized cases. In hepatocellular disorder transfer rate (a) decreased and (b) increased in nonvisualized cases with acute hepatitis and chronic hepatitis. Transfer rate (h) showed a significant decrease in nonvisualized cases with acute hepatitis (**Table 2**).

2. Visualization of the gallbladder and the bile duct

By DIC-A the gallbladder was visualized in 111 cases (66.5%) of 167 cases with clinically suspected gallstone and the common bile duct was visualized in 148 cases (88.6%). The gallbladder was visualized in 20 cases (64.5%) of 31 cases with hepatocellular disorder,

Table 2. Relationship between the visualization of the gallbladder and the result of ICG test

	Visualized				Non-visualized			
	K	a	b	h	K	a	b	h
Cholelithiasis	0.1684 ±0.0362	0.1760 ±0.0393	0.0075* ±0.0045	0.0167* ±0.0093	0.1677 ±0.0272	0.1739 ±0.0312	0.0176* ±0.0116	0.0138* ±0.0100
Acute hepatitis	0.1791* ±0.0454	0.1749* ±0.0444	0.0127* ±0.0088	0.0347* ±0.0181	0.0833* ±0.0381	0.0895* ±0.0390	0.0210* ±0.0074	0.0198* ±0.0105
Chronic hepatitis	0.1063* ±0.0346	0.1267* ±0.0386	0.0128* ±0.0063	0.0423 ±0.0417	0.0558*	0.0633*	0.0253*	0.0187
Liver cirrhosis	0.0786 ±0.0314	0.0808 ±0.0294	0.0082 ±0.0066	0.0566 ±0.0287	0.0606 ±0.0329	0.0622 ±0.0338	0.0091 ±0.0063	0.0399 ±0.0062

*The significant difference ($p<0.05$) was recognized between visualized and nonvisualized cases of the gallbladder through DIC-A.

including 7 cases of acute hepatitis, 7 cases of chronic hepatitis and 6 cases of liver cirrhosis. The common bile duct was visualized in 8 cases (25.8%), including 4 cases of acute hepatitis, 2 cases of chronic hepatitis and 2 cases of liver cirrhosis (**Table 3**).

DIC-B or -D were utilized in 31 cases with suspected gallstone and DIC-C was utilized in 8 cases with hepatocellular disorder, in which the gallbladder failed to visualize through DIC-A. The gallbladder was visualized in 13 cases performed by DIC-B or -D and in 7 cases by DIC-C (**Table 4**).

Consequently the visualization of the gallbladder elevated from 66.5% to 87.3% in patients with suspected gallstone and from 64.5% to 96.4% in patients with hepatocellular disorder through DIC-B, -C or -D in addition to DIC-A.

3. Detection rate of gallstone by DIC

In 69 cases with gallstone was finally confirmed through DIC. Using DIC-A gallstones were detected in 37 cases (53.6%). In 10 of 32 nonvisualized cases by DIC-A gallstones were demonstrated through DIC-B or -D. In the rest of the cases gallstones were confirmed by percutaneous transhepatic cholangiography or surgical operation (**Table 5**).

Consequently the detection rate of gallstone elevated from 53.6% to 68.1% through DIC-B or -D in addition to DIC-A.

4. Examination using ^{131}I-iodipamide

Accumulation of radioactivity in upper and lower abdomen among cases of hepatobiliary disease was observed after a single intravenous injection. The plasma disappearance curves were very similar in both cases of hepatobiliary disease and control. The S_1–S_2 ratio decreased in cases of hepatobiliary disease, although it increased in control subjects (**Fig. 3**).

From these results it was suggested that most of the contrast medium was excreted into the urine in patients with hepatobiliary disease when a single intravenous injection was performed. When DIC was utilized, however, contrast medium in the urine was relatively small and it was accumulated effectively in the gallbladder (**Fig. 4**).

Table 3. Visualization Rate of the Gallbladder and the Bile duct through DIC-A

	Gallbladder	Common bile duct
Suspected gallstone	66.5%	88.6%
Hepatocellular disorder	64.5%	25.8%

Table 4. Visualization rate of the gallbladder through DIC-B, -C or -D in addition to DIC-A

	Visualized cases through DIC-A	Visualized cases through DIC-B or -D	Total of visualized cases
Suspected gallstone (167 cases)	111 (66.5%)	13 of 31 cases	124 of 142 cases (87.3%)
Hepatocellular disorder (31 cases)	20 (64.5%)	7 of 8 cases	27 of 28 cases (96.4%)
Acute hepatitis (11 cases)	7	1	8
Chronic hepatitis (9 cases)	7	1	8
Liver cirrhosis (11 cases)	6	5	11

The visualization of the gallbladder elevated from 66.5% to 87.3% in patients with suspected gallstone and from 64.5% to 96.4% in patients with hepatocellular disorder through DIC-B, -C or -D in addition to DIC-A.

Table 5. Detection rate of the gallstone through DIC-A, and through DIC-B and/or DIC-D in addition to DIC-A

	by DIC-A	by DIC-B or -D	by PTC or surgical operation
in 69 cases gallstone was detected	detected in 37 cases (53.6%)		
	non detected in 32 cases (46.4%)	detected in 10 cases	
		non detected in 22 cases	detected by PTC in one case
			detected by surgical operation in 21 cases

Gallstone was detected in 37(53.6%) of 69 cases finally confirmed through DIC-A. In 10 of 32 nonvisualized cases by DIC-A, gallstone was demonstrated through DIC-B or DIC-D. Consequently gallstone was detected in 47(68.1%) of 69 cases through DIC-B or DIC-D in addition to DIC-A.

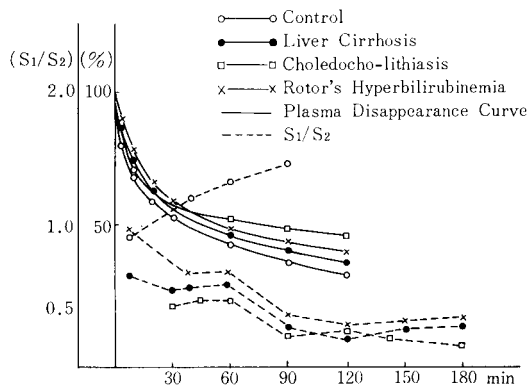


Fig. 3. Accumulation of radioactivity in upper and lower abdomen in hepatobiliary diseases through a single intravenous injection method.
The plasma disappearance curves are very similar in both hepatobiliary disease and control subject. S_1—S_2 ratio, however, decreased rapidly in patients with hepatobiliary disease and increased in control subjects.

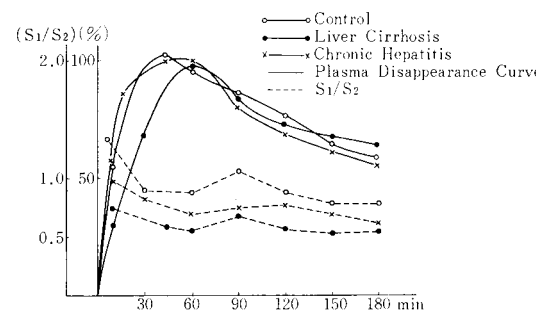


Fig. 4. Accumulation of radioactivity in upper and lower abdomen in hepatobiliary diseases through drip infusion method.
S_1—S_2 ratio slowly decreased both in cases with hepatobiliary disease and control subject.

5. Changes in liver function tests and urinary findings after DIC

In 8 cases with cholelithiasis and 10 cases with acute hepatitis, icterus index, serum GOT, serum GPT and alkaline phosphatase were determined before and on every 2 days after DIC. In 6 cases of cholelithiasis, in which 5 cases were performed by DIC-B or -D and one case by DIC-A, and in 4 cases of acute hepatitis, in which 3 cases were performed by DIC-A and one case by DIC-C, GOT and GPT elevated after DIC. There was no elevation in icterus index and alkaline phosphatase. The elevation of transaminase was

transient and the enzyme activity returned to the value before DIC within 7 or 14 days. No change was indicated in examination of the urine.

Discussion

Iodipamide, one of organic anion products, is a substance which transfers from the blood to the bile through the liver. It binds to albumin in plasma and is taken up into the liver through cytoplasmic protein. Two specific carrier proteins (Y and Z protein) have been described by Levi et al.[7], and these proteins carry also anionic dyes, e.g. BSP and ICG. It is suggested from these results that the transport process of iodipamide is very similar to that of BSP and ICG.

Kanai[8] and Barber-Riley et al.[9] reported the transfer rates of BSP and ICG in hepatobiliary diseases. In acute hepatitis transfer rates of (a) and (h) were low. In liver cirrhosis (a) was apparently low. In cholelithiasis (h) was mainly low. These results suggested that the biliary excretion of iodipamide through the liver is different among these diseases.

Fischer[10] described the appropriate dose of contrast medium for the visualization of the gallbladder and the bile duct, and it was 0.6 ml per kg of body weight of 52% iodipamide in dog. Iodipamide was excreted into the urine when administered dose became over this concentration. Loeb et al.[11] also reported that at low plasma concentration, iodipamide was not excreted in the urine, whereas at high plasma concentration, urinary excretion increased sharply. It appears that a biliary concentration of iodipamide sufficient to achieve adequate radiographic visualization of the biliary tree can be obtained without significant renal excretion by constant infusion of iodipamide at a appropriate rate in dog. Other investigators[12,13] reported that iodine concentration of 1–2% should be maintained in bile for good visualization of the biliary tract. By DIC prolonged optimal doses of contrast medium are able to deliver to the bile through the liver cell according to the parameters of ICG.

The fractional hepatic removal rate of ICG showed significant decrease in nonvisualized cases with acute hepatitis and chronic hepatitis, and the fractional biliary excretory rate decreased in nonvisualized cases with acute hepatitis and cholelithiasis.

From these results four methods of DIC were established. DIC-A is a modified method of Ikeda et al.[14] and Bornhurst et al.[15] It was performed in all patients as a screening test. DIC-B or -D is a method in which a larger amount of iodipamide is administered than that in DIC-A, and these two methods are utilized in patients with gallstone, because of decreased fractional biliary excretory rate with normal fractional hepatic removal rate of ICG. DIC-C is a method which is administered the same amount of iodipamide by DIC-A during long period. This method is utilized in patients with hepatocellular disorder, because of reduced fractional hepatic removal rate of ICG.

The visualization of the gallbladder elevated from 66.5% to 87.3% through DIC-B or -D in addition to DIC-A in cases with suspected gallstone. In cases with hepatocellular disorder the visualization of the gallbladder elevated from 64.5% to 96.4% through DIC-C in addition to DIC-A. The detection rate of gallstone is elevated from 53.6% through DIC-A to 68.1% through DIC-B or DIC-D in addition to DIC-A.

The advantage of DIC to a single injection was confirmed by using ^{131}I-iodipamide. Most of the ^{131}I-iodipamide was excreted into the urine in cases with hepatobiliary disease through a single intravenous injection, whereas

the isotope was accumulated effectively in the liver and the gallbladder through DIC.

It has been reported that iodipamide is one of the most toxic contrast materials in use in radiology[16], and these toxic reactions are related to the dose administered and/or the plasma concentration of iodipamide[17]. In some cases the transaminase activity elevated after DIC in this study, but the elevation was temporary. No change was shown in examination of the urine.

From these results it is concluded that DIC is useful in clinical medicine to diagnose biliary disease, and that the appropriate method should be determined by analysis of the ICG plasma disappearance curve.

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