

Predictive Evaluation of the Effects of Biliary Decompression by Biliary ICG Clearance Test (ICG Bmax) for Patients with Obstructive Jaundice

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ABSTRACT: To quantitate the effects of biliary decompression on hepatic functional reserve before operation in patients with obstructive jaundice, we developed a new method of maximal hepatic removal of indocyanine green in the bile (ICG Bmax). This was calculated from the peak ICG concentration in the bile and the peak concentration time after its administration via antecubital vein using regression analysis.

This study involved 13 normal controls and 26 jaundiced patients. ICG Bmax of the normal controls indicated more than 0.5. Among the jaundiced patients, 17 showed an ICG Bmax value of more than -0.5 early during biliary decompression and 87% of them satisfactorily tolerated further radical operation. The remaining patients in whom ICG Bmax initially showed less than -0.5, but 67% of them had an unfavorable outcome postoperatively. Six of the nine patients whose ICG Bmax was less than -0.5 prior to operation suffered severe postoperative complication, and three of whom died from hepatic failure. These results indicated that ICG Bmax evaluation during an early period of biliary decompression provided a reliable assessment of the effects and a prediction of biliary drainage. ICG Bmax evaluation is also useful to the timely decision of radical operation.

INTRODUCTION

Two-step surgery comprising preliminary biliary decompression followed by a radical operation after improvement of jaundice has become a common surgical treatment for obstructive jaundice.¹⁻³⁾ However, in some cases, biliary decompression may provide only a limited relief of jaundice, and complications will develop subsequent to the radical operation.^{4,5)}

Although reliable indexes predictively evaluating biliary decompression effects and prognosis are indispensable, they have not yet been established. Indocyanine green (ICG) has long

been used to measure hepatic function.^{6,7)} We have previously evaluated hepatic removal of ICG in the bile by using an external T-tube in patients with common bile duct stones, observing the appearance of ICG in the bile for about 15 minutes after injecting the dye and a peak biliary ICG concentration for about 2 hours.⁸⁾ We have also observed that ICG appeared in the bile late and its concentration was lower in jaundiced patients a few days after biliary decompression. However, ICG appeared earlier and the concentration increased with recovery of the hepatic function.

We have devised a new method to calculate the maximal hepatic removal rate in the bile

(ICG Bmax) and report its usefulness for evaluating the effects of biliary decompression on relieving jaundice and establishing the prognosis.

MATERIALS AND METHODS

Twenty-six patients who underwent biliary decompression for obstructive jaundice at the Second Department of Surgery, Nagasaki University Hospital, were involved for this study. Among these patients three had malignant neoplasms; three others included one with chronic pancreatitis, one with intrahepatic stones, and one with choledocholithiasis. Thirteen non-jaundiced patients with cholelithiasis who underwent cholecystectomy and external T-tube drainage of common bile duct comprised control studies; their liver functions were within normal limits.

Measurement of ICG Bmax

After collecting a baseline bile sample early in the morning, 0.5 mg/kg body weight of ICG (Diagnogreen, Daiichi Seiyaku Co., Tokyo) was injected via the antecubital vein in patients who had fasted overnight. The bile was collected at 15-minute intervals for 6 hours in light-shielded test tubes. Each sample of bile (0.1 ml.) was diluted with 2.9 ml. of normal saline solution, and the concentration of ICG was then measured by clinical spectrophotometry (Uvidec 77, Japan spectroscopic Co. Ltd.) at 805 nm within 24 hours after sample collection. ICG Bmax was calculated from the peak ICG concentration in the bile and the peak concentration time by regression analysis as described by Barber *at at.*⁹⁾ ICG Bmax evaluation was carried out 84 times in these patients.

Calculation of ICG Bmax

Patients undergoing percutaneous transhepatic biliary drainage (PTBD) for obstructive jaundice showed low biliary ICG concentration and delayed appearance of the dye in the bile early during biliary decompression. Progressive improvement of hepatic functions by biliary decompression, bile concentration and appearance of ICG in the bile heightened and hastened

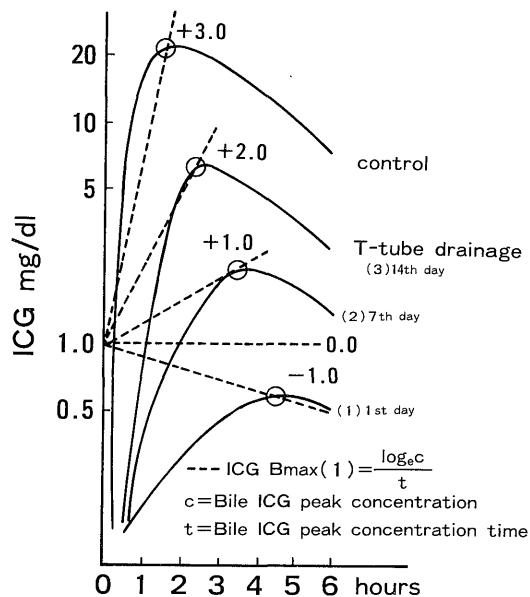


Fig. 1. ICG concentration in the bile and calculated ICG hepatic removal rate on the 1st, 7th and 14th day after T-tube drainage in a case of benign biliary obstruction. Control represented a case of choledocholithiasis without jaundice

(Fig. 1). This phenomenon can be expressed by two factors: the maximum biliary ICG concentration and the time of the peak ICG concentration (peak concentration time).

The values of ICG concentration were plotted in semilogarithmic coordinates to evaluate a wide range of concentration. Peak concentration was determined by 6-hour serial measurement after administration of ICG of 0.5 mg/kg.

$$\text{ICG Bmax (1)} = \frac{\log c}{t}$$

c: peak biliary concentration

t: peak concentration time

With this formula, ICG concentrations of 1 mg/dl or greater are graphically represented as positive values, but those less than 1 mg/dl as negative values (Fig. 1). Therefore, the formula was converted by multiplying the peak concentration values by 10 so that all plots converge at 0.1 mg/dl ICG and 0 hour.

$$\text{ICG Bmax (2)} = \frac{\log (10 \times c)}{t}$$

Since ICG Bmax (2) is never less than 0.1 mg/dl, the slope of this formula is always positive. ICG Bmax (2) was further converted to natural

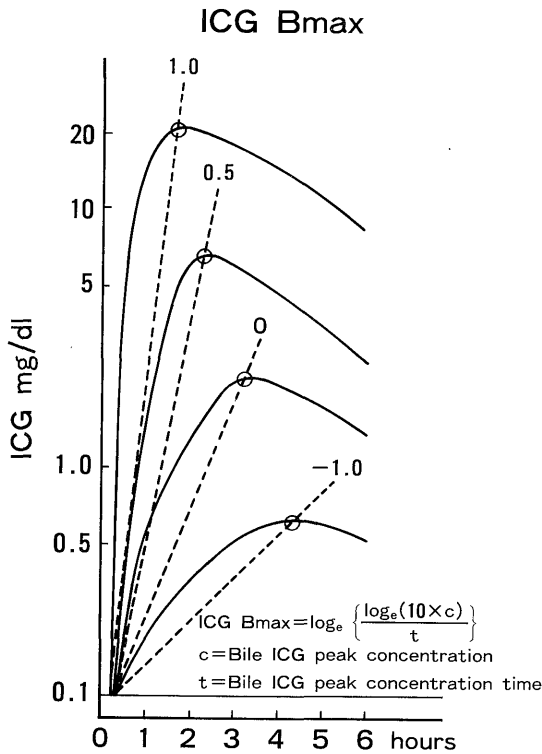


Fig. 2. Graphic representation of calculated ICG Bmax

logarithms for greater ease of the use of the values in subsequent analyses. (Fig. 2)

$$ICG\ Bmax = \text{Loge} \left\{ \frac{\text{log}_e(10 \times c)}{t} \right\}$$

By this formula, ICG Bmax value changes

Table 1. ICG Bmax in Control Group

	Drainage Procedure	Peak Time (hour)	Peak Time (mg/dl)	ICG Bmax
1.	A T-tube	2.0	32.3	1.10
2.	A T-tube	2.75	16.9	0.62
3.	B T-tube	1.5	11.3	1.20
4.	A T-tube	1.75	11.6	1.00
5.	B splint-tube	1.25	11.3	1.30
6.	A T-tube	1.5	20.4	1.30
7.	A T-tube	1.5	26.3	1.30
8.	C splint-tube	2.0	29.5	1.70
9.	A T-tube	1.75	32.8	1.20
10.	B T-tube	2.5	19.1	0.74
11.	A T-tube	1.5	8.0	1.10
12.	A T-tube	2.0	29.4	1.00
13.	A T-tube	2.5	22.7	0.76

serially form negative to positive as the peak concentration increases or the peak concentration time is reduced.

RESULTS

The control group showed maximum ICG concentration ranging from 8 to 33 mg/dl (mean ± SD, 20.1 ± 8.2 mg/dl) and peak concentration time from 1.25 to 2.75 hours (1.9 ± 0.4 hours). All patients in this group showed ICG Bmax greater than 0.5 (1.1 ± 0.27). Twenty-six patients with obstructive jaundice were categorized into three groups according to the level of ICG Bmax values early during biliary decompression:

1. Markedly Low ICG Bmax Group (ICG Bmax < -0.5)

ICG Bmax values were considered to be markedly low when they were -0.5 or less. Nine of the 26 patients were included in this group (Table 2). In this group, the total bilirubin level ranged from 7.5 to 30.8 mg/dl with a mean of 19.91 mg/dl. The peak ICG concentration in the bile ranged from 0.305 to 1.74 mg/dl with a mean of 0.689 mg/dl. The ICG Bmax was from -1.7 to -0.8 with a mean of -1.3 ± 0.41. Eight of these nine patients responded poorly to further biliary decompression. Six of the eight patients who evidence minor improvement in ICG Bmax values prior to the radical operation had severe postoperative complications, three of whom died from hepatic failure. Only three among this group survived without postoperative complication.

2. Moderately Low ICG Bmax Group (0 > Bmax ≥ -0.5)

ICG Bmax values were considered to be moderately low when they range between -0.5 and 0. Seven patients belonged to this group (Table 3). In these patients, the total bilirubin level varied from 7.0 to 25.7 mg/dl with a mean of 15.5mg./dl. The peak ICG concentration range from 1.19 to 5.35 mg./dl (mean value 2.90 mg/dl). The mean ICG Bmax was -0.33. In this group, four of the seven patients showed prolonged jaundice in spite of biliary decompression, and one of the two who had

Table 2. Operative Morbidity of Very Low ICG Bmax group (ICG Bmax \leq 0.5)

	immediately after biliary decompression		before radical operation		prolonged jaundice	repeated cholangitis	operative morbidity
	T.B. mg/dl	ICG Bmax	T.B. mg/dl	ICG Bmax			
1. B	21.1	-1.70	23.0	-1.90	+	-	death
2. B	29.0	-1.20	41.3	-2.00	+	+	death
3. G	10.2	-0.66	14.5	-1.80	+	+	death
4. C	7.5	-0.70	2.9	0.07	+	-	+
5. D	9.6	-1.60	7.9	0.14	+	+	-
6. B	30.8	-1.60	7.8	-0.03	+	+	+
7. B	26.0	-1.20	21.3	0.16	+	+	-
8. A	27.7	-0.85	15.6	-0.69	+	-	-
9. B	17.6	-0.85	10.5	-0.61	-	-	+
19.9 \pm 9.1		-1.3 \pm 0.41	16.1 \pm 11.4		-0.74 \pm 0.93	8/9, 89%	5/9, 56%

B: bile duct carcinoma

D: choledocholithiasis

G: carcinoma of the gallbladder

A: ampullary carcinoma

Table 3. Operative Morbidity of Moderately Low ICG Bmax group (0<ICG Bmax \leq 0.5)

	immediately after biliary decompression		before radical operation		prolonged jaundice	repeated cholangitis	operative morbidity
	T.B. mg/dl	ICG Bmax	T.B. mg/dl	ICG Bmax			
1. B	21.5	-0.19	5.9	0.85	+	-	+
2. B	9.7	-0.38	2.1	-0.31	-	-	-
3. P	25.7	-0.46	5.3	-0.12	-	-	-
4. G	7.0	-0.41	1.3	0.15	-	-	-
5. G	20.0	-0.12	11.1	0.16	+	+	-
6. P	11.5	-0.40	8.0	0.52	+	-	death
7. B	13.5	-0.34	3.8	0.78	+	-	-
15.5 \pm 6.9		-0.33 \pm 0.13	5.3 \pm 3.4		-0.38 \pm 0.35	4/7, 57%	1/7, 14%

G: carcinoma of the gallbladder

B: bile duct carcinoma

P: carcinoma of the pancreas

Table 4. Operative Morbidity of High ICG Bmax group (ICG Bmax \leq 0.5)

	immediately after biliary decompression		before radical operation		prolonged jaundice	repeated cholangitis	operative morbidity
	T.B. mg/dl	ICG Bmax	T.B. mg/dl	ICG Bmax			
1. H	12.8	0.34	2.2		-	-	-
2. B	14.6	0.42	2.1	1.10	-	-	-
3. P	8.1	0.30	3.5	0.55	-	-	-
4. B	8.2	0.26	1.9		-	-	-
5. B	19.9	0.72	3.5	0.46	-	-	-
6. P	12.2	0.34	2.5	1.00	-	-	-
7. G	10.7	0.15	4.1	0.28	-	-	-
8. P	23.5	0.23	3.9	0.37	-	-	death
9. P	20.3	0.13	6.4	0.21	-	-	+
10. A	25.6	0.42	15.3	-0.52	+	-	death
15.6 \pm 6.3		0.33 \pm 0.17	4.5 \pm 4.0		0.44 \pm 0.51	1/10, 10%	1/10, 10%

G: carcinoma of the gallbladder

B: bile duct carcinoma

P: carcinoma of the pancreas

A: ampullary carcinoma

H: hepatoma

severe postoperative complications died from hepatic failure.

3. High ICG Bmax Gorup (ICG Bmax ≥ 0)
Ten patients comprised this group (Table 4). The total bilirubin level was from 8.1 to 25.6 mg/dl (mean 15.6 mg/dl). The peak ICG concentration was 5.12 mg/dl (mean), and ICG Bmax was 0.33 ± 0.17 . Although the total bilirubin level in this group was similar to that of the other two groups, nine of the ten responded favorably to biliary decompression. Two patients who responded well had postoperative complications, one of whom died from an unrelated cause. A patient who failed to recover despite lengthy biliary decompression died from hepatic failure.

DISCUSSION

Recent advances in imaging techniques have facilitated early and accurate diagnosis of obstructive jaundice. Percutaneous transhepatic cholangiography (PTC) or percutaneous transhepatic bile duct drainage (PTCD) has also become a safe technique using ultrasound guidance.^{10,11} In patients with persistent obstructive jaundice, life-threatening postoperative complications will occur if this condition is not successfully treated prior to surgical intervention. It has been well documented that radical operation for malignant obstructive jaundice should not be performed until total serum bilirubin decreases to a level below 5 mg/dl by biliary decompression.^{1,12} Therefore, alleviation of obstructive jaundice by using PTCD or cholecystostomy should be mandatory, especially in the case of hepatic hilar obstruction due to malignant tumor which requires extensive surgical treatment. However, in general, length of the decompression period tends to increase because of an unreasonable fear of postoperative complications and lack of an accurate method to anticipate recovery of hepatic function by decompression, even for patients who are potentially rapidly responsive to decompression, often unnecessarily delaying operation.

To settle this problem, we examined the removal rate of indocyanine green in the bile

and found that this rate correlated well with recovery of impaired hepatobiliary function by decompression in patients with obstructive jaundice, and also that this removal rate at an early time during the decompression period enabled prediction of the varying effects of further biliary decompression. To simplify this effort, we employed the term of ICG Bmax expressed in natural logarithms by using two factors of peak ICG concentration in bile and peak ICG concentration time.

As to the impaired mechanism of bile excretion in the biliary tract in obstructive jaundice, Kojima¹² *et al* reported that the mitochondria in these impaired hepatic cells showed qualitative changes which also affected the energy dependent process of biliary excretion. ICG is excreted competitively with bilirubin by the same mechanism.¹³ These facts suggested that recovery of the impaired hepatic mechanism by biliary decompression in patients with obstructive jaundice could be monitored by examining serial changes of ICG excretion in the bile. In this study, improvements occurred in all patients prior to the radical operation as compared with those observed immediately after biliary decompression. However, improvement was notably limited in those patients with markedly low ICG Bmax group; 89% responded poorly to biliary decompression (prolonged jaundice) in spite of preoperative external biliary drainage for more than 30 days. Moreover, 56% developed cholangitis preoperatively, and 67% experienced an unfavorable outcome. These facts clearly suggest that ICG Bmax values well reflected the effectiveness of the decompression procedure, and are useful not only for prognosis at an early period of decompression but also for evaluating effectiveness of biliary excretion. Consequently, weekly ICG Bmax evaluation will provide useful information for timing radical surgery in jaundiced patients. We believe that radical operation is contraindicated when ICG Bmax value is less than -0.5.

CONCLUSION

ICG Bmax was highly sensitive to the degree of impairment of hepatic function in obstructive

jaundice. Examination immediately after biliary decompression allows early prediction of prognosis, and serial evaluations by this technique in recovery of hepatic function enables early decision making regarding surgery.

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