HEPATIC TRIMETHADIONE-OXIDIZING CAPACITY REMAINS NORMAL IN PATIENTS WITH EXTRAHEPATIC CHOLELITHIASIS

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In the present study, using trimethadione (TMO) as an indicator substrate, we estimated pre- and post-operative differences in hepatic drug-oxidizing capacity in patients with extrahepatic cholelithiasis. Only total and direct bilirubin values were significantly higher in preoperative patients than in the controls. After operative procedures, those parameters did not show significant differences from corresponding control values. The serum dimethadione (DMO)/TMO ratios estimated 4 h after administration of 4 mg/kg of TMO. Neither pre- nor post-operative serum DMO/TMO ratios were significantly different from those in the controls. These results suggest that the hepatic drug-oxidizing capacity in patients with extrahepatic cholelithiasis remains unchanged even though the bilirubin level deviated from normal.

Keywords — trimethadione; dimethadione; extrahepatic cholelithiasis; drug-oxidizing capacity

INTRODUCTION

Cholelithiasis is classified into extrahepatic type (cholecystolithiasis and choledocholithiasis) and intrahepatic type (hepatolithiasis) according to where the gallstones are localized. Only a few reports are available for the hepatic drug-oxidizing capacity in patients with cholelithiasis.^{1–3)}

We have suggested that our trimethadione (TMO) test provides a good indicator for the assessment of hepatic drug-oxidizing capacity in animals^{4–10)} and humans.^{11,12)}

In the present study, using TMO as an indicator substrate, we estimated pre- and post-operative differences in hepatic drug-oxidizing capacity in patients with extrahepatic cholelithiasis which is said to account for 98% of cholelithias found in Japan.¹³⁾ The results were compared with those from a group of age- and sex-matched control subjects.

MATERIALS AND METHODS

Materials — The TMO used was commercially available as a 66.7% powder (Mino-Aleviatin®; Dainippon Pharmaceutical Co., Ltd. Osaka, Japan).

Clinical Study — The study was performed at the Tsukuba Gakuen Hospital, Ibaraki-ken, Japan. Fifteen patients with extrahepatic cholelithiasis (10 patients with cholecystolithiasis,

and 5 with choledocholithiasis), who gave their informed consent, participated in this study. Diagnosis was established by drip infusion cholecystography, ultrasonography and laboratory tests including total cholesterol, total protein, plasma albumin, total and direct bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum γ -glutamyl transpeptidase (SGGTP), cholinesterase, alkaline phosphatase (ALP) and leucine aminopeptidase (LAP). None of the patients had any clinically significant abnormal kidney function, as judged by creatinine clearance. Patients were not taking drugs known to induce or to inhibit hepatic drug-oxidizing capacity. Most of the patients were treated with one or more (up to 3) of the following drugs: ursodesoxycholic acid, sucralfate, aceglutamide aluminium, aluminium hydroxide and magnesium hydroxide.

Ten healthy volunteers from the university staff served as controls. The mean laboratory data and liver function characteristics are listed in Table I.

The study was performed in the morning after a 12 h fast both before and 7–10 d after the surgical operation. TMO 4 mg/kg was given orally with 100 ml water, followed by breakfast 2 h later. Blood samples (0.5 ml) for estimation

of TMO and dimethadione (DMO) were collected at 4 h after administration of TMO and centrifuged. The serum was separated and frozen at -20°C until assays were performed.

TMO and DMO Assay — Serum TMO and DMO levels were determined by a gas-liquid chromatographic (GLC) method using paramethadione as the internal standard, as reported previously.¹⁴⁾

Statistical Analysis — Results are expressed as means $\pm$ S.E.M. The statistical comparison between the different groups was made by Student's *t*-test and paired comparisons test.¹⁵⁾

RESULTS

Table I list liver function characteristics and other laboratory data. As shown in this table, only total and direct bilirubin values were significantly higher in the preoperative patients than in the controls. After operative procedures, the parameters tested did not show significant differences from the corresponding control values (data not shown).

Figure 1 illustrates serum DMO/TMO ratios estimated 4 h after administration of 4 mg/kg of TMO. Thus, neither pre- (0.47 ± 0.03) nor post-operative (0.50 ± 0.03) serum DMO/TMO ratios were significantly different from those in the controls (0.55 ± 0.03).

DISCUSSION

It was reported that out of 2,024 cases of cholelithiasis in Japan, only 50 (2.5%) were of the intrahepatic type. Most (1,593 cases: 78.7%) of the remaining cases were cholecystolithiasis, and 381 (18.8%) were choledocholithiasis.¹³⁾ In the present study, we investigated hepatic drug-oxidizing capacity in patients with extrahepatic cholelithiasis, the predominant type of cholelithiasis in Japan. Before and 7 to 10 d after surgical operation, their serum samples were analyzed for TMO and its only metabolite DMO to calculate DMO/TMO ratios. This postoperative point of time was chosen because direct effects of surgical intervention would subside at about this time.

In estimating the hepatic drug-oxidizing capacity in patients with cholelithiasis, antipyrine has been used for an indicator substrate. Hepner and Vesell²⁾ reported that plasma antipyrine half-life and metabolic clearance were measured after a single oral dose of antipyrine in

FIG. 1. Serum DMO/TMO Ratios at 4 h after Oral Administration of TMO 4 mg/kg in Control Subjects (○) and Patients with Extrahepatic Cholelithiasis (Cholecystolithiasis △, Choledocholithiasis before and after Operation)

Statistically differences (by paired comparisons test) were not identified between before and after operation in patients. Mean values and S.E.M. are indicated by bars.

control subjects, patients with gallstones and patients having undergone cholecystectomy for cholesterol cholelithiasis, to determine whether impairment of hepatic antipyrine metabolism occurs in patients with cholesterol cholelithiasis and showed that the values for antipyrine half-life and metabolic clearance were not statistically different in those three groups. Miguët *et al.*³⁾ also described that the plasma disappearance rate of antipyrine in patients with extrahepatic cholestasis and patients with intrahepatic cholestasis was compared with that of two groups of control subjects without liver disease who were matched for age and showed that antipyrine metabolic clearance was significantly lower in the patients with intrahepatic cholestasis than in their controls, but there was no significant difference between patients with extrahepatic cholestasis and their controls.

In the present study, pre- and post-operative

TABLE I. *Liver Function Characteristics and Other Laboratory Data in Control Subjects and Patients with Extrahepatic Cholelithiasis*

<i>n</i> (Male/Female)	Controls 10 (7/3)	Patients ^{a)} 15 (11/4)	Normal laboratory values
Age (years)	50±5	52±3	—
Body weight (kg)	56±5	56±4	—
Total protein (g/dl)	7.30±0.20	7.38±0.10	6.5–8.2
Plasma albumin (g/dl)	4.08±0.23	4.00±0.08	3.7–5.2
Total bilirubin (mg/dl)	0.52±0.19	0.82±0.22 ^{b)}	0.2–1.0
Direct bilirubin (mg/dl)	0.18±0.03	0.30±0.12 ^{c)}	<0.2
SGOT(U/l)	20.1±3.3	21.5±3.9	7–38
SGPT(U/l)	22.7±4.2	19.3±5.5	8–40
SGGTP (IU/l)	7.9±3.4	7.7±2.1	2–29
Cholinesterase (ΔpH)	0.83±0.12	0.79±0.08	0.6–1.1
ALP(U/l)	161±18.6	170±17.3	100–280
LAP(U)	130±10.2	143±18.4	70–200
ICG ₁₅ (%)	ND	6.9±0.11	<10

Mean values ± S.E.M., ND: not detected. a) These values were obtained before operation. b) $p < 0.05$ and c) $p < 0.01$ in comparison to the control.

estimation of TMO metabolism in patients with extrahepatic cholelithiasis did not reveal any significant difference from control values. Biochemical laboratory tests demonstrated significantly increased total and direct bilirubin in the preoperative phase, which returned to normal after the operation.

Previously, we estimated hepatic drug-oxidizing capacity in three patients with obstructive jaundice whose bilirubin, ALP and LAP were highly elevated (bilirubin: 10.2 ± 2.1 , ALP: 765 ± 52 , LAP: 412 ± 32), and revealed no decrease in their hepatic drug-oxidizing capacity (data not shown here). This finding is consistent with those reported by Elfström and Lindgren.¹⁶⁾ However, Mcpherson *et al.*¹⁷⁾ found that antipyrine half-life was prolonged in patients with obstructive jaundice. These diversified results may be due to unequal durations of jaundice, and therefore, due to unequal degrees of impairment of hepatocellular function.³⁾ It is supported by our findings from α -naphthylisothiocyanate (ANIT)-intoxicated rats. In these cholestasis model animals, decreases in hepatic drug-oxidizing capacity became evident as ANIT doses were increased.⁸⁾

These results suggest that the hepatic drug-oxidizing capacity in patients with extrahepatic cholelithiasis remains unchanged even though bilirubin deviates from normal.

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