Caffeine Clearance in Patients with Hepatocellular Carcinoma after Transcatheter Oily Chemoembolization Treatment

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Abstract

Background : Hepatocellular carcinoma (HCC) is a common neoplasm worldwide, particularly in Asia, with a grave prognosis. Transcatheter Oily Chemoembolization (TOCE) is now universally accepted as the method of choice for the treatment of inoperable HCC. The purpose of this study was to evaluate caffeine clearance, a quantitative liver function assessment, in HCC patients before and after treatment with TOCE.

Method : Both conventional liver function test (LFT) and caffeine clearance were evaluated in twelve patients. Each patient took a 3.5 mg/kg single oral dose of caffeine solution before TOCE, 1 day and 5 weeks after treatment. Blood samples were subsequently collected at 0.5, 1.5, 3, 5, 10 and 24 hours after each dose of caffeine administration and assayed for serum caffeine level by the HPLC technique. Clearance (Cl) was calculated using the equation of Cl = Kel * Vd (Kel = elimination rate constant, Vd = volume of distribution) and half-life was determined using pharmacokinetic analysis.

Results : The mean caffeine clearance 1 day after TOCE (0.51 ± 0.096) and 5 weeks after TOCE treatment (0.43 ± 0.07) was significantly reduced compared with the mean caffeine clearance before treatment (0.79 ± 0.2 ml/min*kg) with the $p = 0.06$ and $p = 0.03$, respectively. No significant changes ($p > 0.05$) in most conventional LFT were observed 5 weeks after treatment.

Conclusions : In the present study, the authors found that caffeine clearance was reduced after TOCE in patients with HCC inspite of no changes in conventional LFT. Thus, the determination of caffeine clearance can serve as a useful parameter for the assessment of hepatic functional reserve in HCC patients post TOCE treatment.

Key word : Caffeine Clearance, Hepatocellular Carcinoma, Chemoembolization

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Hepatocellular carcinoma (HCC) is a common neoplasm world wide, particularly in Asia, with a grave prognosis[1]. Most patients have both malignant tumors as well as hepatic cirrhosis[2]. Transcatheter Oily Chemoembolization (TOCE) is now universally accepted as the method of choice for the treatment of inoperable HCC[3]. The outcome is not only determined by the tumor size, but also by the functional status of hepatic reserve. Conventional liver function tests, such as AST, ALT, albumin, bilirubin and prothrombin time, provide important information on inflammation and cholestasis of hepatic metabolic function. Various quantitative tests have been developed using compounds metabolized by the liver providing a dynamic evaluation of residual metabolic capacity[4]. These include caffeine clearance, aminopyrine breath test, galactose elimination, bromosulphothalein disappearance, and indocyanine green clearance. Many tests are not widely available because of either technical difficulties or adverse effects of the test compounds.

Caffeine is a non toxic substance, well absorbed when taken orally, and almost completely metabolized in the liver by cytochrome P450 1A2. The simplicity of caffeine analysis either in serum or saliva could be an advantage for routine assay[5-7]. Therefore, it seems to be an ideal test for the assessment of liver metabolic function.

In order to determine the effect of TOCE treatment in HCC patients on hepatic functional reserve, the authors evaluated caffeine clearance before and after TOCE treatment compared with conventional liver function tests.

MATERIAL AND METHOD

Subjects

Twelve patients with histologically proven HCC who had received TOCE treatment and attended Chulalongkorn Hospital University were studied. They were informed as to the objective of the study and the patients subsequently provided their consent. Computerized tomography (CT) of the upper abdomen was obtained in all patients prior to the angiographic procedure to ensure no main portal vein thrombosis involvement. None of these patients had other concomitant diseases including cardiovascular disease, asthma, and renal disease, which could interfere with the clearance of caffeine. None of these patients had

a history of caffeine sensitivity, smoking, alcohol abuse, and taking drugs, such as cimetidine, oral contraceptive pill, and quinolone, which could have inhibitory effects on caffeine metabolism[8-10]. Caffeine clearance studies were performed before TOCE, 1 day and 5 weeks after TOCE. The patients were asked to abstain from caffeine containing beverages, food, and medications at least 3 days before and throughout the study. The conventional liver function tests were measured at the same period of caffeine clearance study. This study was approved by the Ethical Committee of the Faculty of Medicine, Chulalongkorn University.

Twelve patients underwent TOCE treatment using a mixture of 10 ml iodized oil (lipiodol : Andre' Guerbet, Aulnay-sous-bios, France) and 20 mg anticancer drug (mitomycin C) selectively infused into the tumor feeder artery or arteries. The feeder arteries were finally embolized with a 1-2 mm gelatin sponge, were cut into pieces under fluoroscopic guidance until cessation of blood flow[11].

Reagents

Caffeine (anhydrous, BP grade, batch no. 71015), 0.35 per cent in aqueous solution, was used for oral administration. 8-chlorotheophylline (Sigma Chemical Co. Ltd.) was used as the internal standard. Zinc sulfate was purchased from Mallinc-krodt Chemical Works; HPLC grade methanol and acetonitrile were obtained from Fison and FSA Laboratory Supplies. HPLC grade sodium acetate was purchased from Fluka Chemic. Double-distilled water was used in the HPLC analyses.

Apparatus

HPLC apparatus from spectra SYSTEM: Thermo Separation Products consisted of a mobile phase delivery device (P1000 model), an automatic injector (AS3000 model) for injection of samples, and a UV detector (UV1000 model) used to monitor. Caffeine and 8-chlorotheophylline were detected at a wavelength of 273 nm. A μ bondapak C18 stainless steel column (30 cm, 3.9 mm I.D. Water associates) was used in the HPLC condition. A computer system with PC1000 software was used to analyze the caffeine peak and set the standard system.

Caffeine clearance study

After an overnight fast, each subject took a 3.5 mg/kg single dose of caffeine orally. Blood samples were subsequently collected at 0.5, 1.5, 3, 5, 10 and 24 hours after each dose of caffeine administration. The sera were separated and stored at -20°C until assayed.

To deproteinized the serum samples, 100 μl of 10 per cent w/v of zinc sulfate solution was added into 500 μl of each serum sample and mixed for 10 seconds. Subsequently, 750 μl of 8-chlorotheophylline in absolute methanol (0.4 mg/ml) was added into the serum mixture. The sample mixture was then vortex-mixed for 30 seconds followed by centrifugation for 5 minutes at 4,000 rpm. The supernatant was separated and filtered. 50 μl of this filtered solution was injected into the HPLC system for caffeine analysis[12].

Data analysis

Caffeine clearance (Cl) (ml/min*kg) was calculated from an equation : Cl = Kel * Vd, where Kel (min^{-1}) was the elimination rate constant, determined from the caffeine slope of five time points, and Vd (L/kg) was the volume of distribution. Cl was determined assuming that the volume of Vd approximately equals the population value of 0.6 L/kg of body weight[13]. The analysis of intraday and interday precision was 3.821 per cent and 6.434 per cent RSD (relation standard deviation), respectively. Quantitative data are shown as mean ± SD. Student paired *t*-test for conventional LFT data before and after treatment was performed. Differences in mean caffeine clearance in the study groups were analyzed by ANOVA and Tukey test was used. Test achieving $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS for window program version 9.0.

RESULTS

The twelve patients were 10 males and 2 females, 31-72 years of age. There were 7 patients in Okuda I, 4 patients in Okuda II, and 1 patient in Okuda III classification. The alpha-fetoprotein levels rising above 400 ng/ml were found in 5 patients (41.67%). The levels were reduced to normal in 2 patients after TOCE treatment. There were no significant changes in size of the mass assessed by CT scan after 5 weeks of TOCE. The mean body weight was 59 ± 15 kg before treatment and 58 ± 13 kg after 5 weeks of TOCE. No significant changes from baseline ($p > 0.05$) were observed in most of all conventional LFT including AST, ALT, TB AP and PT 5 weeks after treatment. However, a significant decrease in mean serum albumin ($p = 0.001$) was

observed (3.96 ± 0.12 *vs* 3.51 ± 0.13 g/dl, before treatment *vs* 5 weeks after TOCE, respectively) (Table 1).

There were no significant changes in Area under curve (AUC), Vd and half life of caffeine. The Vd before treatment, 1 day and 5 weeks after TOCE were 0.88 ± 0.18, 0.89 ± 0.19 and 0.83 ± 0.11 L/kg ($p > 0.05$), respectively. The AUC before treatment, 1 day and 5 weeks after TOCE were 144.23 ± 37.96, 223.7 ± 63.35 and 246.9 ± 73.31 mg*h/L ($p > 0.05$), respectively. The half life of caffeine before treatment, 1 day and 5 weeks after TOCE were 23.2 ± 7.02, 31.1 ± 6.1 and 39.9 ± 11.1 h ($p > 0.05$), respectively. The Kel 1 day after TOCE (0.033 ± 0.005 h^{-1}) and 5 weeks after TOCE (0.039 ± 0.008 h^{-1}) were significantly decreased compared with that before treatment (0.052 ± 0.007 h^{-1}) ($p = 0.011$ and $p = 0.013$, 1 day and 5 weeks after TOCE treatment, respectively (Table 2). The mean caffeine clearance at 1 day after TOCE (0.51 ± 0.096 ml/min*kg) and at 5 weeks after TOCE treatment (0.43 ± 0.07 ml/min*kg) were significantly reduced compared with that before treatment (0.79 ± 0.2 ml/min*kg) with the $p = 0.06$ and $p = 0.03$, for 1 day and 5 weeks after TOCE treatment, respectively (Fig. 1).

DISCUSSION

Caffeine (1, 3, 7 trimethylxanthine) is primarily biotransformed (97%) in the liver and excreted in urine as methylxanthine metabolites[6]. Its elimination depends highly on cytochrome P450, mainly

Table 1. The conventional liver function test before and 5 weeks after TOCE.

Test	Before TOCE	5 weeks after TOCE	P-value
AST	77 ± 19.2	91 ± 18.30	NS*
ALT	46.5 ± 9.44	61.13 ± 13.22	NS
TB	1.06 ± 0.26	2.3 ± 1.43	NS
Alb	3.96 ± 0.12	3.51 ± 0.13	0.001
AP	396.4 ± 89.1	278.8 ± 54.08	NS
PT	3.5 ± 1.47	1.13 ± 0.34	NS

AST = aspatate aminotransferase (normal 0-38 U/L)
ALT = alanine aminotransferase (normal 0-38 U/L)
AP = alkaline phosphatase (normal 39-117 U/L)
Alb = albumin (normal 3.4-5.5 g/dl)
PT = prothrombin time (prolong ≤ 3 second)
*NS = no statistical significance

Table 2. The value of AUC, Vd, Kel, half life and caffeine clearance using pharmacokinetic analysis before treatment, 1 day and 5 weeks after TOCE.

Value	Before treatment	1 day after TOCE	5 weeks after TOCE
AUC (mg*h/L)	144.23 ± 37.96	223.7 ± 63.35	246.9 ± 73.31
Vd (L/kg)	0.88 ± 0.18	0.89 ± 0.19	0.83 ± 0.11
Kel (h^{-1})	0.052 ± 0.007	0.033 ± 0.005*	0.039 ± 0.008**
$T^{1}/_{2}$ (h)	23.2 ± 7.02	31.1 ± 6.1	39.9 ± 11.1
Cl (ml/min*kg)	0.79 ± 0.20	0.51 ± 0.09	0.41 ± 0.07***

*p=0.011, **p=0.013, ***p=0.03 compared with before treatment.
AUC = area under curve
Vd = volume of distribution
Kel = elimination rate constant
$T^{1}/_{2}$ = half life
Cl = caffeine clearance

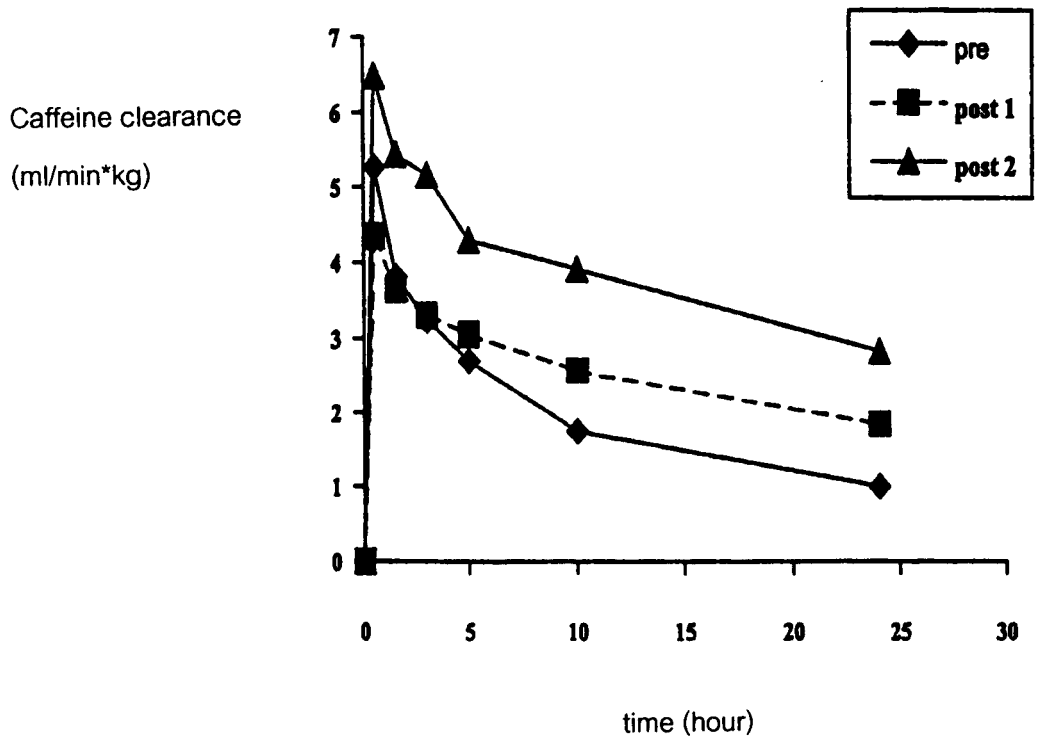

Fig. 1. The mean caffeine clearance before TOCE, 1 day and 5 weeks after TOCE in 12 patients.

pre = before TOCE.
post 1 = 1 day after TOCE.
post 2 = 5 weeks after TOCE.
Significantly reduce mean cafeine clearance at post 1 and post 2 were compared with pre (p = 0.06 and p = 0.03, respectively).

CYP 1A2 activity. The half life (T1/2) of caffeine varies from 3-7 hours in healthy adults and is not affected by ageing or body weight[14,15]. However, cimetidine can decrease the clearance but barbiturates and cigarette smoking can increase the activity of caffeine clearance[16]. Caffeine clearance measured in saliva samples, is a test that allows prediction of survival of cirrhotic patients in an independent way, and is more accurate for this purpose than Child-Pugh's classification[5].

The intraday and interday precision in the presented technique were less than 15 per cent of RSD that means the results can be analyzed. Although caffeine clearance measurement alone is at least as useful as conventional LFT in detecting liver disease, the authors feel that its measurement, in addition to conventional LFT, gives a more comprehensive indicator of the severity of the liver disease. In general practice, conventional LFT is used to evaluate the function of the liver. The high level of transaminase means there is inflammation occurring in hepatocyte, which does not correlate with the severity of liver disease. Therefore, the rising level of transaminase after TOCE does not demonstrate the metabolic reserve function of liver. The rising of bilirubin level is not the sensitive test to illustrate the degree of liver injury. After dearterialization, the authors found transient elevation of bilirubin level from congestion of hepatocyte. In the present study, the albumin level was reduced significantly after 5 weeks of TOCE compared with the level before treatment. Although albumin level can demonstrate the hepatic function, it changes in other diseases that impair the patient's nutrition. A number of transplant centers use caffeine

clearance as a useful prognostic indicator and there is evidence that it is a more sensitive indicator of declining hepatic function than the aminopyrine breath test[17]. After orthotopic liver transplantation, caffeine clearance is a poor means of predicting impending transplant rejection[18]. After partial hepatectomy in patients with liver tumors, the human liver regenerates until a volume of about 75 per cent of the initial liver mass is reached. Caffeine clearance correlates well with the total liver volume[19]. Alpha-fetoprotein (αFP) level can be used for follow-up after treatment. In the present study, αFP level was decreased to normal in 3 patients after TOCE.

Liver transplantation or surgical resection of HCC is the only radical treatment which may prolong survival of the patients[20]. Unfortunately, the resectable rate of HCC is very low because of extensive disease at the time of diagnosis. Thus, only 10 per cent of HCC are amenable to operative resection[21]. Various types of treatment for unresectable tumor have been attempted such as chemotherapy [22,23] and percutaneous ethanol injection[24,25] with unsatisfactory results. In 1989, TOCE was introduced[26] and this technique is now universally accepted as the method of choice for the treatment of inoperable HCC[27-29]. Although TOCE is a useful therapy for HCC, the necrosis rate of the tumor cells after TOCE is estimated at about 90-95 per cent from pathological examination[30]. When the hepatic arteries are interrupted by mechanical injury during catheter placement or arteries are induced by TOCE or by thrombosis from embolization, extrahepatic collateral pathways frequently develops[31]. Pain, nausea, vomiting and low grade fever were related to TOCE. The symptoms were transient and recovery was achieved by symptomatic treatment. Biochemistry values in some cases became elevated to more than two or three times the pre-embolized levels and gradually decreased in 14 days[5].

In pharmacologic analysis, the authors found that volume of distribution (Vd) changed in non-statistic significance (0.875 L/Kg before, 0.892 L/Kg 1 day after TOCE, and 0.834 L/Kg 5 weeks after TOCE) that means changing of serum protein level had no effect in the caffeine clearance level. Half life of caffeine is significantly longer after TOCE than before TOCE. The duration of half life depended on two factors including Vd, and clearance. Vd in the present study was not changed, so the variable that changed was clearance. After TOCE, hepatic circulation is reduced due to the occlusion of hepatic artery. The reduction of oxygen after arterial occlusion effected the oxidative metabolism. Moreover, the progression of hepatic cirrhosis itself affected caffeine clearance metabolism.

Two sampling times within 10 to 24 hours after an oral dose of caffeine served as the best sampling points for determination of caffeine clearance by the simple equation; Cl = Kel * Vd. It is a useful method to evaluate the severity of liver disease and predicts survival of cirrhotic patients[13]. Many studies have documented a higher sensitivity than formal hepatic function test for detecting liver reserve[12]. This test is easy to develop in hospital, harmless, inexpensive, easy to repeat, and provides potentially valuable prognostic information[6]. Therefore, caffeine clearance should no longer be restricted to research institutions but could now become part of the standard evaluation of hepatic functional reserve in any hospital.

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การศึกษาค่าคาเฟอีนเคลียร้านซ์ในผู้ป่วยมะเร็งตับหลังการรักษาด้วยวิธีแทรนแค็ธธิเทอะออยลีเคโมเอ็มโบไลเซชั่น

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มะเร็งตับเป็นมะเร็งที่พบบ่อยโดยเฉพาะประเทศทางเอเชีย การรักษาด้วยวิธีแทรนแค็ธธิเทอะออยลีเคโมเอ็มโบไลเซชั่น (transcatheter oily chemoembolization, TOCE) เป็นทางเลือกหนึ่งในการรักษาที่ยอมรับกัน วัตถุประสงค์ของการศึกษานี้เพื่อต้องการเป็นเทียบค่าของคาเฟอีนเคลียร้านซ์ในผู้ป่วยมะเร็งตับ ก่อนและหลังการรักษาด้วยวิธี TOCE โดยเปรียบเทียบกับการตรวจเลือดดูการทำงานของตับ (conventional liver function test, LFT) โดยมีผู้ป่วยเข้าร่วมโครงการ 12 คน ทำการตรวจวัดหาค่าคาเฟอีนเคลียร้านซ์ ก่อนการรักษา หลังการรักษาที่ 1 วันและ 5 สัปดาห์ ผลการศึกษาพบว่า ค่าเฉลี่ยของคาเฟอีนเคลียร้านซ์หลังการรักษา 1 วันลดลงเมื่อเทียบกับก่อนการรักษา และลดลงอย่างมีนัยสำคัญที่ 5 สัปดาห์หลังการรักษา (0.79 $\pm$ 0.2 มล/นาที*กิโลกรัม, 0.51 $\pm$ 0.096 มล/นาที*กิโลกรัม และ 0.43 $\pm$ 0.07 มล/นาที*กิโลกรัม โดยมีค่า $p = 0.06$, $p = 0.03$ ตามลำดับ โดยไม่พบการเปลี่ยนแปลงเมื่อตรวจเลือด LFT สรุป การศึกษานี้พบว่าการทำงานของตับลดลงเมื่อวัดด้วยวิธีคาเฟอีนเคลียร้านซ์ในผู้ป่วยมะเร็งตับ หลังการรักษาด้วยวิธี TOCE ในขณะที่ยังไม่พบการเปลี่ยนแปลงของ LFT ดังนั้นการวัดการทำงานของตับโดยใช้คาเฟอีนเคลียร้านซ์ น่าจะมีประโยชน์ในการประเมินการทำงานของตับในผู้ป่วยกลุ่มนี้

คำสำคัญ : คาเฟอีนเคลียร้านซ์, มะเร็งตับ, เคโมเอ็มโบไลเซชั่น

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