Diurnal variation in the biliary excretion of flomoxef in patients with percutaneous transhepatic biliary drainage

Shuji Hishikawa, Eiji Kobayashi, Koh-ichi Sugimoto, Michio Miyata & Akio Fujimura

Department of Clinical Pharmacology, Jichi Medical School, Tochigi, and Department of Surgery, Omiya Medical Center, Jichi Medical School, Omiya, Japan

Aims To examine diurnal variation in biliary excretion of flomoxef.

Methods Flomoxef (1 g) was injected intravenously in eight patients with percutaneous transhepatic cholangiography with drainage at 09.00 h and 21.00 h by a cross-over design with a 36 h washout period. Drained biliary fluid was collected for 6 h after each dosing. These patients still had mild to moderate hepatic dysfunction.

Results Bile flow and bile acid excretion for 6 h after dosing did not differ significantly between the 09.00 h and 21.00 h treatments. The maximum concentration of biliary flomoxef was significantly greater and its total excretion for 6 h tended to be greater after the 21.00 h dose [maximum concentration ($\mu\text{g ml}^{-1}$): 34.2 ± 29.9 (09.00 h dose) vs 43.5 ± 28.3 (21.00 h dose) (95% confidence interval for difference: 2.6 ~ 15.9, $P=0.013$); total excretion ($\text{mg } 6 \text{ h}^{-1}$): 1.4 ± 1.3 (09.00 h dose) vs 1.6 ± 1.2 (21.00 h dose) (95% confidence interval for difference: -26.8, 313.7, $P=0.087$)]. The period that biliary flomoxef remained above the minimal inhibitory concentration did not differ significantly between the two treatment times.

Conclusions These results suggest that biliary excretion of flomoxef shows diurnal variation. However, as the difference was relatively small, flomoxef could be given at any time of day without any dosage adjustments.

Keywords: biliary excretion, chronopharmacokinetics, flomoxef

Introduction

Biliary tract obstruction secondary to malignancy of the pancreas head, bile ducts and papilla of Vater frequently causes infections such as cholangitis and cholecystitis. As bacteria are present on bile culture in approximately 75% of these patients [1], drainage of the bile duct and subsequent antibiotic therapy are essential.

It is well known that bile flow and the concentration of biliary constituents show diurnal variation in human subjects [2, 3]. The biliary concentration of antibiotics may also vary with dosing time. However, to our knowledge, there are no data concerning a dosing time-dependent variation in biliary excretion of antibiotics in human subjects. As adequate concentrations of antibiotics in biliary fluid are needed to treat infections, it is important

that chronopharmacokinetic profiles of biliary antibiotics are examined.

In the present study, the biliary excretion of an oxacephem antibiotic, flomoxef sodium (FMOX) (elimination half-life: 50 min) was determined after an intravenous bolus injection at 09.00 h and 21.00 h in patients with percutaneous transhepatic cholangiography with drainage (PTCD).

Methods

Subjects

Eight patients with fever and obstructive jaundice due to malignant tumours (two with pancreas head carcinoma, two with cholangiocarcinoma, two with bile duct carcinoma, one with gastric carcinoma and one with gallbladder carcinoma) participated in this study. Their age and body weight were 64 ± 12 (mean $\pm$ s.d.) years and 48.1 ± 8.1 kg, respectively. They underwent PTCD to improve hepatic function. Biliary recycling of bile acid and other constituents was discontinued in these patients.

Correspondence: Akio Fujimura, M.D., Department of Clinical Pharmacology, Jichi Medical School, Tochigi 329-0498, Japan. Tel.: 81-285-58-7387; Fax: 81-285-44-7562; E-mail: akiofujii@jichi.ac.jp

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After serum concentrations of bilirubin and hepatic enzymes had moderately decreased, surgical procedures were performed to resect the tumour in each patient. The present study was performed 2–3 days before operation (11–42 days after placement of PTCD). Mild to moderate hepatic dysfunction was observed in these patients immediately before the initiation of the study (Table 1). The mean ($\pm$ s.d.) creatinine clearance obtained using the formula of Cockcroft & Gault [4] was 79 ± 26 ml min⁻¹, and was slightly decreased in four patients. All received a range of antibiotics, which were stopped 24 h before the study. The approval of the local ethics committee (Omiya Medical Center, Omiya, Japan) was obtained, and all subjects gave written consent before participation.

Study protocol

The present study was a randomized, cross-over design with a 36 h washout period. The patients were randomly divided into two groups. FMOX (1 g in 20 ml saline, Shionogi & Co., Osaka, Japan) was injected intravenously to group I ($n=4$) at 09.00 h (morning treatment) on day 1 and at 21.00 h (evening treatment) on day 2, and to group II ($n=4$) at 21.00 h on day 1 and at 09.00 h on day 3. Blood samples were taken into tubes containing heparin at 0.25, 0.5, 1, 2 and 4 h after dosing. Plasma was separated by centrifugation and frozen at -20°C until assayed. Drained biliary fluid was collected at 0–0.5, 0.5–1, 1–1.5, 1.5–2, 2–2.5, 2.5–3, 3–3.5, 3.5–4, 4–5, and 5–6 h after dosing, and stored at -20°C until assayed.

The patients were kept in the supine position for at least 3 h after injection. One hour before the trial, they ate breakfast or supper, and thereafter did not eat any food for 4 h. Plasma and biliary FMOX concentrations were

measured by a h.p.l.c. method [5]. The coefficients of variation of this assay were 5.6% at $5 \mu\text{g ml}^{-1}$ ($n=8$) and 8.7% at $20 \mu\text{g ml}^{-1}$ ($n=10$). Detection threshold was $0.5 \mu\text{g ml}^{-1}$. Bile acid concentrations were determined by an autoanalyser (7050, Hitachi, Tokyo, Japan) utilizing the 3α -steroid-dehydrogenase reaction [6].

The results are expressed as the mean $\pm$ s.d. or mean $\pm$ s.d. (95% confidence interval for difference). The correlation was calculated on the basis of least squares linear regression analysis. Comparisons were made using a two-way analysis of variance and a paired Student's *t*-test as appropriate. Statistical significance was accepted at $P<0.05$.

Results

Bile flow and bile acid excretion for 6 h after dosing did not differ significantly between the morning and evening treatments [bile flow (ml 6 h⁻¹): 140 ± 36 (morning) *vs* 127 ± 35 (evening) (95% confidence interval for difference: $-28 \sim 3$, $P=0.089$), bile acid (mmol 6 h⁻¹): 1.16 ± 0.69 (morning) *vs* 1.35 ± 0.71 (evening) (95% confidence interval for difference: $-0.15 \sim 0.37$, $P=0.341$)].

Plasma concentrations of FMOX did not differ significantly at any observation points between the morning and evening treatments (Figure 1). Biliary FMOX concentrations tended to increase in the evening treatment (Figure 2). Maximum concentration (C_{max}) of biliary FMOX was significantly greater and its total excretion over 6 h tended to be greater in the evening than in the morning treatments [C_{max} ($\mu\text{g ml}^{-1}$): 34.2 ± 29.9 (morning) *vs* 43.5 ± 28.3 (evening) (95% confidence interval for difference: 2.6, 15.9, $P=0.013$); total excretion (mg 6 h⁻¹): 1.4 ± 1.3 (morning) *vs* 1.6 ± 1.2 (evening) (95% confidence interval for difference: $-26.8, 313.7$, $P=0.087$)]. There was no significant correlation between the 6 h bile flow (or bile acid excretion) and 6 h FMOX excretion.

Table 1 The results of laboratory tests in eight patients with PTCD immediately prior to the study.

Parameter	Mean $\pm$ s.d.	Normal range
Total protein (g dl ⁻¹)	6.8 ± 0.5	6.9–8.4
Albumin (g dl ⁻¹)	3.6 ± 0.5	3.9–5.1
Direct bilirubin (mg dl ⁻¹)	1.7 ± 1.4	0.1–0.5
Indirect bilirubin (mg dl ⁻¹)	0.8 ± 0.5	0.1–0.5
AST (mU l ⁻¹)	55 ± 23	11–30
ALT (mU l ⁻¹)	64 ± 53	4–30
ALP (mU l ⁻¹)	412 ± 142	89–285
LDH (mU l ⁻¹)	281 ± 46	215–410
γ -GT (mU l ⁻¹)	130 ± 68	<70
BUN (mg dl ⁻¹)	14 ± 5	8–20
Creatinine (mg dl ⁻¹)	0.6 ± 0.2	0.6–1.0
Na (mmol l ⁻¹)	140 ± 4	136–148
K (mmol l ⁻¹)	4.3 ± 0.3	3.6–5.0
Cl (mmol l ⁻¹)	105 ± 3	96–108

Figure 1 Mean ($\pm$ s.d.) plasma FMOX concentrations after a single intravenous injection (1g) at 09.00 h (○) and 21.00 h (●) in eight patients with PTCD.

Figure 2 Biliary FMOX concentrations after a single intravenous injection (1g) at 09.00 h (○) and 21.00 h (●) in eight patients with PTCD.

The period that biliary FMOX remained above the minimal inhibitory concentration ($1.56 \mu\text{g ml}^{-1}$ for *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis* [7]) did not differ significantly between the two treatment times (morning: 3.7 (2.7–4.7) *vs* evening: 3.9 (2.9–4.9) h).

Discussion

FMOX is an oxacephem antibiotic with antimicrobial action against gram-positive and -negative bacteria.

Animal studies showed that 20–30% of FMOX is excreted into biliary tract and 60–80% of the drug into urinary tract [8]. As biliary FMOX concentrations greater than the minimal inhibitory concentration for this antimicrobial have been reported in patients with biliary drainage [9], the drug is frequently used for the treatment of biliary tract infections.

The total biliary excretion of FMOX was about 2 mg (0.2% of the dose) over the 6 h after intravenous injection of 1000 mg of the drug, which was smaller than that reported in rats [8].

It has been demonstrated that the urinary excretion of several antibiotics is greater during daytime than nighttime in human subjects [10]. Consequently, the serum concentrations of these drugs, and in turn their efficacy and adverse effects might be influenced by their dosing time. The present study has demonstrated for the first time that the biliary excretion of FMOX tended to be greater and its $C_{\max}$ was significantly greater in the evening compared to the morning dosing in patients with PTCD. However, plasma concentrations of FMOX did not differ significantly following morning and evening dosing.

A previous study has shown that bile flow was greater during daytime, while bile acid concentration was higher during nighttime in patients after cholecystectomy and fitted with common bile duct T-tube [3], a finding not confirmed in the present study. Bile is completely drained from patients with PTCD, whereas a large amount of bile passes through the small intestine and is reabsorbed in patients with a common bile duct T-tube. The discontinuation of biliary recycling might, in part, affect the potential daily variations in these parameters.

FMOX is mainly eliminated renally (80% of the dose in 8 h) [11], and its elimination half-life is prolonged in patients with renal dysfunction [11]. As renal function decreases during nighttime [12], it is anticipated that plasma FMOX concentration following the evening treatment might be greater than that when the drug is given in the morning. However, the plasma concentrations were found not to differ in this study, partly as a result of the increased FMOX excretion in bile following the evening treatment. The mechanism of the dosing-time dependent change in biliary FMOX excretion is unclear. Some organic anions are excreted in bile by a canalicular multispecific organic anion transporter (cMOAT) [13]. As FMOX is an anionic drug, the drug may also be excreted in bile by the action of cMOAT. Previously, we observed that the biliary excretion of FMOX in the Eisai hyperbilirubinaemic rat, which inherits a defective form of cMOAT [14], is greatly decreased compared with that in the Sprague-Dawley control rats (unpublished data). Thus, it is possible that the activity of cMOAT is enhanced during the night in humans.

The β -lactam antibiotics including FMOX are time-dependent in their antimicrobial action. Thus, drug concentrations must remain above the minimal inhibitory concentration of the infecting pathogen for at least 25–50% of the dosage interval to achieve therapeutic efficacy [15]. In the present study, the mean period above the minimal inhibitory concentration for biliary FMOX was more than 3 h after dosing at morning and evening. Therefore, we think that administration of FMOX every

6–12 h is essential for treatment of biliary tract infections in patients with PTCD. As the period above the minimal inhibitory concentration of the two treatment times did not differ significantly, FMOX might be given without any dosage adjustments at each dosing time.

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