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Effect of Acute Renal Failure on the Disposition of Cefoperazone

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Abstract

The effect of acute renal failure on the disposition of cefoperazone was investigated. Rats, 3 days after uranyl nitrate treatment, were used to model acute renal failure.

Although plasma-protein binding of cefoperazone decreased significantly in acute renal failure compared with control rats, the plasma clearance of total (bound plus unbound) drug after intravenous administration (50 mg kg^{-1}) did not differ significantly between the two groups ($5{\cdot}61 \pm 2{\cdot}37$ mL min^{-1} for control and $4{\cdot}75 \pm 2{\cdot}82$ mL min^{-1} for acute renal failure). Consequently the plasma clearance of the unbound drug in acute renal failure ($6{\cdot}14 \pm 1{\cdot}16$ mL min^{-1}) was significantly lower than in control rats ($15{\cdot}6 \pm 3{\cdot}7$ mL min^{-1}, $P < 0{\cdot}025$). Plasma clearance of the drug (both total and unbound) was also dependent on bile flow, and clearance of the unbound drug in acute renal failure rats was lower than in control rats with identical bile flow rates. To examine the mechanism of reduced unbound cefoperazone clearance, an in-vitro experiment using a simultaneous perfusion system of rat liver and kidney was performed. By changing perfusate plasma protein from bovine serum albumin to human serum albumin, the plasma clearance of the total cefoperazone changed to one-sixth in proportion to the unbound cefoperazone in the perfusate plasma. On the other hand, the plasma clearance of the total and unbound drug in acute renal failure rats decreased significantly compared with controls.

These results demonstrate that the plasma clearance of unbound cefoperazone, which is mainly eliminated by the liver, decreased in acute renal failure in rats, probably due to changes in hepatic transport.

It has long been of interest why drugs which are mainly eliminated from the liver are affected by renal failure (Lowenthal et al l974; Reidenberg 1979; Simon et al l981). Terao & Shen (1983) and Katayama et al (1984) reported that the availability of propranolol (lipophilic and basic) increased in rats with uranyl nitrate-induced acute renal failure compared with healthy control rats. Bowmer et al (1982a,b) showed decreased hepatic uptake of indocyanine green and bromosulphophthalein (hydrophilic and anionic) in rats with glycerol-induced acute renal failure.

Cefoperazone, a hydrophilic organic anion β-lactam antibiotic, is mostly excreted unmodified into the bile. Since biliary excretion of organic anions has been shown to be mediated by a canalicular multispecific organic anion transporter (Ishikawa et al 1990; Kitamura et al 1990; Kobayashi et al 1990), cefoperazone may be excreted by this transporter. Balant et al (1980) and Balton et al (1981) reported that cefoperazone did not require dose adjustments in patients with renal dysfunction. Rho et al (1992) reported that cefoperazone plasma half-life in a subject with badly dysfunctional kidneys was 2·8 times that in a subject with normal kidneys, without significant changes in steady-state volumes of distribution. It is unknown whether the plasma-protein binding of cefoperazone is inhibited by uraemic compounds such as indole acetic acid.

The present study was carried out to investigate the effect of uranyl nitrate-induced acute renal

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failure on the disposition of cefoperazone, which is mostly excreted unmodified into the bile.

Materials and Methods

Chemicals

Sodium cefoperazone was obtained from Toyama Chemical Co., Ltd (Toyama, Japan). All other reagents were of the finest grade available.

Induction of acute renal failure

Male Wistar albino rats (Shizuoka Agricultural Co-operative Association for Laboratory Animals, Shizuoka, Japan), weighing 230–270 g, were used. For the induction of acute renal failure, uranyl nitrate (10 mg kg^{-1}) was administered subcutaneously (Flamenbaum et al 1974). Acute renal failure rats were used 3 days after injection of uranyl nitrate (Katayama et al 1984).

In-vivo studies

Under pentobarbital anaesthesia, cefoperazone was administered (50 mg kg^{-1}) via the femoral vein. Blood samples were obtained from a carotid artery cannula at 3, 5, 10, 20, 40 and 60 min after administration. At 60 min, the liver and kidney were removed, weighed and homogenized in five volumes of 0·03 M KH_2PO_4 for cefoperazone assays.

Perfusion studies

A closed, isolated circulation of rat liver and kidney was performed as previously described (Yasuhara et al 1985). The perfusate consisted of 20% (v/v) bovine red cells and 5% (w/v) bovine or human serum albumin in Krebs–Henseleit buffer solution and equilibrated with 95% O_2/5% CO_2 to maintain a pH of 7·4 at 37°C. After an equilibration period of 10–20 min, cefoperazone (50 mg kg^{-1}) was added to the 30-mL reservoir and samples of reservoir solution were obtained 3, 5, 10, 15, 20, 25 and 30 min later.

Plasma-protein binding

The degree of cefoperazone binding to plasma protein was determined at room temperature for plasma samples obtained from in-vivo and in-vitro perfusion studies at the end of each experiment by an ultrafiltration technique using cellulose tubing (Visking Co., 8/32).

Analysis of cefoperazone

Cefoperazone concentrations were determined by the method of Inui et al (1983) with slight modifications. A high-performance liquid chromatograph (LC-3A Model, Shimadzu, Kyoto, Japan) equipped with a UV monitor set at 265 nm and a Chemcosorb ODS column (4·6 mm i.d. × 15 cm, Chemco Scientific Co., Ltd, Osaka Japan) was used. The mobile phase was 0·03 M KH_2PO_4/methanol (70 : 30, v/v). The flow rate was 1·0 mL min^{-1}.

Data analysis

The rat plasma and the perfusate plasma concentration–time curves were fitted to mono- and bi-exponential equations, respectively, by non-linear least-squares regression analysis (Yamaoka et al 1981). Total body clearance (CL) of cefoperazone was calculated from the equation:

$$CL = Dose/AUC \quad (1)$$

where AUC is the area under the plasma concentration–time curve, obtained by integrating the mono- or bi-exponential equation from time zero to infinity. Total body clearance of the unbound drug (CL_f) was obtained by the following equation:

$$CL_f = CL/f \quad (2)$$

where f is the unbound fraction of the drug in the plasma. Statistical analysis was performed using Student's *t*-test with $P < 0{\cdot}05$ considered significant.

Results

The plasma decay of cefoperazone in-vivo was fitted to a two-compartment open model. The kinetic parameters obtained from this model and parameters used to evaluate the disposition of the drug are summarized in Table 1. No significant differences were observed between control rats and acute renal failure rats in the pharmacokinetic constants A, α, B, β, V_{ss} and AUC. Both plasma-protein binding and CL_f significantly decreased in acute renal failure rats compared with control rats. However, CL did not differ significantly between the two groups. The concentration ratio of cefoperazone in the liver to the plasma (L/P) also did not differ significantly between the two groups. However the ratio of the drug in the liver to the unbound drug in the plasma (L/P_f) in acute renal failure decreased significantly. On the other hand, the ratio of cefoperazone in the kidney to the plasma (K/P) or the plasma water (K/P_f) significantly decreased in acute renal failure.

As shown in Figure 1, both CL and CL_f were dependent on bile flow rates. Although the slope of

Table 1. Effect of acute renal failure on disposition of cefoperazone in-vivo.

	Control	Acute renal failure
A (μg mL^{-1})	153 ± 47	190 ± 50
α (min^{-1})	0·208 ± 0·063	0·286 ± 0·079
B (μg mL^{-1})	57·6 ± 17·9	96·3 ± 51·6
β (min^{-1})	0·0341 ± 0·0115	0·0388 ± 0·0172
V_1 (mL)	64·0 ± 15·6	46·2 ± 6·7**
V_{ss} (mL)	155 ± 82	116 ± 60
AUC (μg min mL^{-1})	2809 ± 1552	4884 ± 4676
CL (mL min^{-1})	5·61 ± 2·37	4·75 ± 2·82
CL_f (mL min^{-1})	15·6 ± 9·1	6·14 ± 3·28**
f[a]	0·412 ± 0·108	0·769 ± 0·97***
K/P[b]	10·4 ± 6·7	4·5 ± 3·0*
K/P_f[c]	24·6 ± 19·4	5·9 ± 3·6**
L/P[d]	2·4 ± 0·7	2·4 ± 0·4
L/P_f[e]	6·6 ± 3·0	3·1 ± 0·4***
Bile flow (μL min^{-1})	17·0 ± 6·1	16·9 ± 7·3

Cefoperazone was administered to rats intravenously (50 mg kg^{-1}). Results are given as the mean ± s.d of 6–8 animals. [a]Unbound fraction in the plasma 60 min after drug administration. [b]Concentration ratio of cefoperazone in the kidney to the plasma 60 min after drug administration. [c]Concentration ratio of cefoperazone in the kidney to the plasma water 60 min after drug administration. [d]Concentration ratio of cefoperazone in the liver to the plasma 60 min after drug administration. [e]Concentration ratio of cefoperazone in the liver to the plasma water 60 min after drug administration. *$P < 0.05$, **$P < 0.025$, ***$P < 0.010$ compared with control.

bile flow rates vs CL (Figure 1a) was nearly identical between the two groups, the slope obtained for acute renal failure for bile flow rates vs CL_f was one-third of that for control rats.

In a simultaneous perfusion system in rat liver and kidney, the perfusate plasma decay of cefoperazone followed a one-compartment open model (Figure 2). As shown in Table 2, the unbound fraction of cefoperazone in experiments with two kinds of albumin was remarkably different. Although the CL in control rats perfused with bovine serum albumin was about 6-fold that in control rats perfused with human serum albumin, corresponding to the unbound fraction of the drug in the perfusate plasma, the CL_f in normal rats did not differ significantly between the two perfusates. On the other hand, both CL and CL_f in acute renal failure (bovine serum albumin perfusate) significantly decreased compared with control rats (bovine serum albumin perfusate). In this case, the unbound fraction of the drug in the perfusate plasma was nearly the same in acute renal failure and control rats (Table 2).

Discussion

Cefoperazone is a water-soluble, anionic drug that is mainly excreted unmodified into the bile (Saikawa et al 1980). There are no previous studies on the transporter of cefoperazone in the liver and the kidney. Gosland et al (1989) showed that cefoperazone effectively modulates the multidrug transporter P-glycoprotein in human sarcoma cells.

Tsuji et al (1986) and Tamai et al (1990) reported that β-lactam antibiotics are taken into the hepatocytes by a carrier-mediated transport system and are actively excreted into the bile. Biliary excretion of organic anions has been shown to be mediated by a canalicular multispecific organic anion transporter (Ishikawa et al 1990; Kitamura et al 1990; Kobayashi et al 1990). The mechanism of the hepatic uptake and biliary excretion of cefoperazone is believed to be via this transporter. In our in-vivo experiments, plasma-protein binding of

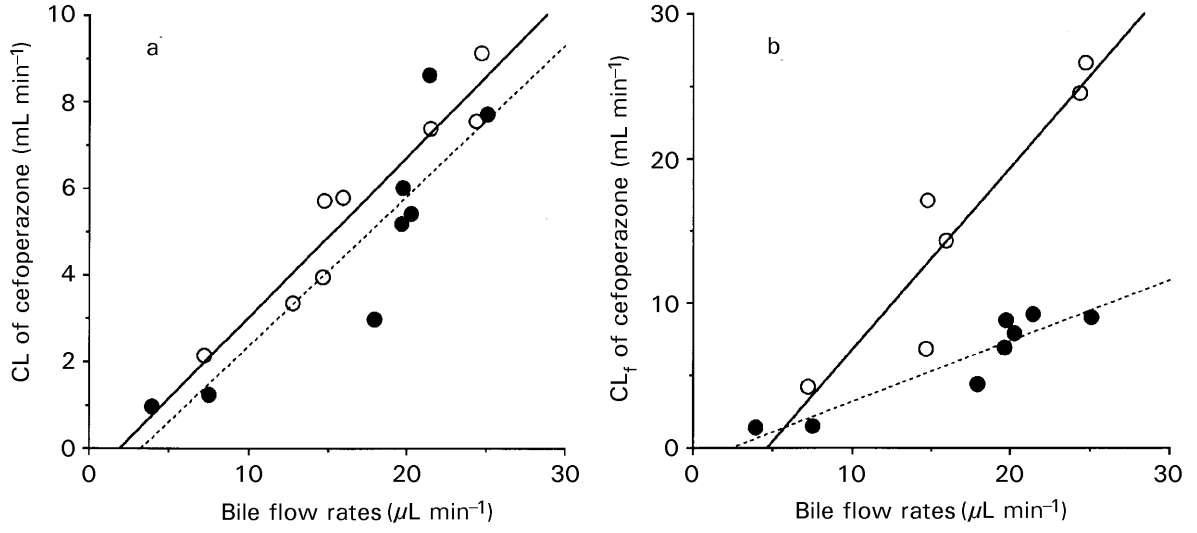

Figure 1. Effect of bile flow rates on cefoperazone clearance in-vivo. ○ Control rats, ● uranyl nitrate-treated rats. Each point represents one rat.

Table 2. Clearance of cefoperazone in a simultaneous perfusion system of rat liver and kidney.

	Bovine serum albumin		Human serum albumin
	Control	Acute renal failure	Control
CL (mL min^{-1})	3·57 ± 0·49	2·42 ± 0·59**	0·60 ± 0·14***
CL_f (mL min^{-1})	4·16 ± 0·67	2·97 ± 0·80*	3·65 ± 0·72
f[a]	0·863 ± 0·079	0·824 ± 0·049	0·165 ± 0·006***

Cefoperazone was added to the reservoir (50 mg kg^{-1}) and perfused for 30 min. Results are given as the mean ± s.d. of 3–5 animals. [a]Unbound fraction in the perfusate plasma at the end of the perfusion. *$P < 0.05$, **$P < 0.025$, ***$P < 0.010$ compared with control.

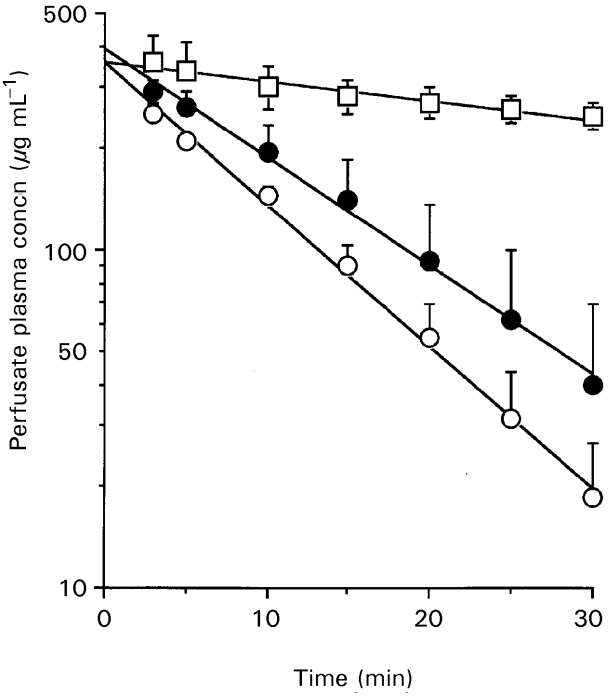

Figure 2. Disappearance of cefoperazone from perfusate plasma in a simultaneous perfusion system of rat liver and kidney. Cefoperazone (50 mg kg^{-1}) was added to the reservoir at time 0. Each point and vertical bar represent the mean ± s.d. of 3–5 animals. ○ Control rats (bovine serum albumin perfusate), □ control rats (human serum albumin perfusate), ● uranyl nitrate-treated rats (bovine serum albumin perfusate).

cefoperazone decreased in acute renal failure rats compared with control rats. Previous reports have suggested that an endogenous protein-binding inhibitor of the anionic drug exists during renal failure (Depner 1981; Gambertoglio 1984; Ikeda et al 1984). If the CL_f of cefoperazone is unchanged in acute renal failure, the CL of cefoperazone in acute renal failure should increase in accordance with increases in the fraction of the drug in plasma (assuming linear kinetics). However the CL of cefoperazone did not differ significantly between the control and acute renal failure rats. The increase in unbound cefoperazone in plasma or the reduced hepatic transport of unbound drug in plasma might be responsible for the decrease in CL_f in acute renal failure. Thus, the tissue distribution of unbound cefoperazone in plasma was relatively low in acute renal failure, and the V_{ss} of cefoperazone in acute renal failure did not increase with increases in the free fraction of the drug in the plasma (Table 1).

Balant et al (1980) studied cefoperazone tissue distribution in Wistar rats. Cefoperazone tissue penetration was good and the renal and hepatic concentrations of cefoperazone were higher than in serum (kidney > liver > serum). The high concentrations of cefoperazone in the kidney and the liver support the existence of an active transport system containing the transporter. The contribution of the kidney to the clearance of cefoperazone is low in patients with normal liver function. The renal uptake of cefoperazone (K/P and K/P_f) decreased in acute renal failure due to renal dysfunction possibly due to transporter damage. The hepatic uptake of the unbound cefoperazone (L/P_f) also decreased in acute renal failure rats compared with normal rats, although L/P was nearly the same in the two groups. Although the mechanism is unclear, the increase in unbound cefoperazone in plasma or reduced hepatic transport of the unbound cefoperazone might be responsible for the reduced hepatic uptake, as described above.

As shown in Figure 1b, CL_f and bile flow rates correlate, and the slope (bile flow rates vs CL_f) significantly differs between the control and acute renal failure rats. On the other hand, CL was dependent on bile flow rates and the slope was nearly the same for the two groups (Figure 1a). Interestingly, neither control nor acute renal failure rats had bile flow rates vs CL_f lines that went through zero. The reason for this is unclear; however the intercept of x-axis in Figure 1 (3–5 μL min^{-1}) might be the threshold value for biliary excretion of cefoperazone. Therefore, hepatic transport of cefoperazone might decrease during uranyl nitrate-induced acute renal failure.

To study the effect of plasma-protein binding on the clearance of cefoperazone, in-vitro perfusion

studies were performed. A simultaneous perfusion system in isolated rat liver and kidney using a red blood cell medium has been developed to study hepato-renal relationships (de Lannoy & Pang 1993; Yasuhara et al 1985). In our perfusion studies we controlled blood flow rates and cefoperazone protein binding by changing the kinds of plasma proteins in the perfusate. We used human serum albumin or bovine serum albumin as the perfusate plasma, and found cefoperazone binds to human serum albumin more strongly than to bovine serum albumin. The CL value for cefoperazone in the human serum albumin perfusate was lower than in the bovine serum albumin perfusate, but CL_f did not differ significantly between the two perfusates. Therefore, protein binding of cefoperazone may be an important factor affecting its disposition in normal rats. On the other hand, CL_f as well as CL significantly decreased in acute renal failure rats compared with control rats in simultaneous perfusion studies with the same plasma-protein binding of cefoperazone. These findings suggest that reduced hepatic uptake, rather than increased unbound cefoperazone, is responsible for the decrease in CL_f in acute renal failure.

Hepatic blood flow rates, plasma-protein binding and intrinsic clearance of unbound drug may be responsible for hepatic extraction of some drugs (Wilkinson & Shand 1975). It has been shown that hepatic blood flow rates do not change in uranyl nitrate-induced acute renal failure in rats 3 days after the injection of the inducer (Katayama et al 1984). Therefore, it has been suggested that the decrease in CL_f in acute renal failure is mainly due to a reduction in the hepatic intrinsic clearance of unbound drug. However, acute renal failure induced by injection of uranyl nitrate selectively produces renal dysfunction and does not affect hepatic function, as indicated by GOT, GPT, albumin and total protein levels (Katayama et al 1984; Hori et al 1985; Yasuhara et al 1985). Terao & Shen (1983) and Katayama et al (1984) previously showed that the availability of propranolol (lipophilic and cationic) increases in uranyl nitrate-treated rats. The mechanism of this increase in acute renal failure is believed to be via a reduction in hepatic presystemic elimination (Katayama et al 1984; Hori et al 1985) due to decreased hepatic uptake of the drug from the blood into the liver cells (i.e. a carrier mediated transport system). Terao & Shen (1985) reported that the reduction in presystemic hepatic extraction of 1-propranolol in the uranyl nitrate renal failure rat model is due to the presence of an inhibitory factor in the uraemic blood. Bowmer et al (1982) reported decreased clearance of indocyanine green and bromosulphophthalein, which are hydrophilic and anionic, in glycerol-induced acute renal failure rats. They demonstrated reduced hepatic uptake of the drug from the plasma and delayed biliary excretion in acute renal failure. Recently, Haghgoo et al (1995) reported a decrease in bile flow rates and biliary excretion of cefoperazone in *Klebsiella pneumoniae* lipopolysaccharide-treated rats. They speculated that decreased flow rate may be caused by endogenous mediators induced by lipopolysaccharides or lipopolysaccharides that inhibit ATP-dependent transport of cefoperazone in the canalicular membrane.

In the present study, we have found that the disposition of cefoperazone, which is mainly excreted unmodified into the bile, is affected in uranyl nitrate-induced acute renal failure in rats. Further, we believe this is due to decreased hepatic uptake, via a carrier-mediated transport system.

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