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Distribution of Ciprofloxacin into the Central Nervous System in Rats with Acute Renal or Hepatic Failure

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Abstract

Pharmacokinetic changes of various drugs have been reported in renal or hepatic failure. The present study employed ciprofloxacin, a quinolone antibiotic having neurotoxic side effects, to assess the influence of these diseases on distribution of ciprofloxacin into the central nervous system (CNS).

After intravenous dosing of ciprofloxacin ($10-30\,mg\,kg^{-1}$), ciprofloxacin levels in plasma and brain were measured in normal rats (Wistar, male, 10-week-old) and those with acute renal and hepatic injuries which were induced by uranyl nitrate and carbon tetrachloride (CCl_4), respectively. In the uranyl nitrate-treated rats, the plasma elimination half-life of ciprofloxacin was prolonged and the total body clearance was reduced when compared with those in the normal rats. Similar but smaller changes were observed in the CCl_4-treated group. Brain levels of ciprofloxacin were significantly increased by both uranyl nitrate and CCl_4 treatments. A proportional correlation between serum unbound levels and brain levels of ciprofloxacin was observed in the normal group. However, brain-to-serum unbound concentration ratios of ciprofloxacin were reduced in the rats with renal or hepatic failure.

These results suggest that renal failure as well as hepatic failure retards elimination of ciprofloxacin from the blood, leading to elevation of the CNS level, and also that ciprofloxacin distribution in the brain is reduced in these disease states.

Ciprofloxacin is one of the fluoroquinolone antibiotics which have been shown to be very active against a wide variety of pathogenic bacteria, including some Gram-positive and most Gram-negative organisms (Ramirez et al 1985; Wolfson & Hooper 1985). This quinolone is known to be eliminated unchanged to any great extent in the urine, and there are many reports that renal failure induces elevation of plasma ciprofloxacin levels (Vance-Bryan et al 1990). It was also reported that this drug had a relatively high non-renal clearance (Höffken et al 1985; Borner et al 1986). It is likely, therefore, that ciprofloxacin pharmacokinetics would be changed in hepatic dysfunction as well.

Ciprofloxacin is known to distribute substantially into a wide variety of tissues, including the CNS. Furthermore, quinolone antibiotics have neurotoxic side effects such as insomnia, drowsiness and convulsion (Janknegt 1986). Consequently, it is important to investigate distribution of ciprofloxacin into the CNS when the kidney or liver is injured.

The aim of this study is to assess the influence of renal and hepatic failure on ciprofloxacin pharmacokinetics, especially distribution into the brain, in rats.

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Materials and Methods

Materials

Ciprofloxacin hydrochloride was purchased from Sigma (St Louis, MO). Uranyl nitrate and carbon tetrachloride (CCl_4) were obtained from Merck (Darmstadt, Germany) and Nacalai Tesque (Kyoto, Japan), respectively. All other chemicals were of analytical grade.

Animals

Male Wistar rats (Nippon SLC, Hamamatsu, Japan) were used in this investigation. According to the

procedure reported by Giacomini et al (1981) uranyl nitrate (5 mg kg^{-1} as a 1·0% solution in normal saline) was injected intravenously via the tail vein 5 days before the ciprofloxacin administration study to induce experimental renal dysfunction. Experimental hepatic dysfunction was induced by oral administration of CCl_4. CCl_4 was dissolved in an equal volume of olive oil (i.e. 1 : 1, v/v) and administered at a dose of 1 mL kg^{-1} (as CCl_4) approximately 24 h before ciprofloxacin administration. Respective control groups to the uranyl nitrate-treated and CCl_4-treated rats were given normal saline and olive oil. These rats were housed in the laboratory and maintained under a 12-h light–dark cycle, a controlled room temperature of $23 \pm 2^{\circ}C$ and a relative humidity of $50 \pm 10\%$. Animal experiments were all carried out in accordance with the Guidelines for Animal Experimentation of Shimane Medical University, which complied with the Guidelines for Animal Experimentation of the Japanese Association for Laboratory Animal Science.

In-vivo drug administration study

Approximately 20 h before ciprofloxacin administration, each rat was cannulated in the right jugular vein with silicone tubing (1·0 mm inner diameter, 1·5 mm outer diameter) in accordance with the method of Upton (1975), and then, was allowed free access to food and water in the individual cage. Ciprofloxacin hydrochloride was dissolved in a small volume of distilled water and diluted with normal saline to obtain a ciprofloxacin concentration of 10 or 20 mg mL^{-1}. Ciprofloxacin solution was administered by bolus injection through the jugular vein cannula at doses of 10, 20 or 30 mg kg^{-1} to the control rats and 10 mg kg^{-1} to the uranyl nitrate-treated or CCl_4-treated rats. The volume of the solution administered was 1·0 mL kg^{-1} for the doses of 10 and 20 mg kg^{-1} and 1·5 mL kg^{-1} for the dose of 30 mg kg^{-1}. The blood samples (0·1 mL) were withdrawn from the cannula into the heparinized tubes at 3, 6, 10, 15, 20, 30, 45, 60, 90 and 120 min after intravenous administration, and plasma was immediately separated by centrifugation. Following the final periodical plasma collection, blood (approximately 2 mL) was withdrawn through the cannula and the rat was killed by decapitation under ether anaesthesia. A small portion of the blood was haemolysed with an equal volume of distilled water for determination of the drug concentration in whole blood. The serum was immediately separated from the blood by centrifugation, and a portion of the serum was ultrafiltered with a micropartition device, Centrifree (Amicon, Beverly, MA), by centrifugation at 2000 *g* for 15 min (Model KR-20000T, Kubota, Tokyo, Japan) to determine the extent of serum protein binding of ciprofloxacin. The brain was readily excised from the skull and weighed after careful removal of the cerebellum, brain stem, dura mater, choroid plexus and large and subarachnoidal vessels.

Assay

Ciprofloxacin concentrations in whole blood, serum, plasma and ultrafiltrate were determined in accordance with the high-performance liquid chromatographic method developed previously by Naora et al (1990). Another high-performance liquid chromatographic method (Katagiri et al 1990) was employed to determine ciprofloxacin concentrations in the brain.

Serum creatinine, urea nitrogen, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were determined with a biochemical assay system, Reflotron (Yamanouchi Seiyaku, Tokyo, Japan). Serum albumin was determined with the BCG method using a commercial kit (Albumin B Test Wako, Wako Pure Chemical Industries, Osaka, Japan).

The measured brain concentrations were corrected by the cerebral intravascular concentration which was obtained from the product of the cerebral blood volume and the whole blood concentration according to the method described previously (Naora et al 1991).

Data analysis

Pharmacokinetic analysis of the plasma concentration–time data was performed based on a two-compartment model. The non-linear least-squares regression program MULTI (Yamaoka et al 1981) was employed for the regression analysis of the plasma concentration–time curves. Pharmacokinetic parameters, i.e. plasma elimination half-life ($t_{1/2\beta}$), total body clearance (CL_{tot}), distribution volumes of the central compartment (V_c) and the peripheral compartment (V_p), were calculated by means of the conventional equations. Assuming that ciprofloxacin is neither metabolized nor decomposed in the brain, the partition coefficient between the brain and the serum unbound fraction (K_{pf}) during the β-phase can be expressed as follows according to the equation of Chen & Gross (1979):

$$K_{pf} = C_{brain} \times Q_{brain} / (C_{serum,u} \times Q_{brain} + V_{brain} \times \beta \times C_{brain}) \quad (1)$$

where C_{brain} and $C_{serum,u}$ are brain and serum unbound concentrations of ciprofloxacin, respectively; Q_{brain} is the blood flow rate in the brain, which has been reported as 1·1 mL min^{-1} (Lin et al 1982); V_{brain} is the volume of the brain and β is a hybrid parameter in two-compartmental analysis. When the values obtained in the present study were substituted into this equation, K_{pf} could approximate to the result of C_{brain} divided by $C_{serum,u}$. Therefore, ciprofloxacin distribution into the brain was evaluated by the brain-to-serum unbound concentration ratio of this drug.

Statistics

The comparison of the plasma concentration–time profiles was performed with repeated measures analysis of variance. In the estimation of statistical significance of differences between the means of two groups for biochemical data, pharmacokinetic parameters, serum and brain concentration data, the Student's *t*-test or Mann–Whitney *U*-test was utilized. Statistical significance was defined as $P < 0.05$.

Results

Biochemical data

Creatinine, urea nitrogen, ALT, AST and albumin levels in the serum collected from the control, uranyl nitrate-treated and CCl_4-treated rats before drug administration are listed in Table 1. Since there was no significant difference in the biochemical data among respective control rats to uranyl nitrate and CCl_4 treatments and the normal rats for the dose-dependence study, these data were combined into one control group in Table 1. The serum creatinine levels of all control rats employed in the present study were lower than 0·5 mg dL^{-1} (the assay limit). High levels of serum creatinine were observed in the uranyl nitrate-treated rats, while the CCl_4-treated rats had the same creatinine levels as the normal rats. Similarly, serum urea nitrogen levels of the uranyl nitrate-treated rats were significantly higher than those of the control rats. The CCl_4 treatment significantly elevated serum ALT and AST levels. Although significantly higher levels of AST were observed in the uranyl nitrate-treated rats, the extent of the change was less compared with that observed in the CCl_4-treated rats. Serum albumin concentrations of the uranyl nitrate-treated rats were significantly lower than those of the controls, whereas the CCl_4 treatment induced no change in the serum albumin concentrations.

Plasma ciprofloxacin concentration

Plasma ciprofloxacin–time profiles after intravenous administration of 10 mg kg^{-1} to uranyl nitrate-treated, CCl_4-treated and the respective control rats are shown in Figure 1. Plasma ciprofloxacin levels of these rats showed a biexponential decline with time. Uranyl nitrate-treated rats had significantly higher plasma concentrations of ciprofloxacin than the control rats. Although significant elevation of plasma ciprofloxacin levels was also observed in the CCl_4-treated rats, the extent of the change was smaller than with uranyl nitrate treatment.

Pharmacokinetic parameters obtained from uranyl nitrate-treated, CCl_4-treated and control rats by the two-compartment model analysis are listed in Table 2. The uranyl nitrate treatment prolonged the $t_{1/2\beta}$ by about 2-fold and reduced the CL_{tot} to approximately 25%. Volumes of distribution for central and peripheral compartments were decreased by about one-half in the uranyl nitrate-treated rats. Prolonged $t_{1/2\beta}$ and reduced CL_{tot} were

Table 1. Biochemical data for sera obtained from control, uranyl nitrate-treated and CCl_4-treated rats.

Measurement	Control	Uranyl nitrate-treated	CCl_4-treated
n	18	5	5
Creatinine (mg dL^{-1})	<0·50	4·90 ± 0·82	<0·50
Urea nitrogen (mg dL^{-1})	18·6 ± 2·7	192·8 ± 51·3***	20·5 ± 1·0
ALT (U L^{-1})	54·8 ± 11·7	56·7 ± 7·7	3756 ± 3226***
AST (U L^{-1})	162·9 ± 27·6	259·2 ± 24·3**	7476 ± 5668***
Albumin (g dL^{-1})	3·91 ± 0·24[a]	3·16 ± 0·22**	3·81 ± 0·16

Each value represents the mean ± s.d. of indicated number of rats ([a]ten rats). The control group includes the respective controls to uranyl nitrate-treated and CCl_4-treated rats as well as the rats employed in the dose-dependence study. There are significant differences compared with the control rats at $^{**}P < 0.01$ and $^{***}P < 0.001$ (Mann–Whitney *U*-test).

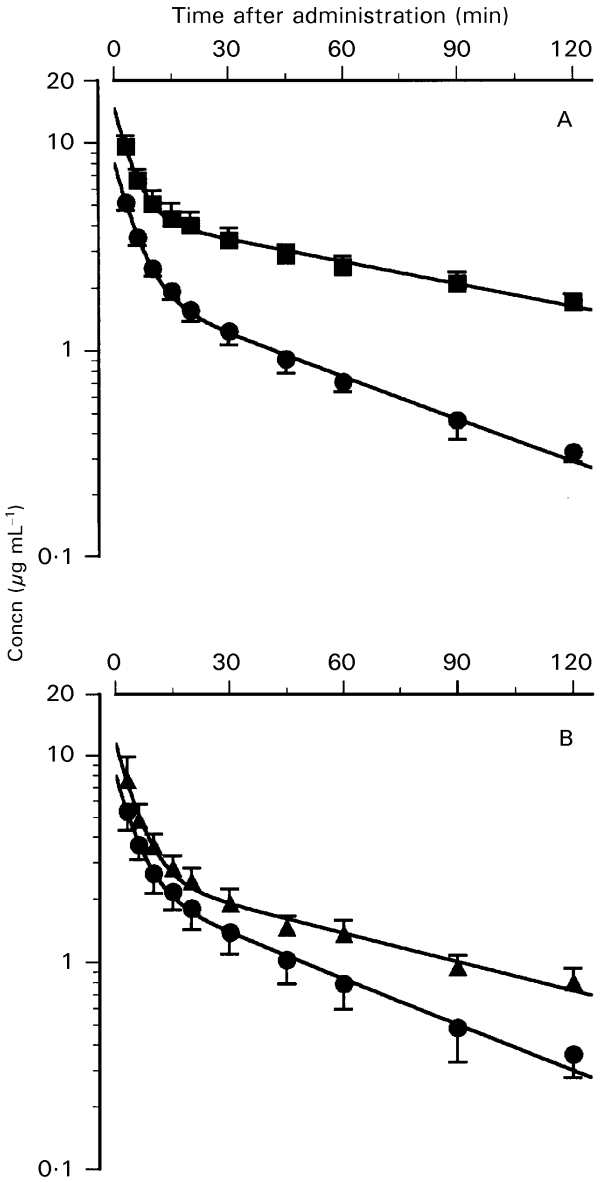

Figure 1. Plasma ciprofloxacin concentration–time profiles after intravenous administration (10 mg kg^{-1}) to uranyl nitrate-treated (A, ■), CCl_4-treated (B, ▲) and respective control rats (●). Each point and vertical bar represent the mean and s.d. of five rats. Solid lines are computer-fitted biexponential curves for the mean data. Plasma ciprofloxacin concentrations in uranyl nitrate-treated and CCl_4-treated rats were significantly higher compared with those in the respective control rats (repeated measures analysis of variance, $P < 0{\cdot}05$).

also found in the CCl_4-treated group, while the distribution volumes of this group were not changed as compared with the control.

Serum total, unbound concentrations and bound fractions of ciprofloxacin measured 120 min after intravenous administration of 10 mg kg^{-1} to uranyl nitrate-treated, CCl_4-treated and control rats are summarized in Table 3. Whereas the serum total and unbound level of ciprofloxacin was increased by uranyl nitrate and CCl_4 treatment, the fraction bound to serum protein was significantly reduced in both groups.

CNS distribution of ciprofloxacin

Ciprofloxacin levels in the brain collected 120 min after bolus intravenous administration of ciprofloxacin at a dose of 10 mg kg^{-1} from uranyl nitrate-treated, CCl_4-treated and the respective control rats are shown in Table 4. Brain levels of ciprofloxacin in the uranyl nitrate-treated rats were about three times higher than those of the control rats. Similarly, in the CCl_4-treated rats, increased brain levels of ciprofloxacin were observed. Brain-to-serum unbound concentration ratios of ciprofloxacin in uranyl nitrate-treated, CCl_4-treated and the respective control rats are also shown in Table 4. In contrast to the ciprofloxacin brain levels, brain-to-serum unbound concentration ratios of ciprofloxacin in uranyl nitrate-treated and CCl_4-treated rats were significantly lower than those in the controls.

Figure 2 demonstrates the relationship between serum unbound levels and brain levels of ciprofloxacin which were determined 120 min after intravenous administration of ciprofloxacin at doses of 10, 20 and 30 mg kg^{-1} to the control rats. Data from both uranyl nitrate-treated and CCl_4-treated rats are also plotted in Figure 2 (closed symbols). It was found that, in the control rats, the brain concentrations proportionally elevated with the serum unbound levels of ciprofloxacin. The result of a regression analysis for these data was as follows: $y = 0{\cdot}0317x + 0{\cdot}00327$ ($R^2 = 0{\cdot}956$, $n = 14$), where y is brain level of ciprofloxacin, x is serum unbound level of ciprofloxacin, R^2 is a coefficient of determination and n is the number of observations. In uranyl nitrate-treated and CCl_4-treated rats, however, measured brain levels were lower than the levels estimated from the corresponding serum unbound levels using a linear regression analysis on the data of the control rats.

Discussion

From the results shown in Table 1, it was observed that there were extremely high levels of creatinine and urea nitrogen in the serum of uranyl nitrate-treated rats and high levels of AST and ALT in the serum of CCl_4-treated rats. Consequently, it is obvious that uranyl nitrate and CCl_4 treatments induced renal and hepatic injuries, respectively. The uranyl nitrate-treated rats showed slightly but significantly higher AST levels than the control rats despite there being no change in ALT. AST is

Table 2. Pharmacokinetic parameters of ciprofloxacin estimated from plasma concentration–time data after intravenous administration (10 mg kg^{-1}) to uranyl nitrate-treated, CCl_4-treated and respective control rats.

Parameter	Control	Uranyl nitrate-treated	Control	CCl_4-treated
$t_{1/2\beta}$ (min)	43·9 ± 4·8	84·8 ± 8·4***	40·8 ± 3·4	67·0 ± 11·1**
CL_{tot} (mL min^{-1} kg^{-1})	65·9 ± 5·9	17·5 ± 1·6***	63·1 ± 11·6	34·7 ± 4·1**
V_c (L kg^{-1})	1·27 ± 0·15	0·682 ± 0·080***	1·29 ± 0·23	1·00 ± 0·40
V_p (L kg^{-1})	2·12 ± 0·25	1·30 ± 0·27***	1·80 ± 0·30	1·86 ± 0·36

Each value represents the mean ± s.d. of five rats. There are significant differences compared with the respective controls at $^{**}P < 0.01$ and $^{***}P < 0.001$ (Student's *t*-test).

Table 3. Serum total, unbound concentrations and bound fractions of ciprofloxacin at 120 min after intravenous administration (10 mg kg^{-1}) to uranyl nitrate-treated, CCl_4-treated and respective control rats.

Group	Ciprofloxacin concn (μg mL^{-1})		Bound fraction
	Serum total	Serum unbound	
Renal dysfunction			
Control	0·493 ± 0·046	0·354 ± 0·041	0·283 ± 0·028
Uranyl nitrate-treated	2·09 ± 0·18***	1·72 ± 0·19***	0·175 ± 0·050**
Hepatic dysfunction			
Control	0·464 ± 0·070	0·327 ± 0·057	0·297 ± 0·027
CCl_4-treated	0·972 ± 0·118***	0·774 ± 0·089***	0·202 ± 0·038**

Each value represents the mean ± s.d. of five rats. There are significant differences compared with the respective controls at $^{**}P < 0.01$ and $^{***}P < 0.001$ (Student's *t*-test).

Table 4. Brain levels and brain-to-serum unbound concentration ratios of ciprofloxacin at 120 min after intravenous administration (10 mg kg^{-1}) to control, uranyl nitrate-treated and CCl_4-treated rats.

Group	Brain ciprofloxacin concn (μg g^{-1})	Brain/serum unbound ratio
Renal dysfunction		
Control	0·014 ± 0·002	0·038 ± 0·007
Uranyl nitrate-treated	0·040 ± 0·002***	0·024 ± 0·003**
Hepatic dysfunction		
Control	0·012 ± 0·001	0·038 ± 0·006
CCl_4-treated	0·023 ± 0·005**	0·029 ± 0·004*

Values represent the mean ± s.d. of five rats. There are significant differences compared with the respective controls at $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (Student's *t*-test).

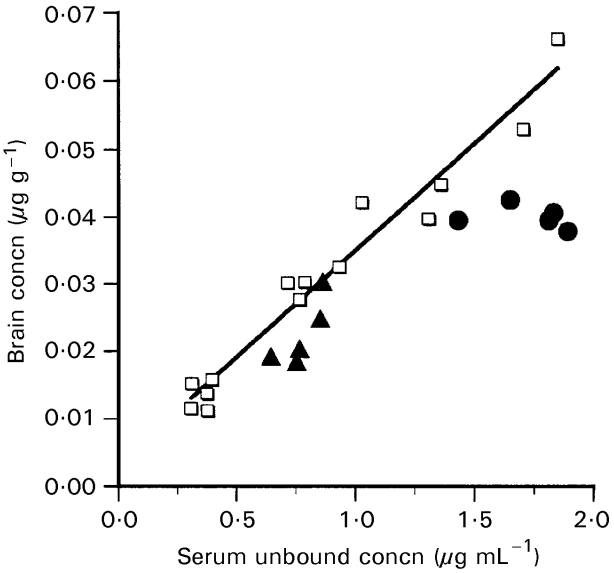

Figure 2. Correlation between serum unbound levels and brain levels of ciprofloxacin at 120 min after intravenous administration to control, uranyl nitrate-treated and CCl_4-treated rats. □, control rats (10–30 mg kg^{-1} dose); ●, uranyl nitrate-treated rats (10 mg kg^{-1} dose); ▲, CCl_4-treated rats (10 mg kg^{-1} dose). The solid line is based on a linear regression analysis of the data of the control rats.

known to be widely distributed not only in the liver but also in other organs including the kidney in rats. Elevation of the AST levels in uranyl nitrate-treated rats may be ascribed to release of this enzyme from the damaged kidney. Thus, renal and hepatic failure, respectively, could be selectively induced by uranyl nitrate and CCl_4 treatments in this study.

It was reported that the non-renal clearance of ciprofloxacin was about 40% of the total body clearance after intravenous administration in healthy humans (Höffken et al 1985; Borner et al 1986). In rats, one-half of the dose was excreted into faeces when ciprofloxacin was administered intravenously (Siefert et al 1986), indicating that the non-renal route for elimination may be relatively large. Therefore, the pharmacokinetics of ciprofloxacin may be altered in hepatic impairment

as well as in renal impairment. As expected, both uranyl nitrate and CCl_4 treatments raised plasma levels of ciprofloxacin and prolonged the $t_{1/2\beta}$ remarkably (Figure 1, Table 2). In the CCl_4-treated rats, the extent of the changes was smaller compared with the changes observed in uranyl nitrate-treated rats. These results suggest that accumulation of ciprofloxacin in the body would occur in severe hepatic dysfunction as well as in renal dysfunction. This aspect coincides with the report that ciprofloxacin kinetics in patients with alcoholic cirrhosis were slightly modified (Montay & Gaillot 1990). On the contrary, Frost et al (1989) reported that there were no differences in pharmacokinetic parameters of ciprofloxacin between normal subjects and cirrhotic patients after oral administration. As is obvious from the transaminase data shown in Table 1, the damage caused by uranyl nitrate to hepatic functions of the rats in this study was severe. The difference in the species and severity of the hepatic impairment may explain the discrepancy.

Another change in the pharmacokinetic parameters was the reduction in the volume of distribution in the rats treated with CCl_4. It has been reported that, for digoxin, the volume of distribution was reduced by virtue of decreased tissue binding in uraemic patients (Lam et al 1997). Since the values of V_c and V_p of ciprofloxacin are relatively large, it may be reasonable to suppose that this quinolone possibly binds to the tissue and that renal failure reduces this tissue binding. However, there has been a recent paper demonstrating that the volume of distribution of ciprofloxacin is not changed in rats with renal failure induced by partial nephrectomy (Nouaille-Degorce et al 1998). Therefore, the possible mechanisms for reduced distribution volumes observed in this study remained unexplainable.

We found serum protein binding of ciprofloxacin in the control rats to be about 0·3. This is in agreement with data reported in our previous paper (Naora et al 1990). Uranyl nitrate and CCl_4 treatments reduced the fraction of ciprofloxacin bound to serum protein by about 40% and 30%, respectively. Although uranyl nitrate-treated and CCl_4-treated rats had higher serum ciprofloxacin levels than the controls, our previous studies demonstrated that serum protein binding of ciprofloxacin was independent of the drug levels in serum (Naora et al 1990, 1991). As shown in Table 1, serum albumin levels were reduced by uranyl nitrate treatment. Therefore, the change in serum protein binding of ciprofloxacin in the rats with renal dysfunction could be explained by decreased plasma albumin levels. Alternatively, there is a possibility that uraemic toxins affected the protein binding of ciprofloxacin, as has been reported for the binding of L-tryptophan to human serum albumin (Mingrone et al 1997). On the other hand, since serum albumin levels were not changed by treatment with CCl_4, the reduced extent of the protein binding observed in hepatic-injured rats may be related to a possible change in protein conformation or to replacement of the drug by increased endogenous substances such as bilirubin. Thus, in these disease states, serum unbound concentrations of ciprofloxacin were elevated not only by the prolonged elimination half-life but also by the reduced protein binding. As a result, both renal and hepatic failure can allow ciprofloxacin to penetrate into tissues, including the CNS, more easily. It is well known that the neurotoxic side effects of quinolones are enhanced in the presence of non-steroidal anti-inflammatory drugs (NSAIDs). However, quinolone treatment without NSAIDs has also induced CNS reactions including convulsive seizures, although the frequency of their incidence is fairly low (Christ 1990). Therefore, elevation of CNS levels of ciprofloxacin in renal or hepatic dysfunction possibly raises the risk of CNS side effects.

To evaluate distribution of ciprofloxacin into the CNS, the ratio of brain level to serum unbound level of ciprofloxacin was calculated. Interestingly, it was found that brain-to-serum unbound concentration ratios were reduced in the rats with renal or hepatic dysfunction in contrast to the remarkable increase in the drug levels. These findings suggest that reduction in the permeation of ciprofloxacin through the blood–brain barrier occurred in renal and hepatic failure. Similar phenomena have been reported for other compounds. Lin et al (1987) reported that propranolol uptake into the brain was inhibited in the rats with acute renal failure. Lo et al (1987) demonstrated that galactosamine-induced hepatic failure could reduce the brain uptake of methylaminoisobutyric acid in rats. However, it was also reported that renal and hepatic failure produced different effects on the blood–brain permeability of drugs. In the previous study in which mice were used, uranyl nitrate-induced renal dysfunction and CCl_4-induced hepatic dysfunction were found to have no effect on brain-to-plasma concentration ratios of a histamine H_2 receptor antagonist, ranitidine (Shimokawa et al 1994). Furthermore, Lin & Lin (1990) demonstrated that brain uptake of diazepam and related benzodiazepines was increased in CCl_4-induced hepatic-injured rats. From these findings, it is supposed that reduction of brain distribution in the disease states is not produced by non-specific changes in drug

penetration through the blood–brain barrier. In addition, Lin et al (1987) demonstrated that brain extraction of inulin, an impermeable marker of the blood–brain barrier, was not altered in uraemic rats. Furthermore, no change in the blood–brain barrier permeability–surface area product of sucrose, another impermeable marker, in rats with hepatic dysfunction induced by D-galactosamine was reported by Lo et al (1987). These findings could support our above supposition. Therefore, changes in the blood–brain barrier permeability of a certain drug by renal and hepatic impairment may be related to some specific transport system in the brain capillary endothelium.

It has been suggested that quinolone antibiotics are transported via the active transport system in the CNS (Ooie et al 1996, 1997). Therefore, it is considered that high concentrations in the blood and brain induced by delayed elimination may cause limited distribution into the CNS in the rats with renal and hepatic dysfunction. To examine this possibility, a dose-dependence study was carried out in normal rats. As the results showed, serum unbound concentrations of ciprofloxacin measured 120 min after intravenous administration of 10, 20 and 30 mg kg^{-1} ranged from 0·2 to 1·8 $\mu g\,mL^{-1}$. The proportional relationship between serum unbound and brain concentrations of ciprofloxacin in the rats with normal renal and hepatic functions indicates linear pharmacokinetics in ciprofloxacin distribution into the CNS within this concentration range (which includes the concentrations observed in the rats with renal or hepatic dysfunction). These findings imply that reduction in brain-to-serum unbound concentration ratios could not be ascribed to the higher ciprofloxacin concentrations in the plasma and brain caused by these disease states.

Although the mechanism for reduction of ciprofloxacin distribution into the CNS in the disease states is unclear, a few possibilities could be suggested. As mentioned above, specific transport systems for quinolone antibiotics may exist in the blood–CNS interface. In disease states such as renal and hepatic failure, many kinds of endogenous substances could accumulate in the body. These substances could modify the ability or function of specific transport systems operating to transport quinolones at the blood–brain barrier.

From this study, it is concluded that renal failure, as well as hepatic failure, induces an increase in ciprofloxacin levels in plasma and brain as a result of delay in the elimination from the body, presumably leading to enhancement of the neurotoxicity of this quinolone. In addition, ciprofloxacin distribution between blood and CNS would be reduced in renal and hepatic dysfunction, so that ciprofloxacin levels in the CNS can not be predicted from the plasma levels and the protein binding in these disease states.

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