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Influence of Glycerol-induced Acute Renal Failure on the Pharmacokinetics of Cyclosporin in Rats

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Abstract

Although it is widely believed that renal dysfunction has no effect on the pharmacokinetics of cyclosporin, many clinical reports suggest that renal dysfunction after renal transplantation is closely related to the pharmacokinetics of cyclosporin. To clarify the relationship between renal dysfunction and the pharmacokinetics of cyclosporin, we examined the influence of acute renal failure (ARF) on its pharmacokinetics in glycerol-induced ARF rats.

The values of indicators of renal function (serum creatinine, blood urea nitrogen), but not those of indicators of hepatic function, were significantly increased in ARF rats that received glycerol compared with values for control rats. The area under the blood cyclosporin concentration–time curve after oral administration (AUC_{po}) were $4{\cdot}976 \pm 0{\cdot}847\,mg\,h\,L^{-1}$ for ARF rats and $9{\cdot}684 \pm 1{\cdot}100\,mg\,h\,L^{-1}$ for control rats; AUC_{po} in ARF was significantly reduced in a manner dependent on renal function. The oral clearance of cyclosporin in ARF and control rats was $1{\cdot}172 \pm 0{\cdot}207$ and $0{\cdot}544 \pm 0{\cdot}062\,L\,h^{-1}\,kg^{-1}$, respectively, whereas total body clearance in ARF and control rats was $0{\cdot}151 \pm 0{\cdot}008$ and $0{\cdot}183 \pm 0{\cdot}010\,L\,h^{-1}\,kg^{-1}$, respectively. The relative bioavailability of cyclosporin in ARF and control rats was 0·118 and 0·336, respectively. In an in-vitro study using everted sac and liver-slice methods, the apparent first-order rate constants for cyclosporin uptake (k_{uptake}) and metabolism (k_{metab}) in gut tissues were reduced, whereas k_{uptake} and k_{metab} in liver were increased. Gastric emptying, measured by use of paracetamol, was significantly reduced in ARF rats.

These results suggest that glycerol-induced ARF results in several changes in the pharmacokinetics of cyclosporin in rats. From these results, we conclude that reduction of the absorbed fraction of cyclosporin strongly contributes to the decrease in AUC_{po} in the presence of ARF.

Cyclosporin is a powerful immunosuppressant used in several types of organ transplantation and to treat autoimmune disease (Bach 1989). Although several disease states, including hepatotoxicity, nephrotoxicity, anaemia, hypertension, diabetes mellitus and infection can appear after several types of organ transplantation, the relationship between the pharmacokinetics of cyclosporin and physiological changes resulting from these disease states in transplant patients has not been clarified.

A task force on cyclosporin monitoring in the United States concluded that renal failure does not alter the pharmacokinetics of cyclosporin because clearance of cyclosporin was not significantly altered in the presence of renal failure (Shaw et al 1987). Therefore, it is widely believed that renal function is independent of the pharmacokinetics of cyclosporin. Several recent clinical reports have, however, suggested that renal function might be

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closely related to be the pharmacokinetics of cyclosporin (Kasiske 1989; Lindholm & Kahan 1993; Schroeder et al 1993; Shibata et al 1993, 1998). Unfortunately, the true contribution of renal dysfunction to the pharmacokinetics of cyclosporin is unclear because these studies were performed on kidney transplant patients receiving other drugs.

The purpose of this work was to use glycerol-induced acute renal failure (ARF) rats to investigate the effects of renal dysfunction on the blood concentration–time curves of cyclosporin after single oral or intravenous administration, on the in-vitro uptake metabolism of cyclosporin by the intestine or liver, and on gastric emptying.

Materials and Methods

Chemicals

Cyclosporin was kindly donated by Sandoz (now Novartis Pharma). Cremophor EL, for the preparation of cyclosporin injection, and paracetamol were from Nacalai Tesque. Other chemicals were of analytical grade.

Preparation of test solutions

The test solution of cyclosporin for oral administration was prepared by suspending cyclosporin ($5\,mg\,mL^{-1}$) in 0·3% sodium carmellose. The standard formulation for injection was prepared in a 7:13 mixture of absolute ethanol and Cremophor EL at a concentration of $50\,mg\,mL^{-1}$ cyclosporin. The test solutions for intravenous administration were prepared by diluting this standard formulation with 0·9% saline to a final concentration of $2{\cdot}5\,mg\,mL^{-1}$ cyclosporin. The test solutions for in-vitro studies were also prepared by diluting this test solution with Krebs–Henseleit buffer to a final concentration of $2{\cdot}5\,\mu g\,mL^{-1}$ cyclosporin.

Animal preparation and induction of acute renal failure

Male Sprague–Dawley rats, 200–250 g, 7–8 weeks old, were obtained from Japan SLC. They were housed for at least two days in a clean room; general food was freely available. Acute renal failure (ARF) was induced by subcutaneous administration of 50% (w/v) glycerol in 0·9% saline at $10\,mL\,kg^{-1}$ in divided doses to two sites in each of the hind limbs under slight diethyl ether anaesthesia. Control rats received sham injections into the hind limbs under the same amount of diethyl ether anaesthesia. Studies on rats with ARF were performed 48 h after the injection of 50% glycerol. On the day before the dosing experiments rats were moved to the laboratory, constrained on an operating table under diethyl ether anaesthesia during the operation, and the test solutions were administered. After the administration, rats were unconstrained.

Oral administration

Rats fasted overnight (control and ARF, 250–350 g, 8–9 weeks old) received an oral dose of cyclosporin ($5\,mg\,kg^{-1}$) given over a period of approximately 10 s by use of an oral feeding tube. Blood samples were drawn without restriction from a neck vein at time 0 (before administration) and 1, 2, 4, 6, 8, 10, 12 and 24 h after administration.

Intravenous administration

Rats fasted overnight (control and ARF, 250–350 g, 8–9 weeks old) received an intravenous dose of cyclosporin ($1{\cdot}25\,mg\,kg^{-1}$) given over a period of approximately 60 s through the femoral vein. Blood samples were drawn without restriction from a neck vein at time 0 (before administration) and 0·25, 0·5, 1, 2, 4, 6, 9, and 12 h after administration.

Everted sac technique

The everted sac technique was performed as described by Barr & Reigelman (1970), with some modification. In brief, rats fasted overnight (250–350 g, 8–9 weeks old) were killed under heavy pentobarbital sodium anaesthesia and the jejunum (15-cm length from the Traiz ligament) and the ileum (15-cm length before the caecum), were removed and everted with a stainless steel probe. Before the experiment the everted sacs, reduced to about 10-cm length, were filled with Krebs–Henseleit buffer (pH 7·4, 1·5 mL) and treated with 95% O_2–5% CO_2 gas. These everted sacs were incubated with cyclosporin ($2{\cdot}5\,\mu g\,mL^{-1}$) at 37°C for 60 min in 50-mL glass test-tubes containing Krebs–Henseleit buffer (pH 6·0, 10 mL); 95% O_2–5% CO_2 was supplied during the experiments. After incubation the serosal and mucosal fluids were sampled, and intestinal tissue was homogenized with a tenfold volume of the buffer solution.

Liver-slice technique

To reflect further in-vivo conditions during cellular uptake and metabolism of cyclosporin in the liver, we used the liver-slice technique. According to the

method of Bachur & Cradock (1970), rats fasted overnight (control and ARF, 250–330 g, 8–9 weeks old) were killed under heavy pentobarbital sodium anaesthesia and their livers were removed. After washing with ice-cooled saline livers were cut into 0·3-mm slices by means of a Natsume (Tokyo, Japan) tissue slicer, and the slices were washed three times with ice-cooled Krebs–Henseleit buffer (pH 7·4). The slices were incubated with cyclosporin (2.5 μg mL^{-1}) at 37°C for 30 min in 50-mL glass test-tubes containing Krebs–Henseleit buffer (10 mL); 95% O_2–5% CO_2 gas was supplied during the experiments. After incubation the incubation fluids were sampled and the liver slices were homogenized with a tenfold volume of buffer solution.

Gastric emptying time

Rats fasted overnight (control and ARF, 250–300 g, 8–9 weeks old) were orally administered paracetamol (30 mg kg^{-1}) suspended in a paste of 80% (w/v) Elental (Ajinomoto, Tokyo); the paste was given over 10 s by means of an oral feeding tube. Blood samples were drawn without restriction from a neck vein 15, 30, 45 and 60 min after administration and the plasma was separated.

Pharmacokinetic analysis

Pharmacokinetic parameters were obtained by moment analysis by a computer program. The elimination rate constants (β) at terminal phase, and after oral and intravenous administration were determined by linear regression of at least three data points from the terminal portion of plots of blood concentration against time. Oral clearance (CL/F) and total body clearance (CL_t) were determined by dividing the oral dose by AUC_{po} and the intravenous dose by AUC_{iv}, where AUC_{po} and AUC_{iv} are the areas under the plots of whole-blood concentration against time after oral and intravenous administration, respectively; they were calculated using the linear trapezoidal rule up to the last measured blood concentration, and extrapolated to infinity. The volume of distribution at steady-state (Vd_{ss}) and the apparent volume of distribution at steady-state (Vd_{ss}/F) for cyclosporin were obtained from the equations $Vd_{ss} = Dose_{iv}MRT_{iv}/AUC_{iv}$ and $Vd_{ss}/F = Dose_{po}MRT_{po}/AUC_{po}$, where MRT_{iv} and MRT_{po} are, respectively, the mean residence times after intravenous and oral administration. To examine further the disposition of cyclosporin in the gut and in liver cells, we defined pharmacokinetic models (Figure 1) and applied data obtained from everted-sac and liver-slice experiments.

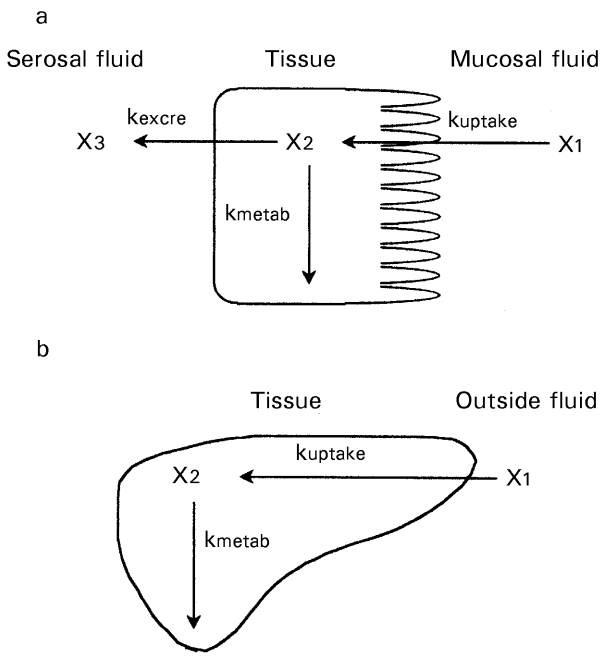

Figure 1. Pharmacokinetic model of cyclosporin in rat small intestine (a) and liver slices (b).

In Figure 1, Xn (n = 1, 2, 3) represents the amount of cyclosporin in each compartment and k_{uptake}, k_{metab}. and k_{excre} are, respectively, the apparent first-order rate constants for uptake of cyclosporin into gut or hepatic cells, metabolism of cyclosporin in the gut or hepatic cells, and permeation of cyclosporin from gut cells to serosal fluid. The values for these constants were obtained by solving simultaneous differential equations.

Assay

Albumin, blood urea nitrogen, creatinine concentration and transaminase activity (GOT, GPT) in plasma were determined colorimetrically by use of commercially available assay kits. Cyclosporin concentrations in whole blood, serosal fluid, mucosal fluid, incubation fluid, and tissue homogenates, and paracetamol concentration in plasma, were measured by fluorescence polarization immunoassay with a monoclonal antibody using the Abbot TDx assay system. Coefficients of variation for repeated analysis of a known concentration (0·5 mg mL^{-1}) cyclosporin in gut and liver homogenates were below 4% and 5%, respectively.

Statistical analysis

Results were expressed as mean ± standard error of the mean (s.e.m.); statistical significance was assessed by use of Student's *t*-test.

Results

The values of creatinine and blood urea nitrogen in rats with ARF induced by glycerol were, respectively, 1·3- to 2-fold and 1·5 to 3-fold those in control rats (n = 5). Although transaminase activity, GPT and GOT were slightly higher in ARF rats the difference was not significant (n = 5). Haematocrit values and albumin were slightly lower in ARF rats, but again the differences were not significant (n = 5).

The mean (± s.e.m.) whole-blood concentration–time profiles obtained in this study after oral and intravenous administration of cyclosporin to ARF and control rats are shown in Figure 2.

Mean creatinine levels for ARF rats in the oral study were significantly higher than those for control rats ($1{\cdot}01 \pm 0{\cdot}10\,mg\,dL^{-1}$ compared with $0{\cdot}74 \pm 0{\cdot}03\,mg\,dL^{-1}$, $P < 0{\cdot}05$), and whole-blood concentrations of cyclosporin after oral administration were significantly lower than those for control rats (Figure 2a). Mean creatinine levels in ARF rats in intravenous studies were significantly higher than those for control rats ($1{\cdot}03 \pm 0{\cdot}06\,mg\,dL^{-1}$ compared with $0{\cdot}74 \pm 0{\cdot}05\,mg\,dL^{-1}$, $P < 0{\cdot}01$). Whole-blood concentrations of cyclosporin after intravenous administration were significantly higher than those for control rats (Figure 2b).

Table 1 lists the pharmacokinetic parameters calculated by moment analysis from the data shown in Figure 2. The AUC_{po} and the elimination rate constant of cyclosporin from the oral study (β_{po}) were significantly lower ($P < 0{\cdot}01$, $P < 0{\cdot}05$, respectively) for ARF rats, whereas CL/F and Vd_{ss}/F of cyclosporin were significantly higher ($P < 0{\cdot}05$). In the intravenous study, AUC_{iv}, CL_t, and Vd_{ss} were significantly increased ($P < 0{\cdot}05$), whereas the elimination rate constant for cyclosporin after intravenous administration (β_{iv}) was significantly reduced ($P < 0{\cdot}05$). Figure 3 shows the relationship between the AUC_{po} and creatinine levels, using all the data obtained from ARF and control rats. There was a significant negative correlation between the AUC_{po} and creatinine levels ($P < 0{\cdot}01$).

Figure 4 shows the mucosal-to-serosal transfer of cyclosporin through everted sacs of small intestine isolated from control and ARF rats. In ARF rats, the amounts of cyclosporin in both intestinal tissues (jejunum and ileum) 60 min after incubation were significantly ($P < 0{\cdot}05$) higher than those for the control rats. In addition, in both groups of rats the amount of cyclosporin in jejunum 60 min after incubation was lower than that in ileum 60 min after incubation. Although recovery of cyclosporin from the jejunum of both groups of rats was relatively small ($P < 0{\cdot}05$), recovery of cyclosporin from the jejunum and ileum of ARF rats was greater than from control rats.

Figure 5 shows the hepatic uptake of cyclosporin in liver slices from control and ARF rats. In ARF rats the amount of cyclosporin in liver slices and its recovery 60 min after incubation were significantly lower than for control rats ($P < 0{\cdot}01$).

The apparent first-order rate constants from the in-vitro uptake experiments are listed in Table 2.

The value of k_{uptake} for the jejunum and ileum in the presence of ARF were 14% less than for control

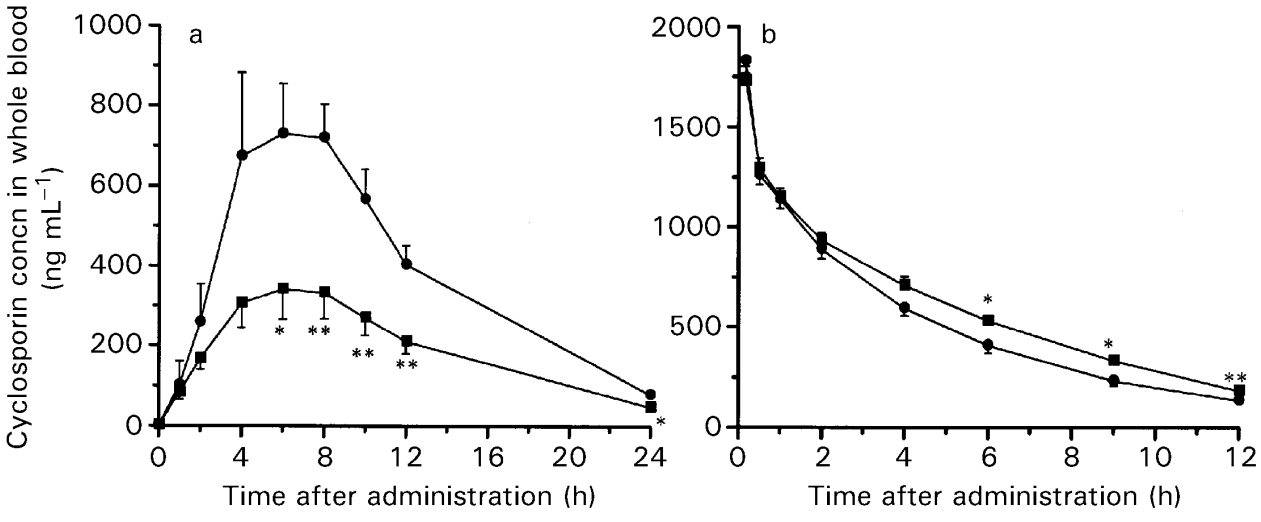

Figure 2. Whole-blood concentrations of cyclosporin after (a) oral administration of 5 mg kg^{-1} and (b) intravenous administration of 1·25 mg kg^{-1}: ●, control rats; ■, acute renal failure rats. Each symbol with bar represents the mean ± the standard error of the mean of results from five or six experiments. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$ compared with control.

Table 1. Pharmacokinetic parameters of cyclosporin after oral and intravenous administration to control rats and to rats with acute renal failure.

Parameter	Control rats	Rats with acute renal failure
Oral administration		
Body weight (kg)	0·255 ± 0·011	0·254 ± 0·008
Creatinine (mg dL^{-1})	0·742 ± 0·028	1·009 ± 0·103*
Elimination rate constant (h^{-1})	0·143 ± 0·005	0·119 ± 0·007*
Area under the blood concentration–time curve (mg h L^{-1})	9·684 ± 1·100	4·976 ± 0·847**
Oral clearance (L h^{-1} kg^{-1})	0·544 ± 0·062	1·172 ± 0·207*
Apparent volume of distribution at steady-state (L kg^{-1})	5·655 ± 0·794	13·060 ± 2·316*
Intravenous administration		
Body weight (kg)	0·291 ± 0·014	0·297 ± 0·018
Creatinine (mg dL^{-1})	0·741 ± 0·045	1·025 ± 0·062**
Elimination rate constant (h^{-1})	0·188 ± 0·004	0·169 ± 0·005*
Area under the blood concentration–time curve (mg h L^{-1})	6·972 ± 0·406	8·378 ± 0·404*
Total body clearance (L h^{-1} kg^{-1})	0·183 ± 0·010	0·151 ± 0·008*
Apparent volume of distribution at steady-state (L kg^{-1})	0·923 ± 0·041	0·904 ± 0·045*
Relative bioavailability[a]	0·336	0·118

[a]The relative bioavailability was calculated from the mean values of the areas under the blood concentration–time curves after oral and intravenous injection as defined by $AUC_{po}D_{iv}/AUC_{iv}D_{po}$, where D_{iv} and D_{po} are the kilogram doses administered intravenously and orally, respectively. Values are the means ± the standard errors of the means of results from five to seven determinations. $^{**}P < 0.01$, $^{*}P < 0.05$ compared with control.

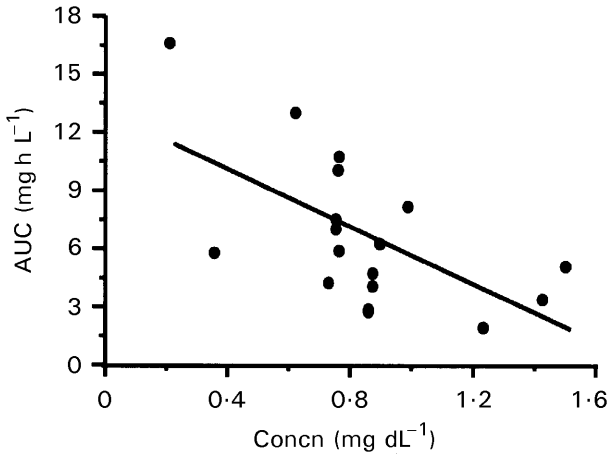

Figure 3. Correlation between serum creatinine and area the under the blood cyclosporin concentration–time curve after oral administration to rats (AUC_{po}). AUC_{po} was calculated by the trapezoidal approximation from the plot of cyclosporin concentration against time after oral administration of 5 mg kg^{-1} cyclosporin. All data obtained in the oral experiment were used for the regression analysis ($P < 0.05$, n = 17).

rats and k_{metab} for the jejunum and ileum were 23 and 58%, respectively, lower than the control values. k_{uptake} and k_{metab} for liver slices from rats with ARF were 12 and 48%, respectively, higher than for control rats.

Gastric emptying time was measured by oral administration of paracetamol, for which there is a positive correlation between concentration in plasma and gastric-emptying rate. The mean plasma concentrations of paracetamol in control rats 15, 30, 45 and 60 min after oral administration were 5·8, 6·0, 6·3, and 5·7 μg mL^{-1}, respectively; in ARF rats the values were significantly lower—4·9, 4·5, 4·1, and 4·0 μg mL^{-1}, respectively.

Discussion

Although it is believed that renal dysfunction has no effect on the pharmacokinetics of cyclosporin (Ptachcinski et al 1986; Shaw et al 1987), recent clinical reports using multivariate analysis clearly suggest that there is some correlation between renal function after renal transplantation and the pharmacokinetics of cyclosporin, and with several factors such as creatinine excretion, age, sex, body weight, obesity, diabetes, cumulative average daily corticosteroid dose, creatinine clearance, haematocrit, race and disease state (Kasiske 1989; Lindholm & Kahan 1993; Shibata et al 1993, 1998). The true contribution of renal dysfunction is unclear because the subjects of these studies were renal transplant patients with potential renal dysfunction who had received many other drugs. The biopharmaceutical research in this report has clarified a relationship between renal dysfunction and the pharmacokinetics of cyclosporin.

The relative bioavailability of cyclosporin in ARF and control rats was 0·118 and 0·336,

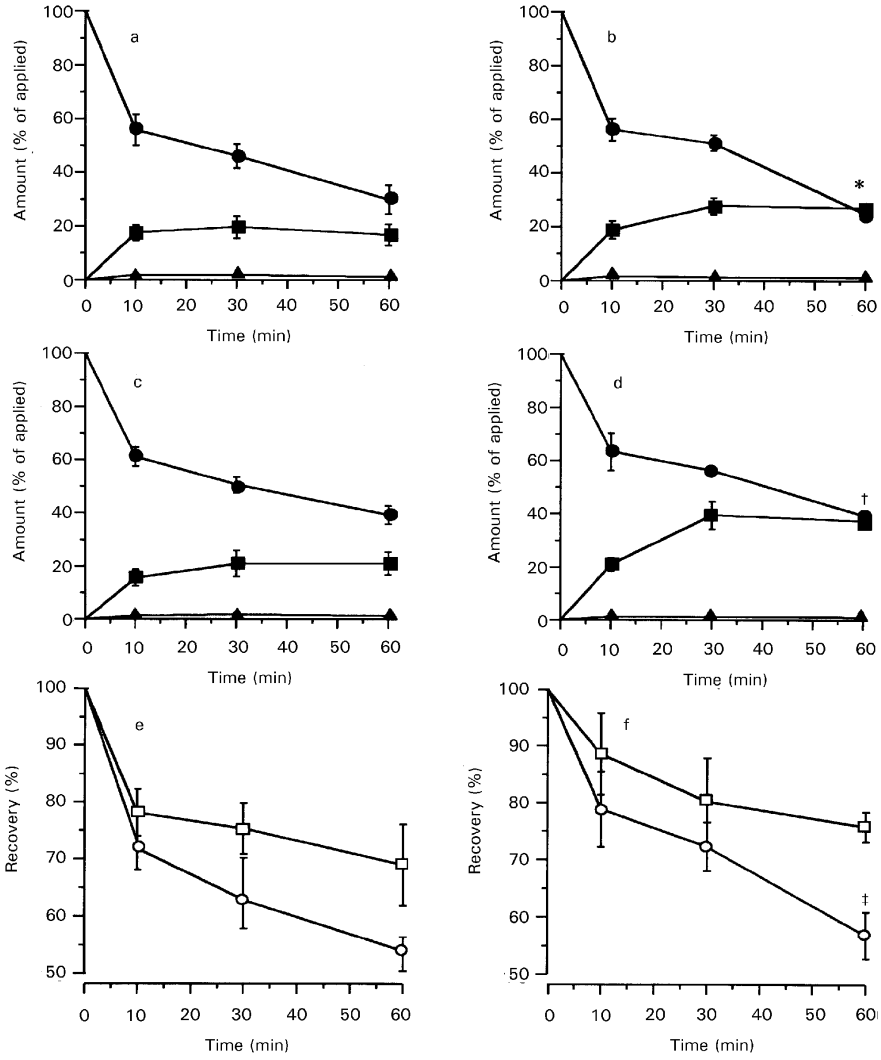

Figure 4. Mucosal-to-serosal transfer of cyclosporin through everted sacs of small intestine isolated from control rats or rats with acute renal failure (ARF). a. Jejunum from control rats. b. Jejunum from ARF rats. c. Ileum from control rats. d. Ileum from ARF rats. Each symbol with bar represents the mean ± the standard error of the mean of results from at least four experiments: ●, mucosal fluid, ■ tissue, ▲ serosal fluid. e. Total recovery of cyclosporin in everted sacs from control. f. Total recovery of cyclosporin in everted sacs from ARF: ○ jejunum, □ ileum. *$P < 0{\cdot}05$ compared with control; †$P < 0{\cdot}05$ compared with ARF; ‡$P < 0{\cdot}05$ compared with ileum.

respectively—the relative bioavailability of cyclosporin was 65% lower in ARF rats than in control rats. In addition, a marked decrease in AUC_{po} was found, creatinine levels were 30–40% higher in control rats, and there was a negative correlation between AUC_{po} and creatinine values. These findings suggests that progress of renal dysfunction leads to a decrease in cyclosporin concentration in the blood. Although it is difficult to distinguish between nephrotoxicity and rejection episodes for renal transplantation in clinical practice, both lead to renal dysfunction, and the bioavailability of cyclosporin probably decreases.

In this in-vitro study of cyclosporin uptake by intestinal or hepatic tissues, we did not directly measure metabolites of cyclosporin. However, different recoveries of cyclosporin indicate variable metabolism of cyclosporin in the tissues. In the small intestine the metabolism of cyclosporin was reduced in the presence of ARF whereas in the liver it was increased. It is believed that cyclosporin is predominately metabolized by CYP3A in the small intestine and in the liver (Watkins et al 1990). Brunner et al (1996) reported that the activities of CYP3A2 and CYP2C11 were dramatically reduced in liver microsomes from cyclosporin-induced ARF rats. However, our results from the ARF model are not comparable with their results from a chronic renal-failure model induced by cyclosporin—the models are pathologically different. Enhancement of cyclosporin metabolism in liver slices in our study might suggest that the activity of other

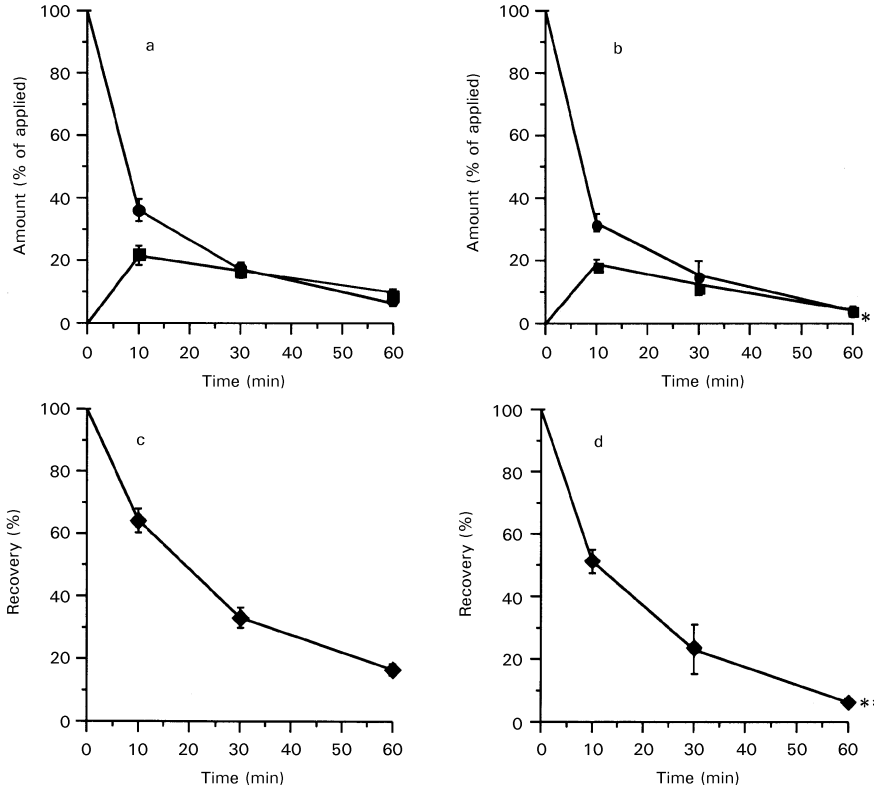

Figure 5. Hepatic uptake and metabolism of cyclosporin by liver slices from (a) control rats and (b) rats with acute renal failure (ARF), and total recovery of cyclosporin in liver slices from (c) control rats and (d) ARF rats: ● outside fluid, ■ tissue, ◆ recovery. Each symbol with bar represents the mean ± the standard error of the mean of results from at least five experiments. $*P < 0{\cdot}01$ compared with control.

metabolic pathways for cyclosporin, besides CYP3A, such as glucuronidated phase II metabolism and hydrolysis are enhanced in the presence of ARF. Nevertheless, further detailed investigations are needed. Generally, gastric-emptying is one factor influencing the pharmacokinetics of cyclosporin. Our results clearly demonstrated that gastric-emptying is retarded by ARF. Reductions in gastric emptying enhances the retention of cyclosporin in the stomach, and leads to a time-lag in the concentration of cyclosporin in whole blood after oral administration of cyclosporin, because absorption of cyclosporin from the intestinal tract is delayed. We have previously shown this time-lag after oral administration of cyclosporin in renal transplant patients receiving haemodialysis because of undesirable recovery of transplanted renal function within 30 days post-transplantation (Shibata et al 1995).

Our results showing that CL/F and Vd_{ss}/F in ARF rats were significantly increased whereas CL_t and Vd_{ss} were significantly reduced suggest that reduced bioavailability (F) strongly contributes to the pharmacokinetics of cyclosporin after oral administration in the presence of ARF. Accordingly, we examined F by dividing it into three availabilities, namely $F = F_a \times F_g \times F_h$, where F_a, F_g and F_h represent, respectively, the fraction of cyclosporin absorbed, the fraction of cyclosporin unmetabolized in gut cells, and the fraction of

Table 2. Pharmacokinetic parameters of cyclosporin in isolated intestine and liver from control rats and rats with acute renal failure (ARF).

Apparent first-order rate constant ($\times 10^{-2}$, min^{-1})	Jejunum[a]		Ileum[a]		Liver[b]	
	Control	ARF	Control	ARF	Control	ARF
Uptake	2·897	2·506	2·039	1·755	5·985	6·724
Metabolism	4·413	3·380	2·838	1·195	9·510	14·058
Excretion	1·687	1·960	1·922	2·010		

Experiments were performed by [a]the everted sac method and [b]the liver-slice method.

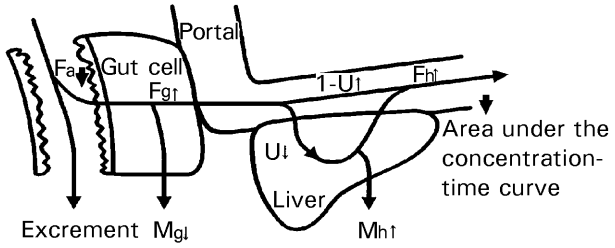

Figure 6. Conceptual illustration of the availability of cyclosporin after oral administration. F_a, F_g, F_h, U and M_g represent, respectively, the fraction absorbed from intestinal tract, the fraction unmetabolized in gut cells, the fraction unmetabolized in the liver, the hepatic uptake, metabolism in gut cells, and metabolism in the liver.

cyclosporin unmetabolized in liver. A conceptual illustration of the availability of cyclosporin after oral administration is shown in Figure 6.

In ARF depression of cyclosporin metabolism in gut cells causes an increase in F_g. Reduction of the binding of cyclosporin to erythrocytes and plasma proteins causes inhibition of hepatic uptake of cyclosporin (Lemaire et al 1988). Although in this study we could not find significant differences between the amounts of blood proteins as a result of ARF, the values of haematocrit and albumin tended to decrease. Therefore, hepatic uptake of cyclosporin might be inhibited by decreases in protein-bound cyclosporin as a result of ARF, even though liver metabolism of cyclosporin continues, resulting in an increase in F_h. Hence, F_g and F_h are increased. In addition, that AUC_{po} was significantly reduced in ARF rats whereas the AUC_{iv} was significantly increased suggests a rate-determining process is located at the site of absorption in the small intestine. We therefore concluded that the reduction of F_a strongly contributes to the decrease in AUC after oral administration of cyclosporin in ARF rats.

Our results strongly suggest that renal dysfunction affects the pharmacokinetics of cyclosporin. There are many changes in the disposition of cyclosporin after oral administration to ARF rats. In this study, however, we could not determine the factors that retarded F_a. Cholestatis, uremic toxin, intestinal oedema as a result of ARF, and p-glycoprotein which is the MDR1 gene product (Gottesman & Pastan 1993; Watkins 1997), might affect intestinal absorption of cyclosporin. Experiments are currently in progress in our laboratory to determine the role of these factors on the absorption of cyclosporin from the intestinal tract in ARF rats.

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