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The increased intestinal absorption rate is responsible for the reduced hepatic first-pass extraction of propranolol in rats with cisplatin-induced renal dysfunction

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Abstract

The mechanisms responsible for the increased bioavailability of propranolol in renal dysfunction were investigated in rats. Experimental acute renal failure (ARF) was induced by intraperitoneal injection of cisplatin (5 mg kg^{-1}). ARF induced a significant increase in blood propranolol concentration after intra-intestinal administration. The extent of bioavailability (F) of propranolol at an intestinal dose of 15 mg kg^{-1} was 16.4% and 26.9% in control and ARF rats, respectively, and the F value at a 37.5 mg kg^{-1} dose was 54.7% and 81.4% in control and ARF rats, respectively. In contrast, the blood propranolol concentration following intraportal infusion was not increased significantly in ARF rats. The hepatic first-pass extraction (E_h) was dose-dependent and saturable: E_h of propranolol in control rats was 58.0% and 18.3% at 8 and 20 mg kg^{-1}, respectively, and E_h in ARF rats was 50.8% and 19.9% at 8 and 20 mg kg^{-1}, respectively. The initial absorption rate of propranolol from the intestine in ARF rats was significantly greater compared with control rats. These results indicated that the increased bioavailability of propranolol in rats with cisplatin-induced renal dysfunction was mainly a result of the increased absorption rate in the intestine followed by the partial saturation of hepatic first-pass metabolism.

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Introduction

The intestinal absorption of orally administered propranolol is essentially complete, and the metabolism of propranolol does not occur in the gut (Shand & Rangno 1972; Laganiere & Shen 1987). After oral administration of propranolol the liver is the principal site of extensive pre-systemic and systemic metabolism, and less than 1% of the intact drug is found in the urine (Shand & Rangno 1972; Walle et al 1978). Consequently, renal failure is not expected to alter to any large extent the kinetic behaviour of the intact drug. However, Bianchetti et al (1976) showed that the area under the concentration–time curve of orally administered propranolol in renal failure patients not on haemodialysis was 7- to 8-fold higher than in healthy volunteers.

The pharmacokinetics of propranolol has been investigated extensively in rats with uranyl nitrate-induced acute renal failure (ARF). The plasma disappearance of propranolol after intravenous administration at a dose of 12.5 mg kg^{-1} does not differ significantly between control and ARF rats (Katayama et al 1984). In contrast, the plasma drug concentration after oral administration of 12.5 mg kg^{-1} is increased significantly in ARF rats as compared with control rats (Katayama et al 1984). The mechanisms of the increased bioavailability of propranolol have been investigated (Terao & Shen 1983, 1984, 1985; Hori et al 1985). Despite the decreased pre-systemic clearance of propranolol in rats with ARF, there are no alterations in the hepatic blood flow, plasma protein binding of the drug, or intrinsic metabolic activity in the liver (Katayama et al 1984; Hori et al 1985). Thus, the decreased pre-systemic clearance was concluded to be due to the decreased hepatic uptake in uranyl nitrate-induced ARF

rats (Hori et al 1985). In contrast, Terao & Shen (1985) reported that the intrinsic metabolic activity in the liver was not altered in ARF rats, and that the presence of an inhibitory factor in uraemic blood decreased the hepatic extraction of propranolol. On the other hand, it was recently revealed that propranolol, as well as metoprolol, is mainly metabolized by cytochrome P450 (CYP) 2D6 in the human liver (Masubuchi et al 1994; Huang et al 1999). Interestingly, although metoprolol undergoes hepatic first-pass effects, the bioavailability of metoprolol is not altered in patients with renal failure (Jordo et al 1980).

Previously, we examined the pharmacokinetics of ajmaline, a class I antiarrhythmic drug, in rats with uranyl nitrate-induced ARF (Hashimoto et al 2001). This drug was also mainly metabolized by the CYP2D subfamily and underwent extensive pre-systemic and systemic clearance after oral administration, and the urinary recovery of unchanged ajmaline was less than 4% in man (Zekorn et al 1985; Yamada et al 1986; Padrini et al 1993). The bioavailability of ajmaline was increased significantly in ARF rats, whereas the blood ajmaline concentration following intraportal infusion was not increased in ARF rats. The hepatic first-pass metabolism of ajmaline was infusion rate-dependent and saturable, and the initial absorption rate from the small intestine was significantly greater in ARF rats compared with control rats. These results indicated that the increased bioavailability of ajmaline in ARF rats was mainly a result of partially saturated extraction in the liver, which was caused by an increased absorption rate in the intestine and non-linear extraction in the liver (Hashimoto et al 2001).

Terao & Shen (1983) suggested that differences in absorption rate as a cause of increased bioavailability of propranolol was unlikely, because the time to reach peak serum concentration following oral administration did not differ significantly between normal and uranyl nitrate-induced ARF rats. Katayama et al (1984) investigated the effects of uranyl nitrate-induced ARF on the intestinal absorption process with an in-situ loop method and everted sac technique. ARF rats showed a tendency of more rapid absorption of propranolol than control, but the difference was not statistically significant (Katayama et al 1984). In contrast, Kimura et al (1988) reported that the intestinal absorption rate of drugs (sulfanilic acid, procainamide ethobromide, cefazoline, sulfafurazole, quinine, salicylic acid, imipramine, cefadroxil, ciclacillin etc.) was significantly increased in rats with glycerol-induced ARF. Moreover, we reported recently that the accelerated absorption rate in the intestine might be one of the mechanisms of increased bioavailability of tacrolimus in rats with cisplatin-induced ARF (Okabe et al 2002).

This study was designed to evaluate the bioavailability of propranolol in rats with cisplatin-induced ARF. We have examined the mechanisms responsible for the altered pre-systemic clearance. That is, the hepatic extraction ratio of propranolol was evaluated following intraportal administration. We have estimated the initial absorption rate using the Loo-Riegelman method (Chau et al 1977) and the intestinal barrier function in closed loops of the small intestine in-situ (Okabe et al 2002).

Materials and Methods

Materials

Propranolol was obtained from Nacalai Tesque (Kyoto, Japan). Cisplatin (Platosin® injection, 0.5 mg mL^{-1}) was purchased from Kyowa Hakko (Tokyo, Japan). Pentobarbital sodium salt was obtained from Tokyo Kasei Kogyo Co., Ltd (Tokyo, Japan). All other chemicals were of the highest grade available.

Animals

Male Wistar rats (240–310 g) were used. Before the experiments, the rats were housed in a temperature and humidity-controlled room with free access to water and standard rat chow. ARF was induced by intraperitoneal administration of 5 mg kg^{-1} cisplatin (Platosin® injection) (Okabe et al 2000). In some experiments, ARF was induced by injection of glycerol dissolved in saline (50% v/v, 10 mL kg^{-1}) into the leg muscle after a 24-h period of water deprivation (Huang et al 2000). Saline-treated rats served as controls. Animals were used for experiments 72 h after the treatment. All animal experiments were performed in accordance with The Guidelines for Experiments of Toyama Medical and Pharmaceutical University.

Effect of cisplatin-induced ARF on the pharmacokinetics of propranolol

Cisplatin induced-ARF and control rats were anaesthetized with 30–50 mg kg^{-1} sodium pentobarbital. Body temperature was maintained with appropriate heating lamps. The femoral artery was cannulated with a polyethylene tube (SP-31, Natsume Seisakusyo, Tokyo, Japan) for blood sampling. The femoral vein was cannulated with a polyethylene tube (SP-31) for intravenous infusion of propranolol (10 mg kg^{-1}). Propranolol solution (1 mg mL^{-1}) was infused via the catheter with a constant rate infusion pump for 30 min. Arterial blood samples for measurement of propranolol concentration were obtained 8, 15, 30, 33, 60, 90, 120 and 150 min after initiation of 30-min intravenous infusion. For the intraportal administration study (8 and 20 mg kg^{-1}), a catheter with a 26 G needle was carefully inserted into the portal vein and held in place with surgical glue. Arterial blood samples were obtained at 8, 15, 30, 33, 60, 90, 120 and 150 min after the start of 30-min intraportal infusion of drug solutions (333 μL min^{-1} kg^{-1}). For the intraintestinal administration study (15 and 37.5 mg kg^{-1}), a 3-cm middle incision was made in the abdomen, and the upper end of duodenum was ligated twice with silk sutures. The drug solution (1.875 mL kg^{-1}) was injected into the lumen using the syringe with a 26 G needle. Blood samples were withdrawn at 3, 8, 15, 30, 60, 90, 120 and 150 min.

Effect of cisplatin- and glycerol-induced ARF on the intestinal absorption rate of propranolol

Under pentobarbital anaesthesia, the absorption rate of propranolol ($20\,mg\,kg^{-1}$) in cisplatin- and glycerol-induced ARF was determined by the in-situ closed loop method (Okabe et al 2002). Propranolol solution ($2\,mL\,kg^{-1}$) was injected into the closed loop (15 cm) of the upper region of the small intestine. At the end of the specified period, an arterial blood sample was obtained and the loop was dissected. The contents in the lumen were collected with $30\,mL\,kg^{-1}$ 0.01 M HCl. The intestinal tissue was homogenized with 9 volumes isotonic saline for the assay of propranolol. The net absorption of propranolol was calculated by subtracting the amount remaining in the tissue and in the lumen from the dose administered.

Analytical method

Propranolol concentration was determined with an HPLC method. Briefly, the assay involved extraction of 0.1 mL sample, 0.1 mL distilled water and 1.0 mL glycine buffer (pH 10.0, 0.1 M, saturated with sodium chloride) with 5 mL diethylether. Propranolol was re-extracted from the organic phase with 0.2 mL 0.01 M HCl. A 50-μL sample of the water phase was subjected to an HPLC system. This system was composed of a pump (LC-10AD vp, Shimadzu, Kyoto, Japan), an analytical column (Cosmosil Packed column 5 μm, 150×4.6 mm i.d., Nacalai Tesque, Kyoto, Japan), and a fluorescence spectromonitor (RF-10Axl, Shimadzu, Kyoto, Japan) operated at an excitation wavelength of 296 nm and an emission wavelength of 353 nm. The mobile phase consisted of methanol and 10 mM phosphate buffer (pH 2.5) (40:60, v/v), the flow rate was $1\,mL\,min^{-1}$ and the column temperature was 45 °C. The sensitivity of the assay of propranolol in this HPLC condition was $10\,ng\,mL^{-1}$ ($0.01\,\mu g\,mL^{-1}$). The coefficient of variation of the assay was 2.2% and 0.67% at the blood concentration of 0.1 and $0.8\,\mu g\,mL^{-1}$, respectively.

Pharmacokinetic analysis

The systemic clearance of propranolol depends largely on hepatic blood flow rate because of the extremely high hepatic intrinsic clearance. When propranolol is administered intravenously in rats the pharmacokinetics is almost linear or dose-independent at the dose range of 2.5–12.5 $mg\,kg^{-1}$ (Suzuki et al 1981; Yasuhara et al 1985). The pharmacokinetic parameters of propranolol following intravenous infusion were estimated using the software package NONMEM Version V (Beal & Sheiner 1992). The two-compartment model was parameterized in terms of central volume of distribution (Vd_1), systemic clearance (CL), volume of distribution at steady state (Vd_{ss}), and intercompartmental clearance (Q).

The area under the blood concentration–time curve (AUC) after intra-intestinal injection and intraportal infusion were calculated using the linear trapezoidal rule and extrapolated to infinity by adding the ratio of the last measurable propranolol concentration to the mean terminal disposition rate constant. The apparent clearance values (CL/F) expressed by the CL and bioavailability (F) following the intra-intestinal and intraportal administration were calculated from Dose/AUC. The mean F values following intra-intestinal injection were calculated from the CL and CL/F values. The mean hepatic extraction ratio (E_h) following intraportal infusion was calculated by the following equation:

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

Moreover, intestinal absorption rate after intra-intestinal administration was calculated using the Loo-Riegelman method (Loo & Riegelman 1968; Chau et al 1977), assuming that the systemic clearance of propranolol is constant at the observed blood concentration range (Suzuki et al 1981; Yasuhara et al 1985). Briefly, the amount absorbed until a time assay t_n ($A(t_n)$) was calculated by the following equation:

$$A(t_n) = Vd_1C_1(t_n) + k_{el}\int_0^{tn} Vd_1C_1(t)dt + k_{12}/k_{21} \bullet Vd_1C_2(t_n) \quad (2)$$

where:

$$C_2(t_n) = \exp(-k_{21}\Delta t_{n-1}) \bullet C_2(t_{n-1}) + (1 - \exp(-k_{21}\Delta t_{n-1})) \bullet C_1(t_{n-1}) + (\Delta C_1/\Delta t_{n-1})/k_{21} \bullet (\exp(-k_{21}\Delta t_{n-1}) + k_{21}\Delta t_{n-1} - 1)$$

$$\Delta t_{n-1} = t_n - t_{n-1},\ \Delta C_1 = C_1(t_n) - C_1(t_{n-1})$$

C_1 represents the propranolol concentration in the central compartment. k_{el}, k_{12} and k_{21} represent the mean elimination rate constant, transfer rate constant from the central to the peripheral compartment and transfer rate constant from the peripheral to the central compartment, respectively (Chau et al 1977). Finally, the fraction of the amount absorbed until a time assay t_n ($A(t_n)/A(t_\infty)$) was calculated by the following equation:

$$A(t_n)/A(t_\infty) = A(t_n)/k_{el}\int_0^{t\infty} Vd_1C_1(t)dt \quad (3)$$

Statistical analysis

Values are expressed as means ± s.d. for n animals. Statistical difference between mean values was calculated using non-paired *t*-test provided that the variances were similar. If this was not the case, the Mann-Whitney U-test was applied. *P* values less than 0.05 (two-tailed) were considered to be statistically different.

Results

The mean blood concentration–time courses of propranolol following 30-min intravenous infusion in cisplatin-induced ARF and control rats are shown in Figure 1. After infusion was finished, the blood propranolol concentration declined rapidly in a biexponential manner.

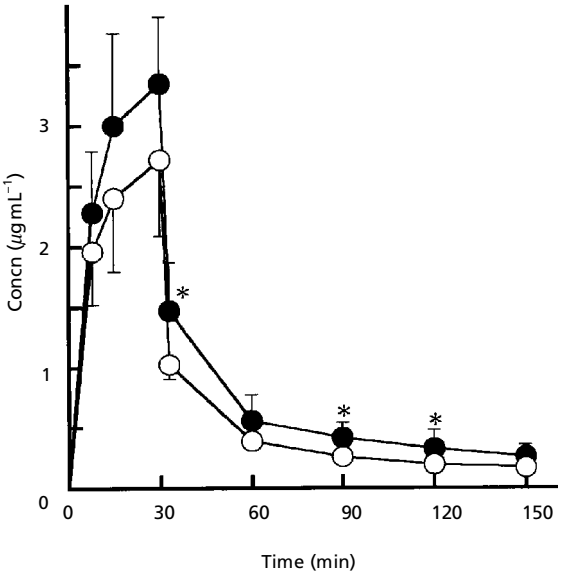

Figure 1 Mean blood concentration–time course of propranolol following intravenous infusion (10 mg kg^{-1}) to rats with cisplatin-induced ARF (•) and control rats (○). Bars represent ±s.d. of seven rats. *$P < 0.05$ compared with the corresponding value of the control rats.

The blood propranolol concentration in ARF rats was similar to that in control rats (Figure 1). Table 1 lists the pharmacokinetic parameters calculated with NONMEM software. The CL value was decreased in ARF rats as compared with control rats, whereas Vd_1, Q and Vd_{ss} in ARF were similar to those in control rats.

Figure 2 shows the time courses of mean blood concentration of propranolol after the intra-intestinal injection in cisplatin-induced ARF and control rats. After intra-intestinal injection of propranolol, the mean blood concentrations in ARF rats were significantly higher compared with control rats, though the terminal elimination half-lives were similar in both groups (Figure 2). The CL/F and F values of propranolol after intra-intestinal administration are listed in Table 2. The CL/F values in ARF and control rats were dose-dependent, and the F values in rats with cisplatin-induced ARF were increased markedly as compared with control rats (Table 2).

Table 1 Pharmacokinetic parameters of propranolol in rats with or without cisplatin-induced renal dysfunction.

Parameter	Control	ARF
CL (mL min^{-1} kg^{-1})	82.4 ± 12.5	62.3 ± 14.7*
Vd_1 (L kg^{-1})	0.34 ± 0.04	0.34 ± 0.02
Q (mL min^{-1} kg^{-1})	71.8 ± 8.1	67.9 ± 6.6
Vd_{ss} (L kg^{-1})	4.29 ± 0.41	3.90 ± 0.27

Values are expressed as means ± s.d. of seven rats. *$P < 0.05$ compared with control.

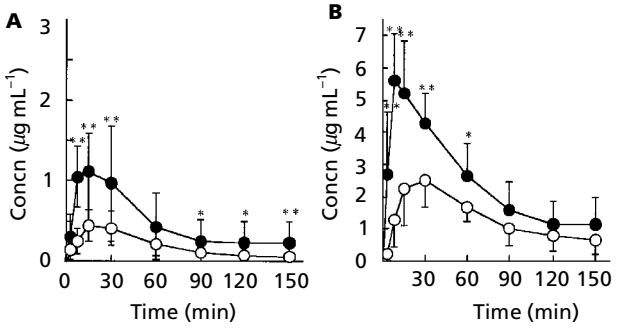

Figure 2 Mean blood concentration–time course of propranolol after intra-intestinal administration (A, 15 mg kg^{-1}; B, 37.5 mg kg^{-1}) to rats with cisplatin-induced ARF (•) and control rats (○). Bars represent ± s.d. of seven rats. *$P < 0.05$ and **$P < 0.01$ compared with the corresponding value of the control rats.

To evaluate the effect of ARF on the hepatic extraction (E_h) of propranolol, the AUC and CL/F values following intraportal infusion were calculated. Figure 3 shows the blood propranolol concentration after the initiation of drug infusion into the portal vein in control and ARF rats. The blood concentration of propranolol in ARF rats was similar to that in the control rats (Figure 3). The CL/F and E_h values of propranolol following intraportal infusion are listed in Table 2. The E_h values in ARF rats were not significantly different from those in control rats, indicating that ARF had little effect on the hepatic metabolism of propranolol. In addition, the E_h of propranolol was shown to be highly dose-dependent over the concentration range measured (Table 2).

Since the hepatic extraction of propranolol following intraportal administration was not affected by renal failure (Figure 3), it was supposed that the change in intestinal absorption rate was thought to be responsible for the increased bioavailability after intra-intestinal administration in ARF rats. We investigated the absorption rate of propranolol from the intestinal lumen to the systemic circulation using the Loo-Riegelman method (Figure 4). The increase in the fraction of amount absorbed ($A(t_n)/A(t_\infty)$) following intra-intestinal injections in ARF rats was not statistically significant at 15 mg kg^{-1} (Figure 4A), probably because of the high degree of deviation. The absorption rate of propranolol after the intra-intestinal administration of 37.5 mg kg^{-1} was significantly increased in rats with cisplatin-induced ARF as compared with control rats (Figure 4B).

We evaluated the intestinal absorption rate of propranolol with the in-situ closed loop method by estimating the net absorption from the drug remaining in the intestinal lumen and tissue. Table 3 shows the percentage remaining in the lumen of intestinal closed loop and in the intestinal tissue, the net absorption, and the blood propranolol concentration at 8 and 30 min after administration in rats with or without cisplatin-induced ARF. The net absorption of propranolol from the intestinal loop at 8 min after administration was approximately 68% higher in rats with ARF as compared with control rats. The

Table 2 Bioavailability and hepatic extraction of propranolol in rats with or without cisplatin-induced ARF.

	Control	ARF
Intra-intestinal 15 mg kg^{-1}		
CL/F (mL min^{-1} kg^{-1})	502.3 ± 242.7	231.7 ± 155.4**
F (%)	16.4	26.9
Intra-intestinal 37.5 mg kg^{-1}		
CL/F (mL min^{-1} kg^{-1})	150.7 ± 65.0	76.5 ± 31.2*
F (%)	54.7	81.4
Intraportal 8 mg kg^{-1}		
CL/F (mL min^{-1} kg^{-1})	196.0 ± 67.6	126.5 ± 64.0*
E_h (%)	58.0	50.8
Intraportal 20 mg kg^{-1}		
CL/F (mL min^{-1} kg^{-1})	100.9 ± 26.2	77.8 ± 21.4
E_h (%)	18.3	19.9

Values are expressed as means ± s.d. of seven to eight rats. *$P < 0.05$ and **$P < 0.01$ compared with control.

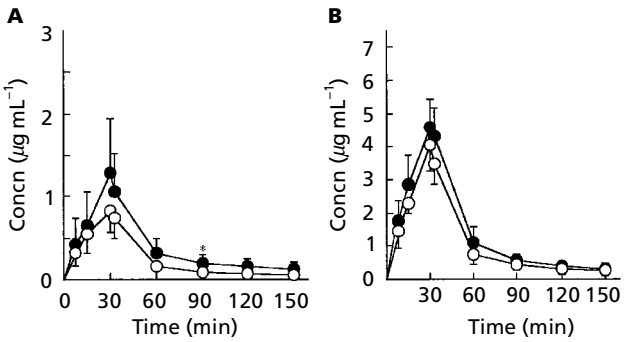

Figure 3 Mean blood concentration–time course of propranolol following intraportal infusion (A, 8 mg kg^{-1}; B, 20 mg kg^{-1}) to rats with cisplatin-induced ARF (●) and control rats (○). Bars represent ± s.d. of seven rats. *$P < 0.05$ compared with the corresponding value of the control rats.

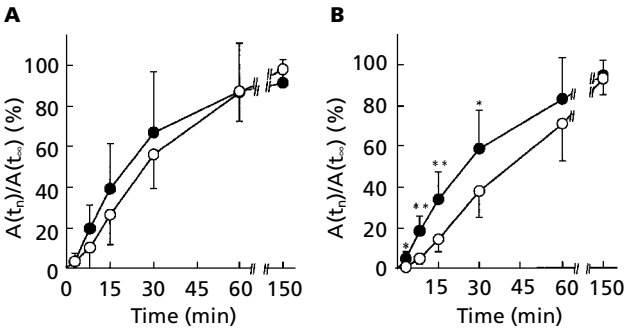

Figure 4 Intestinal absorption rate after intra-intestinal administration (A, 15 mg kg^{-1}; B, 37.5 mg kg^{-1}) in rats with (●) or without (○) cisplatin-induced ARF calculated by the Loo-Riegelman method. Bars represent ± s.d. of seven rats. *$P < 0.05$ and **$P < 0.01$ compared with the corresponding value of the control rats.

blood concentration at that time was approximately 5.2-fold in ARF rats as compared with controls. Again, these results indicated the non-linear hepatic extraction of propranolol (Table 3). Furthermore, the increase in the initial absorption rate of propranolol was observed in rats with glycerol-induced ARF (Table 4). The net absorption of propranolol at 8 min after administration in glycerol-induced ARF rats was 40% higher than in control rats (Table 4). The blood concentration was approximately 5.0-fold in glycerol-induced ARF rats as compared with the control rats (Table 4). These results indicated that the increased bioavailability of propranolol in renal dysfunction was mainly a result of the increased absorption rate in the intestine followed by the partial saturation of hepatic first-pass metabolism.

Discussion

We have investigated the pharmacokinetics of propranolol in a cisplatin-induced ARF rat model. The bioavailability of propranolol after intra-intestinal administration was markedly increased in rats with cisplatin-induced ARF (Table 2). This result was consistent with the observations obtained in other ARF models induced by the injection of uranyl nitrate or bilateral ureter ligation (Katayama et al 1984; Laganiere & Shen 1987). We found that the hepatic extraction of propranolol following intraportal infusion was not altered significantly in rats with cisplatin-induced ARF, and that the hepatic extraction following intraportal infusion was dose-dependent and saturable (Table 2). The blood propranolol concentration after intra-intestinal administration was analysed using the Loo-Riegelman method. The results indicated that the fraction of the amount absorbed from the intestinal lumen to the systemic circulation was significantly increased in ARF rats as compared with control rats

Table 3 Effect of cisplatin-induced ARF on the intestinal absorption rate of propranolol.

	Control	ARF
At 8 min		
Remaining in the lumen (% of dose)	53.3 ± 7.7	40.9 ± 7.5**
Remaining in the tissue (% of dose)	25.3 ± 7.0	23.1 ± 6.9
Net absorption (% of dose)	21.4 ± 5.2	36.0 ± 13.2*
Blood concentration ($\mu g\,mL^{-1}$)	0.33 ± 0.17	1.71 ± 0.66**
At 30 min		
Remaining in the lumen (% of dose)	23.9 ± 4.7	17.0 ± 6.7
Remaining in the tissue (% of dose)	15.8 ± 6.0	10.2 ± 3.9
Net absorption (% of dose)	60.2 ± 5.1	72.8 ± 8.8*
Blood concentration ($\mu g\,mL^{-1}$)	1.03 ± 0.38	2.23 ± 0.30**

Values are expressed as mean ± s.d. of five to seven rats. *$P < 0.05$ and **$P < 0.01$ compared with controls.

Table 4 Effect of glycerol-induced ARF on the intestinal absorption rate of propranolol.

	Control	ARF
At 8 min		
Remaining in the lumen (% of dose)	52.1 ± 13.9	40.2 ± 6.8
Remaining in the tissue (% of dose)	18.4 ± 6.2	18.3 ± 2.0
Net absorption (% of dose)	29.5 ± 10.4	41.5 ± 5.7*
Blood concentration ($\mu g\,mL^{-1}$)	0.73 ± 0.38	3.67 ± 1.65**

Values are expressed as mean ± s.d. of seven rats. *$P < 0.05$ and **$P < 0.01$ compared with controls.

(Figure 4). This result suggested that the increased intestinal absorption rate significantly contributed to the increased bioavailability in rats with ARF.

The absorption of orally administered propranolol is essentially complete, and the metabolism of propranolol does not occur in the gut (Terao & Shen 1983; Laganiere & Shen 1987). Therefore, we evaluated the intestinal absorption rate using the in-situ closed loop method, and demonstrated the significantly increased intestinal absorption rate in rats with cisplatin-induced ARF (Table 3). An important issue was whether the increased intestinal absorption rate was due to the renal disease state or to the direct effect of cisplatin on the intestinal barrier function. Therefore, we evaluated the intestinal absorption rate of propranolol in glycerol-induced ARF rats, and demonstrated a significant effect of renal dysfunction on the net absorption of the drug (Table 4). In addition, Kimura et al (1984) reported that intestinal absorption rate of sulfanilic acid was increased in rats with $HgCl_2$- and glycerol-induced ARF, and in 5/6 nephrectomized rats as compared with control rats. They also reported that the permeability of drugs with molecular weights lower than 1000 was increased in glycerol-induced renal failure (Kimura et al 1988). The mechanisms responsible for the increased intestinal absorption rate of drugs in renal failure rats have not been fully elucidated; however, morphological abnormalities of the intestinal mucosa are observed in ARF rats (Kimura et al 1988). Furthermore, it was suggested that a reduction of the thickness of the unstirred water layer adjacent to the membrane was related to the increased intestinal absorption of lipophilic drugs (Kimura et al 1988). An explanation for the decreased intestinal barrier function might be due to the accumulation of harmful, endogenous low molecular weight substances in serum in the uraemic state (Magnusson et al 1991). These uraemic toxins could affect the intestinal integrity and allow larger molecules to pass more freely over the mucosal barrier than under normal conditions. This hypothesis may be consistent with the observation that the bioavailability of propranolol in patients on regular dialysis treatment was significantly lower than in patients not on haemodialysis (Bianchetti et al 1976).

Non-linear hepatic first-pass metabolism of propranolol and bufuralol have been shown in man (Shand & Rangno 1972; Dayer et al 1985), and the bioavailability of these drugs is significantly increased in patients with renal dysfunction (Bianchetti et al 1976; Balant et al 1980). It is conceivable that a more rapid intestinal absorption in

renal dysfunction could lead to an increase in the bioavailability of drugs which exhibit non-linear kinetics for hepatic metabolism (Hashimoto et al 2001; Okabe et al 2002). On the other hand, for drugs with linear disposition kinetics, the fraction of dose cleared in the first-pass through the liver remains constant, and the bioavailability, i.e. the fraction of the dose administered appearing in the systemic circulation, is independent of dose and/or absorption rate unless absorption is incomplete (Gibaldi & Feldman 1969). In fact, impairment of renal function has no important effect on the bioavailabili ty of metoprolol (Jordo et al 1980).

We found decreased systemic clearance of propranolol in cisplatin-induced ARF rats after intravenous administration (Table 1). In-vivo and in-vitro studies have shown that the extraction of propranolol across the rat liver is quite high (Terao & Shen 1984). Therefore, the systemic clearance of propranolol in rat is rate-limited by blood flow rate to the liver (Terao & Shen 1984). Katayama et al (1984) reported that the hepatic blood flow, measured by the continuous indocyanine green infusion method, did not significantly differ between control and uranyl nitrate-induced ARF rats. Therefore, the measurement of hepatic blood flow in cisplatin-induced ARF rats was not designed in this study. In our preliminary study, however, we found that the wet weight of the liver in cisplatin-induced ARF rats was 2.68 $\pm$ 0.16 g/100 g body weight ($n = 16$, mean $\pm$ s.d.) compared with 2.99 $\pm$ 0.44 g/100 g body weight ($n = 14$, $P < 0.01$) in the controls. The correlation between the weight of the liver and the hepatic blood flow rate in ARF rats remains to be clarified.

When propranolol was infused into the portal vein, the hepatic extraction did not differ between the rats with cisplatin-induced ARF and control rats (Table 2). Therefore, further investigation on the hepatic metabolic activity was not performed. On the other hand, Terao & Shen (1985) reported that the hepatic extraction was reduced in the presence of an inhibitory factor in uraemic blood perfusate in steady-state single-pass rat liver perfusion studies. Hori et al (1985) reported that the hepatic uptake rate of propranolol was decreased in ARF rats with the multiple-indicator dilution method. Therefore, further studies of the alteration of hepatic drug metabolism in renal failure are necessary.

In conclusion, we investigated the pharmacokinetics of propranolol in rats with cisplatin-induced renal failure. Our results indicated that the bioavailability of propranolol was increased in rats with cisplatin-induced renal failure. The increased bioavailability of propranolol was due to partial saturation of hepatic extraction as a result of the accelerated absorption rate in the intestine in rats with cisplatin-induced renal dysfunction. This study may provide new insights for understanding the pharmacokinetics of drugs in renal dysfunction.

References

Balant, L., Francis, R. J., Tozer, T. N., Marmy, A., Tschopp, J. M., Farbe, J. (1980) Influence of renal failure on the hepatic clearance of bufralol in man. *J. Pharmacokinet. Biopharm.* **8**: 421–438

Beal, S. L., Sheiner, L. B. (1992) *NONMEM users guide*. University of California, San Francisco

Bianchetti, G., Graziani, G., Brancaccio, D., Morganti, A., Leonetti, G., Manfrin, M., Sega, R., Gomeni, R., Ponticelli, C., Morselli, P. L. (1976) Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. *Clin. Pharmacokinet.* **1**: 373–384

Chau, N. P., Weiss, Y. A., Safar, M. E., Lavene, D. E., Georges, D. R., Milliez, P. L. (1977) Pindolol availability in hypertensive patients with normal and impaired renal function. *Clin. Pharmacol. Ther.* **22**: 505–510

Dayer, P., Balant, L., Kupfer, A., Striberni, R., Leemann, T. (1985) Effect of oxidative polymorphism (debrisoquine/sparteine type) on hepatic first-pass metabolism of bufuralol. *Eur. J. Clin. Pharmacol.* **28**: 317–320

Gibaldi, M., Feldman, S. (1969) Pharmacokinetic basis for the influence of route of administration on the area under the plasma concentration-time curve. *J. Pharm. Sci.* **58**: 1477–1480

Hashimoto, Y., Aiba, T., Yasuhara, M., Hori, R. (2001) Effect of experimental renal dysfunction on bioavailability of ajmaline in rats. *J. Pharm. Pharmacol.* **53**: 805–813

Hori, R., Okumura, K., Yasuhara, M., Katayama, H. (1985) Reduced hepatic uptake of propranolol in rats with acute renal failure. *Biochem. Pharmacol.* **34**: 2679–2683

Huang, J., Chuang, S., Cheng, C., Lai, M. (1999) Pharmacokinetics of metoprolol enantiomers in Chinese subjects of major CYP2D6 genotypes. *Clin. Pharmacol. Ther.* **65**: 402–407

Huang, Z., Murakami, T., Okochi, A., Yumoto, R., Nagai, J., Takano, M. (2000) Expression and function of P-glycoprotein in rats with glycerol-induced acute renal failure. *Eur. J. Pharmacol.* **406**: 453–460

Jordo, L., Attman, P. O., Aurell, M., Johansson, L., Johnsson, G., Regardh, C. G. (1980) Pharmacokinetics and pharmacodynamic properties of metoprolol in patients with impaired renal function. *Clin. Pharmacokinet.* **5**: 169–180

Katayama, H., Fujiwara, J., Yasuhara, M., Okumura, K., Hori, R. (1984) Increased availability of propranolol in rats with uranyl nitrate-induced acute renal failure. *J. Pharm. Dyn.* **7**: 536–544

Kimura, T., Ikeda, K., Kobayashi, A., Nakayama, T. (1984) Effect of experimental acute renal failure on intestinal barriers to drug absorption. *Chem. Pharm. Bull.* **32**: 2471–2473

Kimura, T., Kobayashi, A., Kobayashi, M., Numata, K., Kawai, Y., Nakayama, T., Mori, M., Awai, M. (1988) Intestinal absorption of drugs in rats with glycerol-induced acute renal failure. *Chem. Pharm. Bull.* **36**: 1847–1856

Laganiere, S., Shen, D. D. (1987) Altered S(-)-propranolol disposition in bilateral ureter-ligated rats. *Nephron* **46**: 305–311

Loo, J. C. K., Riegelman, S. (1968) New method for calculating the intrinsic absorption rate of drugs. *J. Pharm. Sci.* **57**: 918–928

Magnusson, M., Magnusson, K., Sundqvist, T., Dennneberg, T. (1991) Impaired intestinal barrier function measured by differently sized polyethylene glycols in patients with chronic renal failure. *Gut* **32**: 754–759

Masubuchi, Y., Hosokawa, S., Horie, T., Suzuki, T., Ohmori, S., Kitada, M., Narimatu, S. (1994) Cytochrome P450 isozymes involved in propranolol metabolism in human liver microsomes. The role of CYP2D6 as ring-hydroxylase and CYP1A2 as N-desisopropylase. *Drug Metab. Dispos.* **22**: 909–915

Okabe, H., Hashimoto, Y., Inui, K. (2000) Pharmacokinetics and bioavailability of tacrolimus in rats with experimental renal dysfunction. *J. Pharm. Pharmacol.* **52**: 1467–1472

Okabe, H., Yano, I., Hashimoto, Y., Saito, H., Inui, K. (2002) Evaluation of increased bioavailability of tacrolimus in rats with experimental renal dysfunction. *J. Pharm. Pharmacol.* **54**: 65–70

Padrini, R., Iovan, D., Javarnaro, A., Cucchini, F., Ferrari, M. (1993) Pharmacokinetics and electrophysiological effects of intravenous ajmaline. *Clin. Pharmacokinet.* **25**: 408–414

Shand, D. G., Rangno, R. E. (1972) The disposition of propranolol. I. Elimination during oral absorption in man. *Pharmacology* **7**: 159–168

Suzuki, T., Ohkuma, T., Isozaki, S. (1981) Nonlinear first-pass metabolism of propranolol in the rat. *J. Pharm. Dyn.* **4**: 131–141

Terao, N., Shen, D. D. (1983) Effect of experimental renal failure on the disposition kinetics of l-propranolol in rats. *J. Pharmacol. Exp. Ther.* **227**: 295–301

Terao, N., Shen, D. D. (1984) Pharmacokinetics of l-propranolol during repetitive dosing in normal and uranyl nitrate-induced renal failure rats. *J. Pharmacokinet. Biopharm.* **12**: 479–493

Terao, N., Shen, D. D. (1985) Reduced extraction of l-propranolol by perfused rat liver in the presence of uremic blood. *J. Pharmacol. Exp. Ther.* **233**: 277–284

Walle, T., Conradi, E. C., Walle, U. K., Fagan, T. C., Gaffney, T. E. (1978) The predictable relationship between plasma levels and dose during chronic propranolol therapy. *Clin. Pharmacol. Ther.* **24**: 668–677

Yamada, K., Yatsuzuka, A., Yasuhara, M., Okumura, K., Hori, R., Sakurai, T., Kawai, C. (1986) Mechanisms of pharmacokinetic interaction between ajmaline and quinidine in rats. *J. Pharmacobio-Dyn.* **9**: 347–351

Yasuhara, M., Fujiwara, J., Kitada, S., Katayama, H., Okumura, K., Hori, R. (1985) Effect of altered plasma protein binding on pharmacokinetics and pharmacodynamics of propranolol in rats after surgery: role of alpha-1-acid glycoprotein. *J. Pharmacol. Exp. Ther.* **235**: 513–520

Zekorn, C., Achtert, G., Hausleiter, H. J., Moon, C. H., Eichelbaum, M. (1985) Pharmacokinetics of N-propylajmaline in relation to polymorphic sparteine oxidation. *Klin. Wochenschr.* **15**: 1180–1186