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Effects of Cyclosporin on the Pharmacokinetics of Propranolol after Intravenous and Oral Administration to Control Rats and to Rats with Uranyl Nitrate-induced Acute Renal Failure

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Abstract

The effects of cyclosporin on the pharmacokinetics of propranolol have been investigated after intravenous and oral administration of the drugs to control rats and to rats with uranyl nitrate-induced acute renal failure.

The effects of intravenous cyclosporin, 30 mg kg^{-1}, on the pharmacokinetics of intravenous propranolol, 3 mg kg^{-1}, were significant both in control rats and in rats with uranyl nitrate-induced acute renal failure; after intravenous administration of cyclosporin plasma concentrations of propranolol were significantly lower, the area under the plasma concentration–time curve (AUC) for propranolol from time zero to time infinity was significantly smaller, and the time-averaged total body clearance of propranolol was significantly faster. The effects of oral cyclosporin, 100 mg kg^{-1}, on the pharmacokinetics of oral propranolol, 10 mg kg^{-1}, were also significant, both in control rats and in rats with uranyl nitrate-induced acute renal failure; after administration of oral cyclosporin plasma concentrations of propranolol were significantly higher and the AUC of propranolol was significantly greater.

These data suggest that cyclosporin increases the elimination of propranolol, and that the first-pass effects of propranolol are reduced, or gastrointestinal absorption of propranolol is increased, or both, by cyclosporin.

Propranolol, one of the most widely prescribed β-blockers in clinical practice, is usually taken orally on a chronic basis, although an intravenous form is available for acute administration. Although propranolol is rapidly and almost completely absorbed from the gastrointestinal tract (less than 5% of the orally administered dose is recovered in the faeces; Kazierad et al 1992), the absolute oral bioavailability (F) is low (30–40% at therapeutic dose) because of a high hepatic extraction ratio and significant first-pass effect (a saturable process). The plasma-protein binding of propranolol is approximately 90% and the drug is widely distributed throughout the body (volume of distribution, Vd, 150–260 L). Propranolol is almost completely eliminated from plasma via hepatic metabolism by CYP2C19 and 2D6 (Parkinson 1996) and so urinary recovery as unchanged propranolol is less than 1% of the administered dose.

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Cyclosporin is a powerful immunosuppressive drug used in organ transplantation medicine and to treat autoimmune disease (Fahr 1993). Pharmacokinetic drug interactions between cyclosporin and other drugs have been reported (Yee & McGuire 1990a, b). Co-administered drugs could affect the pharmacokinetics of absorption, distribution, metabolism, and excretion of cyclosporin by the various mechanisms (Yee & McGuire 1990a, b). Although the effects of other drugs on the pharmacokinetics of cyclosporin have been extensively studied (Yee & McGuire 1990a, b), the effects of cyclosporin on the pharmacokinetics of propranolol do not seem to have been investigated.

This paper reports the effects of cyclosporin on the pharmacokinetics of propranolol after intravenous and oral administration of the drugs to

control rats and to rats with uranyl nitrate-induced acute renal failure.

Materials and Methods

Chemicals

Cyclosporin (Sandimmune for injection, 50 mg mL^{-1}, 5 mL vial, and Sandimmune Neoral for oral administration, 25 mg capsule) was obtained from Sandoz Pharmaceutical (Basle, Switzerland). Propranolol (as the hydrochloride powder) and labetalol (internal standard for high-performance liquid-chromatographic (HPLC) assay of propranolol) were from Daewoong (Seoul, Korea) and Glaxo (Seoul, Korea), respectively. Uranyl nitrate (powder) was purchased from BDH Chemicals (Poole, UK). Other chemicals were of reagent or HPLC grade and therefore used without further purification.

Animals

Male Sprague–Dawley rats, 8 weeks old, were purchased from Dai-Han Laboratory of Animal Development (Seoul, Korea). They were housed in a specific pathogen-free room (College of Pharmacy, Ewha Womans University, Seoul, Korea) with 12-h–12-h light–dark cycle at $22 \pm 2^{\circ}C$. The rats were randomly divided into two groups—control rats and rats with uranyl nitrate-induced acute renal failure.

Induction of acute renal failure in rats by uranyl nitrate injection

Uranyl nitrate (0·5% in 0·9% NaCl injectable solution; 1 mL kg^{-1}, equivalent to 5 mg kg^{-1}), was injected once into the tail vein of a rat to induce acute renal failure (Kim et al 1996, 1998). The same volume of 0·9% NaCl injectable solution was injected into control rats. Food (Cheiljedang Corporation, Seoul, Korea) and water were freely available.

Pretreatment of rats

In the early morning on the fifth day after injection of uranyl nitrate (rats with uranyl nitrate-induced acute renal failure) or 0·9% NaCl injectable solution (control rats) the left femoral artery and the left femoral vein were cannulated with polyethylene tubing (PE 50; Clay Adams, Parsippany, NJ) under light ether anaesthesia (Kim et al 1996, 1998). The exposed areas were surgically sutured. Each rat was left for 2 h to recover from anaesthesia before the study began. Rats were held in a supine position during the experiment by tying the four feet to a plate. For preliminary study, serum was collected from control rats ($n = 6$) and rats with uranyl nitrate-induced acute renal failure ($n = 6$) for measurement of the concentrations of urea nitrogen and creatinine, and the whole kidney and liver of each rat were excised, rinsed or perfused with 0·9% NaCl injectable solution, blotted dry with paper tissue, and weighed.

Intravenous study

Sandimmune intravenous solution was diluted with 5% dextrose-in-water for injection to furnish cyclosporin concentrations of 3 or 30 mg mL^{-1}. Propranolol hydrochloride was dissolved in water for injection to furnish a propranolol free-base concentration of 3 mg mL^{-1}. Propranolol, 3 mg kg^{-1} ($n = 5$), propranolol, 3 mg kg^{-1}, with cyclosporin, 3 mg kg^{-1} ($n = 7$), and propranolol, 3 mg kg^{-1}, with cyclosporin, 30 mg kg^{-1} ($n = 5$) were administered intravenously to control rats. Propranolol, 3 mg kg^{-1} ($n = 5$), and propranolol, 3 mg kg^{-1}, with cyclosporin, 30 mg kg^{-1} ($n = 5$) were administered intravenously to rats with uranyl nitrate-induced acute renal failure. Cyclosporin was injected over a period of 5 s via the left femoral vein and propranolol was then injected immediately over a period of 5 s. The volume of each injection was 1·0 mL kg^{-1}. Blood samples (0·15 mL) were collected via the left femoral artery 0 (to serve as a control), 2, 5, 10, 15, 30, 60 and 90 min, and 2, 4 and 8 h after intravenous administration. Approximately 0·15 mL of heparinized 0·9% NaCl injectable solution (50 units mL^{-1}) was used to flush the cannula after each sampling of blood, to prevent blood clotting. Blood samples were centrifuged immediately and 50-μL samples of plasma sample were stored frozen at $-20^{\circ}C$ until HPLC analysis of propranolol.

Oral study

The contents of Neoral capsules were suspended in water for injection to furnish cyclosporin concentrations of 6·67 or 66·7 mg mL^{-1}. Propranolol hydrochloride was dissolved in water for injection to furnish a propranolol free-base concentration of 10 mg mL^{-1}. Propranolol, 10 mg kg^{-1} ($n = 5$), propranolol, 10 mg kg^{-1}, with cyclosporin, 10 mg kg^{-1} ($n = 5$), and propranolol, 10 mg kg^{-1}, with cyclosporin, 100 mg kg^{-1} ($n = 5$) were administered orally to control rats. Propranolol, 10 mg kg^{-1} ($n = 5$), and propranolol, 10 mg kg^{-1}, with

cyclosporin, 100 mg kg^{-1} (n = 4) were administered orally to rats with uranyl nitrate-induced acute renal failure. Cyclosporin was administered orally by use of a feeding tube (Solco, Seoul, Korea), followed by immediate administration of propranolol. Total oral volume was 1·5 mL kg^{-1} for cyclosporin and 1·0 mL kg^{-1} for propranolol. Blood samples (0·15 mL) were collected 0 (to serve as a control), 5, 15, 30, 45, 60 and 90 min, and 2, 4 and 8 h after oral administration. Other procedures were similar to those followed in the intravenous study.

HPLC analysis of propranolol

A stock solution of propranolol (free-base concentration 10 μg mL^{-1}) was prepared by dissolving the hydrochloride in methanol. Appropriate dilutions of the stock solution were made with methanol. Standard solutions of propranolol in plasma were prepared by adding appropriate volumes of the diluted stock solutions to plasma ($< 10\,\mu$L (mL plasma)$^{-1}$) to furnish final propranolol free-base concentrations of 50, 100, 200, 500 and 1000 ng mL^{-1}. HPLC was performed with a model 7125 injector, a model LC-9A pump (both from Shimadzu, Kyoto, Japan), a model 8450 fluorescence detector (Shimadzu Europa, Germany), and a model CR5A Chromatopac integrator (Shimadzu, Japan). Compounds were separated on a 30 cm × 3·9 mm i.d. reversed-phase column (10 μm μ-Bondapak C_{18}; Waters, Milford, MA). Internal standard (labetalol, 200 μg mL^{-1}, in methanol; 50 μL) and methanol (150 μL) were added to the plasma sample (50 μL). After vortex-mixing for 3 min and centrifugation for 30 s at 3000 rev min^{-1}, the supernatant (25 μL) was injected directly on to the column. The mobile phase, 60 : 40 (v/v) 10 mM phosphate buffer (pH adjusted to 3·4 with 5 M HCl)–methanol, was delivered at 1·2 mL min^{-1} and the column effluent was monitored by fluorescence detection with excitation and emission wavelengths of 295 and 360 nm, respectively. The retention times of propranolol and the internal standard were 10·1 and 7·0 min (approx.), respectively. The detection limit for propranolol in plasma was 10 ng mL^{-1}. There was no interference from endogenous substances present in the plasma. The propranolol and labetalol peaks were symmetrical, and the within-day coefficients of variation were less than 11·5% (n = 5).

Measurement of urea nitrogen and creatinine in serum

The concentrations of urea nitrogen and creatinine in serum were measured by means of an Hitachi (Tokyo, Japan) 747 Automatic Analyser.

Pharmacokinetic analysis

The total area under the plasma concentration–time curve (AUC) from time zero to time infinity was calculated by the trapezoidal rule-extrapolation method (Kim et al 1993); this method employed the logarithmic trapezoidal rule for the calculation of the area during the declining plasma-level phase (Chiou 1978) and the linear trapezoidal rule for the rising plasma-level phase. The area from the last data point to time infinity was estimated by dividing the last measured plasma concentration by the terminal rate constant.

Standard methods (Gibaldi & Perrier 1982) were used to calculate the time-averaged total body clearance (CL), the area under the first moment of the plasma concentration–time curve (AUMC), the mean residence time (MRT), and the apparent volume of distribution at steady state (Vd_{SS}).

The mean values of Vd_{SS} (Chiou 1979), CL (Chiou 1980), and terminal half-life (Eatman et al 1977) were calculated by the harmonic mean method.

Statistical analysis

The statistical significance of differences between results was determined by use of the unpaired *t*-test or Duncan's multiple range test of a posteriori analysis of variance for unpaired mean data, by means of the SAS program; $P < 0{\cdot}05$ was considered to be indicative of significance. All data are expressed as means ± standard deviation (s.d.).

Results and Discussion

Uranyl nitrate-induced acute renal failure in rats

Impaired kidney function was observed in rats with uranyl nitrate-induced acute renal failure; serum levels of urea nitrogen (359 ± 94·8 compared with 35·5 ± 9·48 mg%) and creatinine (9·00 ± 2·72 compared with 0·880 ± 0·247 mg%) increased significantly and kidney weight (0·783 ± 0·0872 percent of body weight compared with 0·716 ± 0·0416; $P < 0{\cdot}0703$) increased considerably more than for control rats. Note that body weight gain was significantly reduced by pretreatment with uranyl nitrate (from 273 ± 13·1 to 243 ± 21·7 g) whereas it increased significantly in control rats (from 268 ± 18·4 to 295 ± 15·9 g). Impaired kidney function in rats with uranyl nitrate-induced acute renal failure has been reported by other workers (Terao & Shen 1984; Kim 1991; Kim et al 1996, 1998).

Pharmacokinetics of propranolol after intravenous administration with or without cyclosporin to control rats and to rats with uranyl nitrate-induced acute renal failure

The mean arterial plasma concentration–time profiles of propranolol after intravenous administration

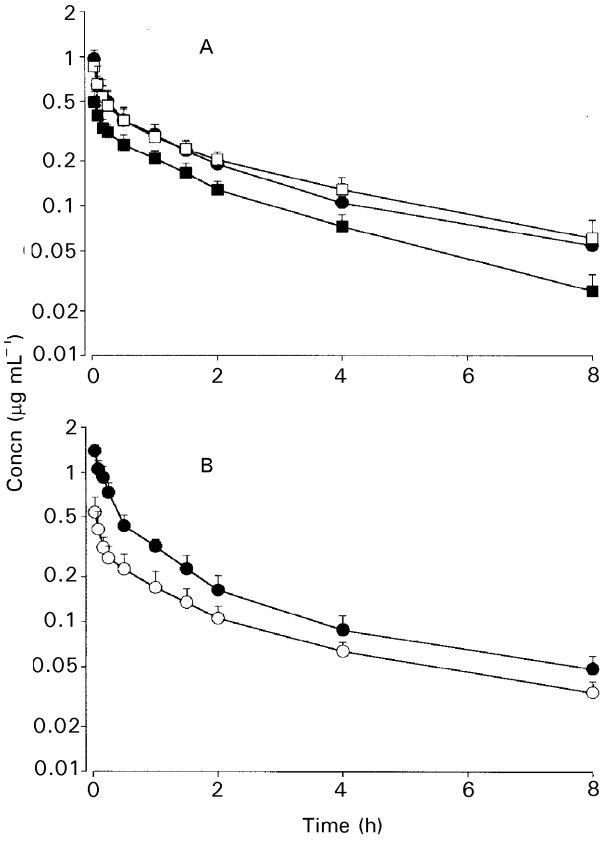

Figure 1. Mean arterial plasma concentration–time curves of propranolol after intravenous administration with or without intravenous cyclosporin to A. control rats (●, propranolol, 3 mg kg^{-1} (n = 5); □, propranolol, 3 mg kg^{-1}, plus cyclosporin, 3 mg kg^{-1} (n = 7); ■, propranolol, 3 mg kg^{-1}, plus cyclosporin, 30 mg kg^{-1} (n = 5)) and B. rats with uranyl nitrate-induced acute renal failure (●, propranolol, 3 mg kg^{-1} (n = 5); ○, propranolol, 3 mg kg^{-1}, plus cyclosporin, 30 mg kg^{-1} (n = 5)). Bars represent standard deviation.

with or without cyclosporin to control rats and to rats with uranyl nitrate-induced acute renal failure are shown in Figure 1; the relevant pharmacokinetic parameters are listed in Table 1. After intravenous administration mean arterial plasma concentrations of propranolol declined polyexponentially for all rats studied (Figure 1). In control rats, the effects of intravenous cyclosporin on the pharmacokinetics of intravenous propranolol were dependent on the dose of cyclosporin. For example, for 3 mg kg^{-1} cyclosporin the effects were almost negligible—plasma concentrations (Figure 1A) and propranolol pharmacokinetic parameters (Table 1) were not significantly different from those in the absence of cyclosporin. At 30 mg kg^{-1}, however, the effects of intravenous cyclosporin on the pharmacokinetics of intravenous propranolol were significant (Table 1); plasma propranolol concentrations were significantly lower (Figure 1A), the terminal half-life of propranolol was significantly shorter (32% decrease), the AUC of propranolol was significantly lower (41% decrease), and the clearance of propranolol was significantly faster (68% increase) than in the absence of cyclosporin. The significantly lower plasma concentrations of propranolol after administration of 30 mg kg^{-1} cyclosporin could be because of faster clearance in the presence of cyclosporin, resulting in a shorter terminal half-life and smaller AUC. Note that intravenous administration of the different doses of propranolol resulted in significant differences between some of the pharmacokinetic parameters of propranolol; after 30 mg kg^{-1} the AUC of cyclosporin was significantly smaller (41% decrease), clearance was significantly faster (70% increase), and Vd_{SS} was significantly larger (43% increase) than after 3 mg kg^{-1} (Table 1).

In rats with uranyl nitrate-induced acute renal failure the effects of intravenous cyclosporin, 30 mg kg^{-1}, on the pharmacokinetics of intravenous propranolol, 3 mg kg^{-1}, were also significant (Table 1); after administration of cyclosporin

Table 1. Pharmacokinetic parameters of propranolol after intravenous administration with or without intravenous cyclosporin to control rats and to rats with uranyl nitrate-induced acute renal failure.

Treatment	n	t½ (h)	$AUC_{0\rightarrow\infty}$	MRT	CL	Vd_{SS}
Control rats						
Propranolol, 3 mg kg^{-1}	5	3·84 ± 0·755*	1·63 ± 0·244	4·69 ± 1·67	1·84 ± 0·114	8·37 ± 1·64
plus cyclosporin, 3 mg kg^{-1}	7	3·12 ± 0·354	1·65 ± 0·360	4·02 ± 1·97	1·82 ± 0·141	7·15 ± 1·51‡
plus cyclosporin, 30 mg kg^{-1}	5	2·60 ± 0·455	0·969 ± 0·253†	3·36 ± 1·55	3·10 ± 0·329†	10·2 ± 1·15
Rats with renal failure						
Propranolol, 3 mg kg^{-1}	5	5·41 ± 1·36	1·79 ± 0·481§	5·47 ± 3·15	1·68 ± 0·200§	8·80 ± 2·02§
plus cyclosporin, 30 mg kg^{-1}	5	4·32 ± 0·518	1·01 ± 0·335	5·37 ± 1·44	2·97 ± 0·443	15·8 ± 2·59

t½, terminal half-life; $AUC_{0\rightarrow\infty}$, area under the plasma concentration–time curve from time zero to time infinity; MRT, mean residence time; CL, time-averaged total body clearance; Vd_{SS}, apparent volume of distribution at steady state. Results are means ± s.d. *$P < 0.05$ compared with control rats given propranolol plus 30 mg kg^{-1} cyclosporin. †$P < 0.05$ compared with control rats given propranolol alone and with control rats given propranolol plus 3 mg kg^{-1} cyclosporin. ‡$P < 0.05$ compared with control rats given propranolol plus 30 mg kg^{-1} cyclosporin. §$P < 0.05$ compared with renal failure rats given propranolol plus 30 mg kg^{-1} cyclosporin.

plasma concentrations of propranolol were significantly lower (Figure 1B), the AUC was significantly smaller (44% decrease), clearance was significantly faster (77% increase), and Vd_{SS} was significantly larger (80% increase) than in the absence of cyclosporin. More studies are required to elucidate the reason for the faster clearance of intravenous propranolol in the presence of the high ($30\,mg\,kg^{-1}$) dose of intravenous cyclosporin in both control rats and in rats with uranyl nitrate-induced acute renal failure.

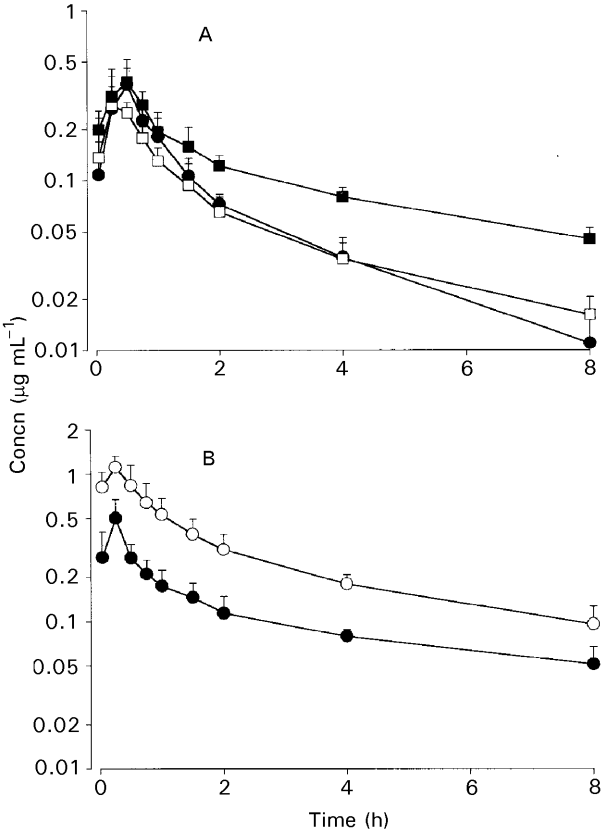

Figure 2. Mean arterial plasma concentration–time curves of propranolol after oral administration with or without oral cyclosporin to A. control rats (●, propranolol, $10\,mg\,kg^{-1}$ (n = 5); □, propranolol, $10\,mg\,kg^{-1}$, plus cyclosporin, $10\,mg\,kg^{-1}$ (n = 5); ■, propranolol, $10\,mg\,kg^{-1}$, plus cyclosporin, $100\,mg\,kg^{-1}$ (n = 5)) and B. rats with uranyl nitrate-induced acute renal failure (●, propranolol, $10\,mg\,kg^{-1}$ (n = 5); ○, propranolol, $10\,mg\,kg^{-1}$, plus cyclosporin, $100\,mg\,kg^{-1}$ (n = 4)). Bars represent standard deviation.

Pharmacokinetics of propranolol after oral administration with or without cyclosporin to control rats and to rats with uranyl nitrate-induced acute renal failure

Because cyclosporin and propranolol are usually administered orally, the effects of cyclosporin on the pharmacokinetics of propranolol were investigated after oral administration of the drugs to control rats and to rats with uranyl nitrate-induced acute renal failure. The mean arterial plasma concentration–time profiles of propranolol after oral administration with or without cyclosporin to control rats and to rats with uranyl nitrate-induced acute renal failure are shown in Figure 2; the relevant pharmacokinetic parameters are listed in Table 2. After oral administration absorption of propranolol was rapid; the mean plasma concentration of propranolol reached its peak 15–30 min after administration and thereafter declined polyexponentially for all rats studied (Figure 2). In control rats, the effects of oral cyclosporin on the pharmacokinetics of oral propranolol were also dependent on cyclosporin dose. For example, after $10\,mg\,kg^{-1}$ cyclosporin, the effects were almost negligible—the plasma concentrations and pharmacokinetic parameters of propranolol were not significantly different from those measured in the absence of cyclosporin. After $100\,mg\,kg^{-1}$ cyclosporin, however, plasma propranolol concentrations were significantly higher (Figure 2A) and the AUC of propranolol was significantly greater (106% increase) than in the absence of cyclosporin.

Table 2. Pharmacokinetic parameters of propranolol after oral administration with or without oral cyclosporin to control rats and to rats with uranyl nitrate-induced acute renal failure.

Treatment	n	$t_{1/2}$ (h)	$AUC_{0\to\infty}$	C_{max}	T_{max}
Control rats					
Propranolol, $10\,mg\,kg^{-1}$	5	2·16 ± 0·298*	0·574 ± 0·329	0·395 ± 0·237	0·400 ± 0·306
plus cyclosporin, $10\,mg\,kg^{-1}$	5	3·36 ± 1·14	0·575 ± 0·95	0·295 ± 0·147	0·400 ± 0·306
plus cyclosporin, $100\,mg\,kg^{-1}$	5	4·03 ± 1·13	1·18 ± 0·235†	0·391 ± 0·297	0·417 ± 0·322
Rats with renal failure					
Propranolol, $10\,mg\,kg^{-1}$	5	5·11 ± 1·10‡	1·26 ± 0·644‡	0·505 ± 0·371‡	0·250 ± 0·000
plus cyclosporin, $100\,mg\,kg^{-1}$	4	3·59 ± 0·547	2·69 ± 1·16	1·18 ± 0·238	0·313 ± 0·250

$t_{1/2}$, terminal half-life; $AUC_{0\to\infty}$, area under the plasma concentration–time curve from time zero to time infinity; C_{max}, peak concentration ($\mu g\,mL^{-1}$); T_{max}, time of maximum concentration. Results are means ± s.d. *$P < 0.05$ compared with control rats given propranolol plus $100\,mg\,kg^{-1}$ cyclosporin. †$P < 0.05$ compared with control rats given propranolol alone and with control rats given propranolol plus $10\,mg\,kg^{-1}$ cyclosporin. ‡$P < 0.05$ compared with renal failure rats given propranolol plus $100\,mg\,kg^{-1}$ cyclosporin.

In rats with uranyl nitrate-induced acute renal failure the effects of oral cyclosporin, 100 mg kg^{-1}, on the pharmacokinetics of oral propranolol, 10 mg kg^{-1}, were also significant (Table 2); in the presence of cyclosporin plasma concentrations of propranolol were significantly higher (Figure 2B), the AUC of propranolol was significantly greater (113% increase), the terminal half-life of propranolol was significantly shorter (30% decrease), and the peak concentration of propranolol was significantly higher (134% increase) than in the absence of cyclosporin. The significant increase in the AUC of propranolol after administration of 100 mg kg^{-1} cyclosporin both for control rats and for rats with uranyl nitrate-induced acute renal failure could be because of increased gastrointestinal absorption or reduced first-pass elimination of propranolol, or both, because the clearance of propranolol was faster in the presence of cyclosporin in the intravenous study (Table 1).

In conclusion, intravenous cyclosporin, 30 mg kg^{-1}, had significant effects on the pharmacokinetics of intravenous propranolol, 3 mg kg^{-1}, both in control rats and in rats with uranyl nitrate-induced acute renal failure; after intravenous administration of cyclosporin plasma concentrations of propranolol were significantly lower, the AUC was significantly smaller, and clearance was significantly faster than in the absence of cyclosporin. The effects of oral cyclosporin, 100 mg kg^{-1}, on the pharmacokinetics of oral propranolol, 10 mg kg^{-1}, both in control rats and in rats with uranyl nitrate-induced acute renal failure were also significant; however, the effects on propranolol plasma concentrations and AUC were the opposite of those in the intravenous study; after oral administration of cyclosporin plasma concentrations and AUC of propranolol were significantly higher than in the absence of cyclosporin.

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