INCREASED AVAILABILITY OF PROPRANOLOL IN RATS WITH URANYL NITRATE-INDUCED ACUTE RENAL FAILURE*

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The effect of acute renal failure (ARF) on the pharmacokinetics of propranolol was investigated. The model of ARF was produced by the subcutaneous injection of uranyl nitrate to rats (10 mg/kg) and was used 3 d after treatment. Uranyl nitrate-treated rats showed significantly higher plasma concentrations of propranolol after oral administration and the area under the plasma concentration-time curve increased about 3-fold compared to control rats. The plasma disappearance of propranolol after intravenous administration did not differ significantly between control and ARF. The mean availability of propranolol after oral administration increased from 0.120 in control to 0.215 in ARF ($p < 0.005$). Absorption of propranolol was almost complete and no significant difference was found between two groups. No changes in plasma protein binding of propranolol and hepatic blood flow were observed in ARF. On the other hand, hepatic clearance of propranolol determined by liver perfusion studies showed a significant reduction in ARF and the calculated intrinsic clearance of unbound propranolol at a dose of 6.25 mg was 26.8 ± 2.3 ml/min in control and 16.0 ± 2.3 ml/min in ARF ($p < 0.01$). These results demonstrate that the oral availability of propranolol increased in ARF due to a reduction in the hepatic presystemic elimination as compared to healthy control rats.

Keywords — propranolol; renal failure; pharmacokinetics; availability; hepatic clearance; presystemic elimination; uranyl nitrate; rat

Patients with chronic renal disease often have hypertension, which at times is associated with an elevation of peripheral plasma renin activity.¹⁾ In these cases of hypertension, propranolol should be particularly indicated and useful because of its marked suppressive effect on plasma renin activity.²⁾

Propranolol has a high extraction ratio and is metabolized virtually completely in the liver,^{3,4)} and less than 1% of the intact drug is found in the urine.⁵⁾ Consequently, in renal failure the kinetic behavior of the intact drug is not expected to be altered to any large extent. However, there are some clinical reports suggesting the al-

tered pharmacokinetics of propranolol in renal disease.⁶⁻⁸⁾ Lowenthal *et al.*⁷⁾ reported that peak serum concentrations of propranolol in patients with chronic renal disease were about 3-fold higher than those in the healthy volunteers following a single oral dose. In contrast, Wood *et al.*⁹⁾ reported that the oral and systemic clearance of propranolol were unaffected by chronic renal failure. Thus, previous studies of propranolol disposition in renal disease have been conflicting. The reason for these divergent views seems to be related, at least in part, to an understandable reluctance to subject patients to invasive studies.

These backgrounds prompted the present in-

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vestigation, which was designed to evaluate the effect of renal failure on the pharmacokinetics of propranolol.

MATERIALS AND METHODS

Materials — DL-Propranolol hydrochloride was obtained from Nakarai Chemicals Co. (Japan). Analytical reagents for JEOL Automated Assay System were purchased from Iatron Laboratories, Inc. (Japan). All other chemicals were of the finest grade available.

Induction of Acute Renal Failure — Male Wistar albino rats, weighing 180–270 g, were used. For the induction of acute renal failure (ARF), uranyl nitrate was administered subcutaneously, 10 mg/kg body weight in physiologic saline solution (10 mg/ml).¹⁰ The studies on rats with ARF were performed 3 d after the injection of uranyl nitrate.

Kinetic Studies in Vivo — Rats for oral studies were fasted for about 16 h before experiments with free access to water. Under light ether anesthesia, the carotid artery was cannulated with the polyethylene tubing which passed subcutaneously to the back of the neck. Then, heparin was administered intravenously (1000 unit/kg) and a 0.3 ml of blood sample was collected. After recovery from the anesthesia, rats received a single dose of propranolol (12.5 mg/kg) and were kept in individual cages without any constraint. In the case of oral studies, propranolol in saline solution (5 mg/ml) was administered by gastric tube and blood samples (0.25 ml) were obtained for the determination of propranolol at 15, 30, 60, 90, 120 and 180 min. In the case of intravenous dose, propranolol in saline solution (12.5 mg/ml) was injected into a tail vein and blood samples were obtained at 3, 5, 10, 15, 30, 60, 90, 120, 150 and 180 min. The plasma was separated immediately by the centrifugation and stored at 4°C until assayed. Plasma samples before propranolol administration were stored at –40°C for the analysis of blood urea nitrogen (BUN), creatinine, transaminase activity, total protein and albumin.

Plasma Protein Binding — The degree of pro-

pranolol binding to rat plasma protein was determined at 20°C by the ultrafiltration technique using Micropartition system (MPS-1, Amicon Far East Ltd., Japan).

Intestinal Absorption — The absorption rate of propranolol from the small intestine was determined by the *in situ* loop method.¹¹ The physiological saline solution of propranolol (2 mg/ml, 1.25 ml/kg) was injected into the loop of whole small intestine under pentobarbital anesthesia. At the end of the specified period, the luminal content was withdrawn and the intestine was washed with the saline. The luminal content and washings were combined and completed to 50 ml with the saline. Then, the residual amount of drug was determined.

In the *in vitro* studies, everted sac of the small intestine 20 cm in length, was prepared.¹² The sac was filled with 2 ml of isotonic phosphate buffer solution (pH 7.4) and placed in the mucosal fluid, 10 ml of isotonic phosphate buffer solution containing propranolol (0.1 mg/ml, pH 6.5). The sac was incubated with continuous shaking and aerating 95% O₂ + 5% CO₂ at 37°C. At the end of the incubation period, the sac was cut open and the serosal fluid was collected. Then, the sac was rinsed, weighed and homogenized in 3 volumes of pH 6.5 phosphate buffer solution. The concentration of propranolol in the tissue, mucosal and serosal fluid was determined.

Measurement of Hepatic Blood Flow — Hepatic vein catheterization was performed by the method of Lebrec *et al.*¹³ under pentobarbital anesthesia and hepatic blood flow was determined by a continuous indocyanine green (ICG) infusion method.¹⁴ The infusion rate of ICG was 13.25 µg/min. Arterial blood samples were collected from the carotid artery by catheterization.

Liver Perfusion Studies — A closed, isolated circulation of rat liver was performed by the method of Mortimore *et al.*¹⁵ The liver was perfused *via* the hepatic portal vein with 20% (v/v) bovine blood cell, 5% (w/v) bovine serum albumin in Krebs-Henseleit buffer solution, equi-

librated with 95% O₂ + 5% CO₂ to maintain a pH of 7.4 at 37°C. A constant flow rate of 15 ml/min and a constant temperature of 37°C were maintained and the liver was allowed to equilibrate with the buffer solution for 10 to 20 min before the recirculation of drug-containing solution. Then, propranolol was added to the 30 ml of reservoir and 0.2 ml samples of the reservoir solution were obtained at 3, 5, 10, 15, 20, 25 and 30 min.

Analytical Methods — Determination of propranolol concentration was performed within 24 h after plasma sampling by a slightly modified method of Lo and Riegelman.¹⁶⁾ A 0.1 ml quantity of plasma sample was transferred into an Eppendorf polypropylene micro test tube and 0.2 ml of acetonitrile was added. After the sample was vortexed for 15 s it was centrifuged for 2 min using an Eppendorf Microcentrifuge, Model 5412. A 50 µl of clear supernatant was injected onto the column. A Shimadzu Model LC-3A high performance liquid chromatograph equipped with a Shimadzu RF-500LC fluorescence spectromonitor and a Zorbax CN column (25 cm × 4.6 mm i.d.; 5 µm particle size; Shimadzu-Dupont, Japan) was used. The mobile phase was composed of acetonitrile, 0.0871 M phosphoric acid and water (5 : 1 : 3, v/v). The flow rate was 2 ml/min. The fluorometer was set at an excitation wavelength of 296 nm and an emission wavelength of 353 nm.

ICG concentration in plasma was measured

with Hitachi Model 200-20 spectrophotometer with a microcell at 800 nm after 11 times dilution with deionized water.¹⁴⁾ The analysis of BUN, creatinine, glutamic-oxalacetic transaminase activity (GOT), glutamic-pyruvic transaminase activity (GPT), total protein and albumin in plasma was performed by an Automated Assay System-Clinalyzer, JCA-SI6 (JEOL Ltd, Japan) with Hyland Control Serum II (Travenol Laboratories, Inc., U.S.A.) as the standard.

Data Analysis — Pharmacokinetic parameters in terms of two compartment open model for propranolol were determined by non-linear least squares regression¹⁷⁾ using a FACOM M-200 digital computer at Kyoto University Data Processing Center. Area under the plasma drug concentration-time curve for infinite time (*AUC*) after oral administration of propranolol was calculated by the trapezoidal method for the measured values and then extrapolated to infinity by dividing the final concentration time point by the terminal rate constant. The terminal rate constant was determined by least squares regression of the loglinear portion of the curve.

Mean values are reported with standard errors. Statistical analysis was performed using Student's *t*-test with *P* = 0.05 as the minimal level of significance.

RESULTS

Induction of Acute Renal Failure with Uranyl Nitrate

TABLE I. *Effect of Uranyl Nitrate Treatment on Laboratory Values of Rat Plasma*

Items	Control	Uranyl nitrate
BUN (mg/dl)	15.2 ± 0.8	50.8 ± 2.6 ^{a)}
Creatinine (mg/dl)	0.65 ± 0.03	1.83 ± 0.09 ^{a)}
GOT (IU/l)	115.1 ± 17.1	129.1 ± 13.5
GPT (IU/l)	33.3 ± 3.5	29.7 ± 1.2
Total protein (g/dl)	5.50 ± 0.09	5.63 ± 0.12
Albumin (g/dl)	3.84 ± 0.05	3.83 ± 0.07

Plasma samples were obtained from rats 3 d after the injection of uranyl nitrate (10 mg/kg, s.c.). Results are given as the mean ± S.E. (control: n = 24, uranyl nitrate: n = 21).

a) p < 0.001.

The development of renal dysfunction was determined by measurement of plasma creatinine and BUN concentrations. Uranyl nitrate-treated rats exhibited a gradual increase of plasma creatinine concentrations with time, from 0.65 ± 0.03 mg/dl before uranyl nitrate injection, to 1.21 ± 0.08 mg/dl on day 2, 1.83 ± 0.09 mg/dl on day 3 and 5.67 ± 0.51 mg/dl on day 5. The same tendencies were observed with respect to BUN concentrations (15.2 ± 0.8 , 40.1 ± 3.2 , 50.8 ± 2.6 and 156.0 ± 15.7 mg/dl on 0, 2, 3 and 5 d after treatment). Plasma GOT and GPT did not increase above normal levels (Table I). Even on 5 d after uranyl nitrate treatment, GOT and GPT were 128.4 ± 16.9 IU/l and 25.0 ± 2.5 IU/l, respectively. Plasma concentrations of total protein and albumin were also unchanged by uranyl nitrate injection. Thus, uranyl nitrate injection selectively caused the renal dysfunction of rats and we used the rats 3 d after the injection of uranyl nitrate as the model of ARF.

FIG. 1. Plasma Concentrations of Propranolol after Oral Administration of Propranolol (12.5 mg/kg) in Control and Uranyl Nitrate-Treated Rats

Each point and vertical bar represent the mean $\pm$ S. E. of seven (control) or five (uranyl nitrate-treated) rats. $\circ$: control rats, $\bullet$: uranyl nitrate-treated rats.

Kinetic Studies in Vivo

When propranolol was administered orally at a dose of 12.5 mg/kg, uranyl nitrate-treated rats showed significantly higher plasma concentrations of propranolol compared to control rats (Fig. 1). Peak plasma concentration of propranolol increased from 147 ± 33 ng/ml in control rats to 507 ± 167 ng/ml in ARF ($p < 0.05$). *AUC* of propranolol after oral administration increased from 87.5 ± 11.3 to 222.7 ± 21.4 $\mu\text{g} \cdot \text{min}/\text{ml}/\text{kg}$ ($p < 0.001$). The plasma disappearance of propranolol after intravenous administration at the same dose as in the oral studies is shown in Fig. 2. The disappearance of drug followed biexponential curves and no significant difference was observed between control and ARF in the plasma concentrations or the pharmacokinetic constants β , Vd_{ss} and CL_{sys} (Table II). In addition, there was no significant difference in the plasma protein binding of propranolol determined by the ultrafiltration technique (93.9 ± 0.1 and $94.1 \pm 0.2\%$ in control and ARF at the plasma concentration of 200 ng/ml). The availability of propranolol (*F*) calculated by dividing *AUC* of

FIG. 2. Plasma Disappearance Curves of Propranolol after Intravenous Administration of Propranolol (12.5 mg/kg) in Control and Uranyl Nitrate-Treated Rats

Each point and vertical bar represent the mean $\pm$ S. E. of five (control) and four (uranyl nitrate-treated) rats. Curves were drawn by using the mean pharmacokinetic parameters shown in Table II. $\circ$: control rats, $\bullet$: uranyl nitrate-treated rats.

propranolol after oral administration by *AUC* after intravenous administration increased from 0.120 ± 0.015 in controls to 0.215 ± 0.021 in ARF ($p < 0.005$). These results suggest that the intestinal absorption and/or presystemic elimination process of propranolol may be changed in rats with uranyl nitrate-induced ARF.

Intestinal Absorption of Propranolol

In order to investigate the effect of ARF on the absorption process, propranolol was administered to the loop of rat small intestine. Propranolol was rapidly absorbed and about 90% of dose disappeared from the intestinal lumen at 15 min. Uranyl nitrate-treated rats showed a tendency of more rapid absorption of propranolol than control, but the difference was not statistically significant (Table III). The intestinal uptake of propranolol was further investigated

by using the everted sac technique, where the effect of blood flow could be excluded. No significant difference was found in the transfer of propranolol from mucosal side to intestinal tissue and serosal side between control and ARF (Table IV). The total recoveries of intact propranolol in the everted sac experiments were 93.3 ± 0.9 and $94.6 \pm 1.4\%$ in control and ARF, respectively, and therefore the metabolism of propranolol in the small intestine could be almost negligible in this condition. Thus, the intestinal absorption process of propranolol seems to be not altered by the induction of ARF.

Effect of Acute Renal Failure on Hepatic Blood Flow

For a drug with a high hepatic extraction ratio such as propranolol, an alteration of hepatic blood flow causes a significant effect on its phar-

TABLE II. *Pharmacokinetic Parameters after Intravenous Administration of Propranolol (12.5 mg/kg) in Control and Uranyl Nitrate-Treated Rats*

Parameters	Control	Uranyl nitrate
<i>A</i> ($\mu\text{g/ml}$)	1.30 ± 0.23	1.54 ± 0.11
<i>B</i> ($\mu\text{g/ml}$)	1.58 ± 0.31	1.35 ± 0.06
α (min^{-1})	0.354 ± 0.106	0.245 ± 0.053
β (min^{-1})	0.0093 ± 0.0017	0.0063 ± 0.0015
Vd_{ss} (l/kg) ^{a)}	9.39 ± 2.68	8.81 ± 0.43
<i>AUC</i> ($\mu\text{g} \cdot \text{min/ml/kg}$)	727.6 ± 77.4	1038.4 ± 115.8
CL_{sys} (ml/min/kg) ^{b)}	72.1 ± 7.2	55.6 ± 9.8

Results are given as the mean $\pm$ S.E. (control: $n = 5$, uranyl nitrate: $n = 4$).

a) The apparent volume of distribution at steady state (Vd_{ss}) was calculated by the equation of $Vd_{ss} = \text{dose} \cdot (A/\alpha^2 + B/\beta^2) / (A/\alpha + B/\beta)^2$

b) The systemic clearance (CL_{sys}) was calculated by the equation of $CL_{sys} = \text{dose} / (A/\alpha + B/\beta)$.

TABLE III. *Absorption of Propranolol from Rat Small Intestine in Situ*

Time (min)	Control	% disappeared	Uranyl nitrate
3	66.7 ± 2.2		74.9 ± 4.5
5	76.5 ± 1.6		83.8 ± 3.0
15	87.2 ± 1.9		92.0 ± 3.7

Results are given as the mean $\pm$ S. E. of at least three experiments.

macokinetics.¹⁸⁾ Then, the hepatic blood flow rate was measured by a continuous ICG infusion method and the results are given in Table V. Hepatic blood flow, expressed either in ml/min or in ml/min per g of liver, did not significantly differ between control and ARF.

Hepatic Clearance of Propranolol

In order to clarify the effect of ARF on the hepatic clearance of propranolol, the elimination of propranolol from the perfused rat liver preparation was investigated. The disappearance of propranolol from the perfusate followed biexponential curves and significantly higher concentrations of propranolol were observed in the recirculation of rat livers with ARF compared to control livers (Fig. 3). The viability of perfused liver was checked by the bile flow rate and GOT levels in the perfusate at the end of the experiment. The bile flow was constant and did not sig-

nificantly differ between control (6.51 ± 0.49 $\mu\text{l}/\text{min}$) and ARF (6.38 ± 0.42 $\mu\text{l}/\text{min}$). GOT levels were quite low both in control (10.8 ± 1.3 IU/l) and in ARF (6.6 ± 2.0 IU/l) and no significant difference was observed between two groups. The apparent hepatic clearance of propranolol (CL_h) was calculated by the equation, $\text{CL}_h = \text{dose}/\text{AUC}$, and decreased from 3.16 ± 0.11 ml/min in control to 2.11 ± 0.37 ml/min in ARF ($p < 0.01$) at the dose of 12.5 mg/30 ml reservoir. Similar results were obtained at the dose of 6.25 mg/30 ml reservoir; CL_h was 6.03 ± 0.29 and 4.42 ± 0.47 ml/min in control and ARF, respectively ($p < 0.025$). The average binding of propranolol to the perfusate was determined from samples at the end of the experiment using the ultrafiltration technique and was 56.6 ± 2.0 and $56.5 \pm 1.7\%$ in control and ARF, respectively. The calculated intrinsic

TABLE IV. *Transfer of Propranolol in Everted Sacs of Rat Small Intestine*

	Region of intestine	Control	Uranyl nitrate
Mucosal level ($\mu\text{g}/\text{ml}$)	Jejunum	77.4 ± 0.4	77.3 ± 0.9
	Ileum	79.0 ± 1.1	80.9 ± 0.9
Tissue level ($\mu\text{g}/\text{g}$ tissue)	Jejunum	90.6 ± 6.9	105.3 ± 7.8
	Ileum	100.2 ± 9.0	100.3 ± 7.3
Serosal level ($\mu\text{g}/\text{ml}$)	Jejunum	0.69 ± 0.20	1.04 ± 0.31
	Ileum	1.14 ± 0.49	0.82 ± 0.13

The everted sac (20 cm) was incubated in the mucosal fluid, 10 ml of pH 6.5 isotonic buffer solution containing propranolol (initial concentration, 100 $\mu\text{g}/\text{ml}$) for 15 min at 37°C. Results are given as the mean $\pm$ S.E. ($n = 6$).

TABLE V. *Hepatic Blood Flow by a Continuous ICG Infusion Method in Control and Uranyl Nitrate-Treated Rats*

	Control	Uranyl nitrate
Extraction ratio	0.362 ± 0.046	0.346 ± 0.023
Hepatic clearance (ml/min/g liver)	0.243 ± 0.018	0.270 ± 0.011
Hepatic blood flow (ml/min)	11.6 ± 1.0	11.3 ± 0.6
Hepatic blood flow (ml/min/g liver)	1.27 ± 0.13	1.48 ± 0.09

Results are given as the mean $\pm$ S.E. (control: $n = 5$, uranyl nitrate: $n = 7$).

hepatic clearance of unbound drug (CL'_{int}) was 26.8 ± 2.3 ml/min in control and 16.0 ± 2.3 ml/min in ARF ($p < 0.01$).

DISCUSSION

The results of the present study demonstrated the increased availability of orally administered propranolol in rats with uranyl nitrate-induced ARF. These results are consistent with clinical observations of Lowenthal *et al.*⁷⁾ and Bianchetti *et al.*⁸⁾ in patients with chronic renal failures, though our studies were performed in acute disease model.

In this study, uranyl nitrate was selected to induce ARF because it is not a known hepatotoxin and it has the advantages of technical simplicity, a high survival rate and relatively consistent diminution of renal function.¹⁹⁾ Uranyl nitrate-treated rats showed a gradual increase of plasma

concentrations of BUN and creatinine for 5 d. Giacomini *et al.* also reported a progressive renal dysfunction of rats after uranyl nitrate injection (5 mg/kg, *i.v.*) for 6 d.¹⁹⁾ In the present study, we used the rats 3 d after uranyl nitrate-treatment as the model of ARF in order to investigate the propranolol disposition at relatively early stage in the course of ARF. The increased plasma concentration of propranolol after oral administration was found in rats with ARF not only on day 3, but also on day 2 and 5 (data not shown).

It is an important problem whether the increased propranolol availability is due to the renal disease state or to the direct effect of uranyl nitrate. As is evident from Table I, plasma GOT and GPT did not increase above normal levels by the injection of uranyl nitrate. No significant difference was found in bile flow rate or perfusate GOT levels in liver perfusion studies between control and uranyl nitrate-treated rats. These results suggest that the physiological function of rat liver was not damaged by uranyl nitrate injection. Furthermore, we have some evidences that similar changes of propranolol disposition could have occurred in other renal disease model, *i.e.* in partly nephrectomized rat.²⁰⁾ Consequently, observed increase in propranolol availability can be considered to be due to the effect of renal disease.

Increased plasma concentrations of oral propranolol could result either from (1) increased absorption from the small intestine, (2) decreased removal by the liver and/or the intestinal mucosa during initial transit from the intestine to the general circulation (presystemic elimination), or (3) decreased rate of removal after entry into the general circulation (systemic clearance).

There are some reports indicating the alteration of intestinal absorption in renal disease.^{6,21)} Chan *et al.* reported the increased initial rate of pindolol absorption in patients with chronic renal failure.²¹⁾ Therefore, we investigated the absorption of propranolol from rat small intestine. The results confirm that propranolol is

FIG. 3. Disappearance of Propranolol from Perfusate Plasma in Rat Liver Recirculation

The liver was perfused at a constant flow rate of 15 ml/min and propranolol was added to the 30 ml of reservoir at the dose of 6.25 mg (Δ , $\blacktriangle$) or 12.5 mg ($\circ$, $\bullet$). Each point and vertical bar represent the mean $\pm$ S.E. of at least five experiments. $\circ$, Δ : livers of control rats, $\bullet$, $\blacktriangle$: livers of uranyl nitrate-treated rats.

almost completely absorbed and no significant difference was found between control and ARF both *in situ* and *in vitro* studies (Table III, IV); hence, change in absorption could not account for the changes in oral availability.

The studies of systematic clearance by intravenous administration showed no significant differences between control and ARF (Fig. 2, Table II). By exclusion of changes in absorption and systemic clearance, the change in oral availability must reflect a change in presystemic clearance.

The organs that may be potentially involved in the presystemic elimination of drugs are the intestine and the liver. Suzuki *et al.* demonstrated that the major site for presystemic metabolism of propranolol in rat is the liver.²²⁾ No intestinal metabolism of propranolol was found in dog²³⁾ and man.³⁾ In this study, the metabolism in the rat small intestine was negligible. The increased availability of propranolol, therefore, must result from the decreased hepatic clearance.

It has been recognized that hepatic blood flow, the intrinsic ability of the overall elimination process (intrinsic clearance), protein binding of drug in blood and the anatomical arrangement of the hepatic circulation are the major biological determinants of hepatic drug clearance.¹⁸⁾ Since no difference in hepatic blood flow and plasma protein binding was found between control and ARF, the decreased hepatic clearance should be considered to reflect a change in the intrinsic clearance.

These results can be also interpreted by the well-stirred model.^{18,24)} According to this model, AUC of propranolol following intravenous administration (AUC_{iv}) can be expressed as

$$AUC_{iv} = \frac{\text{Dose} (Q + f \cdot CL_{int})}{Q \cdot f \cdot CL_{int}}$$

where Q is the hepatic blood flow and f is the unbound fraction of drug in the blood. When CL_{int} is much larger than flow, AUC_{iv} is essentially equal to Dose/Q indicating AUC_{iv} is limited by blood flow. Observed data that both AUC_{iv} and hepatic blood flow did not differ be-

tween control and ARF are consistent with the predictions of the well stirred model. On the other hand, AUC of propranolol following oral administration (AUC_o) can be given as

$$AUC_o = \frac{\text{Dose}}{f \cdot CL_{int}}$$

Thus, AUC_o depends only on intrinsic clearance of free drug, drug binding and dose, and is independent of flow. Consequently, increased AUC_o of propranolol observed in ARF must be due to the decrease in CL_{int} .

The decreased CL_{int} was confirmed by the liver perfusion studies, where perfusate constituent (5% bovine serum albumin and no α_1 -acid glycoprotein) and flow rate (15 ml/min) could be controlled. In this study, tolerably high doses of propranolol (6.25 and 12.5 mg) were administered to the reservoir, so that the hepatic clearance of propranolol was not flow rate-limited.

It is well known that in patients with terminal liver failure, the kidney may also be involved, producing a condition known as the hepatorenal syndrome. On the other hand, there are some information on the influence of renal disease on the liver function.²⁵⁾ Turner *et al.* observed a reduction in the hepatic microsomal enzyme activity in uremic rats.²⁶⁾ Leber and Schutterle reported the diminished content of microsomal P-450 in uremic rats.²⁷⁾ Bowmer *et al.* reported the decreased hepatic uptake of ICG²⁸⁾ and bromosulphophthalein²⁹⁾ in rats with renal failure. The present data support the hypothesis that renal failure can disturb the pharmacokinetics of drugs not only by reducing the renal excretion but also by affecting the hepatic elimination.

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