Pharmacokinetics of Theophylline and Phenobarbital during Peritoneal Dialysis Compared with Intestinal Dialysis in Rats

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The transfer rates of theophylline and phenobarbital from blood into the peritoneal cavity were investigated after their intravenous administrations at a dose of 10 mg/kg each in rats. Appreciable amounts of both drugs were transported into the dialysate with their transfer rates decreasing as the serum concentrations declined. The average amount of theophylline transferred into the dialysate was 17% and 24% of dose in 2 and 4 h, respectively, while that of phenobarbital was 13% and 45% of dose in 2 and 8 h, respectively. The amounts appeared to be greater than those transported into the intestinal lumen which was previously reported by the authors. Peritoneal dialysis decreased the serum half-life and the area under the serum concentration–time curve (*AUC*) value of theophylline from 2.1 to 1.5 h and from 38 to 26 μg·h/ml, respectively and increased the total body clearance by 47% as compared with the control. The dialysis also decreased the serum half-life and the *AUC* value of phenobarbital from 8.3 to 5.3 h and from 116 to 83 μg·h/ml, respectively and increased the total body clearance by 112% as compared with the control. Overall, the effectiveness of peritoneal dialysis in removing theophylline and phenobarbital appears to be not very different from that of intestinal dialysis with oral activated charcoal which has been previously reported by the authors in spite of the difference in transport into the intestinal lumen and peritoneum.

Keywords theophylline; phenobarbital; peritoneal dialysis; gastrointestinal dialysis; pharmacokinetic parameter; transfer rate; rat

Various hemopurification methods including the oral administration of activated charcoal to inhibit the absorption of an excess amount of drugs from the gastrointestinal (g.i.) lumen into the blood, have been developed and used in the treatment of acute drug overdoses.

In acute drug overdoses, hemoperfusion, hemodialysis, peritoneal dialysis, and combined hemodialysis–hemoperfusion have all been used as methods of hemopurification.[1,2] The g.i. mucous membranes have a large surface area (when overall membranes including the stomach and the small and large intestines are considered). In particular, the total absorptive and/or exsorptive area of the small intestine has been calculated to be about 200 m^2 in an adult human, and is far larger than that of the peritoneal membrane.[3] Accordingly, if the g.i. mucous membrane shows its ability to the full as a dialysis membrane, a considerable amount of drug could be expected to enter by passive diffusion in drug overdoses.

We have previously reported that intravenously administered drugs are more or less transported into the small intestinal lumen and the bile of rats, and that drugs can be removed by adsorption onto orally administered activated charcoal.[4-8] However, g.i. dialysis by the oral administration of activated charcoal has not been clearly established as an effective means of removing drugs which have been parenterally administered or have already been absorbed into systemic circulation from the g.i. tract. It is very important to evaluate g.i. dialysis for comparison with other means of hemopurification which have been established. The present study was, therefore, undertaken to compare the removal efficiency of peritoneal dialysis with that of g.i. dialysis previously reported in rats.[6] Theophylline and phenobarbital were selected for this study, since their toxicity can be severe in drug overdoses.

Experimental

Materials Aminophylline (Neophylline®) and theophylline were purchased from Eisai Co., Ltd., Tokyo, Japan and Wako Pure Chemical Industries, Ltd., Osaka, Japan, respectively. Phenobarbital sodium was obtained from Daiichi Seiyaku Co., Ltd., Tokyo, Japan. All other chemicals used in this study were of analytical grade.

Peritoneal Dialysis Male Wistar albino rats weighing 220—360 g were fasted overnight with free access to water. They were then anesthetized by an intraperitoneal injection of ethyl carbamate (1.2 g/kg). A small incision was made in the abdomen and 20 ml of lactated Ringer's solution (37 °C) was injected into the peritoneal cavity as the solution for dialysis. The dialysate was exchanged from a corresponding volume of a new Ringer's solution every 15 min for the initial 2 h and then hourly for the next 2—4 h (theophylline) or 2—8 h (phenobarbital). In the control group of rats, the same operation as for peritoneal dialysis was performed without injection of the Ringer's solution. Aminophylline and phenobarbital were injected over about 1 min at a dose of 10 mg/kg each into the right femoral vein. Blood samples (0.2 ml) were taken at the mid-point of the dialysate collection time through a cannula introduced into the left femoral artery.

Analytical Methods Theophylline and phenobarbital levels in the serum and dialysate were determined by high-pressure liquid chromatography using methods previously reported.[4,5]

Pharmacokinetic Analysis A one compartment model was used for pharmacokinetic analysis. The apparent volume of distribution (V_d = dose/C_0), the total body clearance ($Cl_{tot} = k_{el} V_d$), and the area under the serum concentration–time curve extrapolated to time infinity ($AUC = C_0/k_{el}$) were also calculated, with C_0 being the extrapolated initial serum concentration at time zero, and k_{el} being the elimination rate constant. The dose of theophylline was calculated by multiplying the ratio of the molecular weight of theophylline to that of aminophylline. The unpaired *t*-test was used to assess the pharmacokinetic parameters.

Results and Discussion

Drug Transport into the Peritoneal Cavity The transfer rates of theophylline and phenobarbital from the blood into the dialysate across the peritoneal membrane were examined after their intravenous administrations at a dose of 10 mg/kg each in rats (Fig. 1). Both drugs were appreciably transported from the blood into the peritoneal cavity with their transfer rates decreasing as the serum concentrations declined. The average amount of theophylline transferred into the dialysate was 17% and 24% of dose in 2 and 4 h, respectively, while that of phenobarbital was 13% and 45% of dose in 2 and 8 h, respectively.

In the previous *in situ* single-pass perfusion study, it was found that 12—14% of theophylline[4] and 6% of phenobarbital[5] were exsorbed into the intestinal lumen,

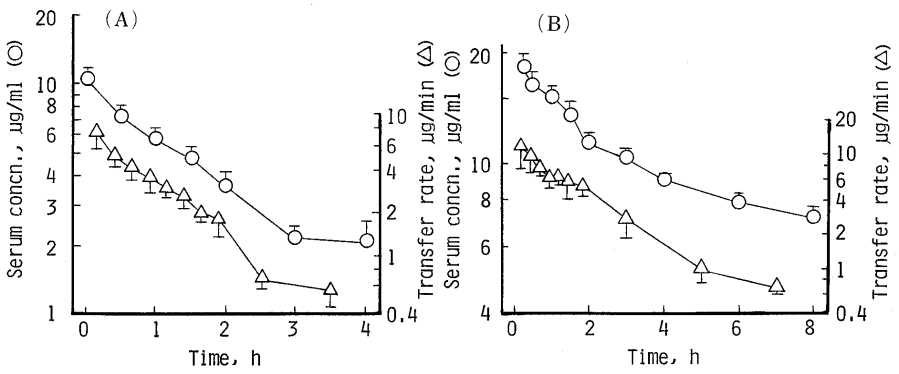

Fig. 1. The Serum Concentration of Theophylline and Phenobarbital and Their Transfer Rates from the Blood into the Peritoneal Cavity after Intravenous Administration of Aminophylline and Phenobarbital at a Dose of 10 mg/kg Each to Rats

Each point represents the mean ± S.E.M. of 4 rats. (A) theophylline, (B) phenobarbital.

TABLE I. Pharmacokinetic Parameters of Theophylline and Phenobarbital during Peritoneal Dialysis Following Intravenous Administration of the Drugs at a Dose of 10 mg/kg to Rats

Pharmacokinetic parameters	Theophylline[a]		Phenobarbital	
	Control	Peritoneal dialysis	Control	Peritoneal dialysis
$t_{1/2}$ (h)	2.05 ± 0.96	1.45 ± 0.04[b]	8.31 ± 0.92	5.28 ± 0.77[b]
V_d (ml/kg)	739 ± 45.3	848 ± 59.7	557 ± 49.3	589 ± 44.5
Cl_{tot} (ml/kg/h)	279 ± 27.9	409 ± 38.0[b]	37.4 ± 7.66	79.4 ± 5.01[c]
AUC (μg·h/ml)	38.0 ± 1.46	26.3 ± 1.82[c]	116 ± 8.95	82.9 ± 2.25[c]

Each value represents the mean ± S.E.M. of 4 rats. *a*) Aminophylline was administered at a dose of 10 mg/kg. *b*) $p<0.05$, *c*) $p<0.01$.

and only 0.2% of theophylline and 0.5% of phenobarbital were excreted into the bile in 2 h after the intravenous administration of the drugs. In the present study, the percentages of the intravenous doses of theophylline and phenobarbital transported into the peritoneal cavity appeared to be greater than those transported into the intestinal lumen.

It is known that most drugs are transported into the peritoneal cavity or g.i. lumen by diffusion along concentration gradients. Our data also showed that the transfer rates of both drugs from the blood into the dialysate reflected the serum level. However, transport of both drugs into the small intestine appear to be less than those into the peritoneum in spite of the fact that the small intestine has a much larger surface area than the peritoneal membrane. Such a difference in transport of both drugs between the peritoneal and intestinal membranes can be due to the difference in the morphological factors of the membrane, such as its thickness. However, when considered as a whole, an appreciable amount of drugs would be expected to enter the g.i. lumen since they may be exsorbed into not only the small intestine but also the overall digestive tract such as the oral cavity, the esophagus, and the stomach.

Effect of Peritoneal Dialysis on the Pharmacokinetics of Both Drugs Table I shows the pharmacokinetic parameters of theophylline and phenobarbital during peritoneal dialysis in rats. Peritoneal dialysis decreased the serum half-life and the *AUC* value of theophylline to 71% and 69%, respectively, compared with the control. Total body clearance showed an increase of 47% as compared with the control. The volume of distribution was not significantly different between the control and the dialysis. The peritoneal dialysis also decreased the serum half-life and the *AUC* value of phenobarbital to 64% and 71%, respectively, while the total body clearance increased to 212% in comparison with the control.

Our previous study showed that the g.i. dialysis with oral activated charcoal caused similar changes in the disposition of both drugs.[6] Treatment with the oral activated charcoal decreased the serum half-life of theophylline from 4.6 to 2.8 h (61% decrease) and the *AUC* value from 138 to 88 μg·h/ml (64% decrease), respectively, while total body clearance increased from 67 to 101 ml/kg/h (51% increase) in comparison with the control.[6] The oral activated charcoal also decreased the serum half-life of phenobarbital from 8.5 to 5.7 h (67% decrease) and the *AUC* value from 184 to 119 μg·h/ml (65% decrease), while total body clearance increased from 50 to 77 ml/kg/h (53% increase) *versus* the control.[6] These results suggest that g.i. dialysis with oral activated charcoal can remove intravenously administered theophylline and phenobarbital to the same extent as the peritoneal dialysis in rats although there is the difference in transport into the intestinal lumen and peritoneum.

In conclusion, it appears that g.i. dialysis by the oral administration of activated charcoal may serve as a useful hemopurification method of similar efficacy to peritoneal dialysis. Furthermore, it may be a less expensive, more widely accessible, and safer mode of treatment than methods like hemoperfusion, peritoneal dialysis, and hemodialysis for performing hemopurification in theophylline and phenobarbital overdoses.

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