Increased Transport of Theophylline into Gastrointestinal Lumen and Gastrointestinal Dialysis by Activated Charcoal in Rats with Hepatic Cirrhosis

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The characteristics of exsorption and/or excretion of theophylline into the small intestinal lumen in rats with hepatic cirrhosis (HC rats) induced by carbon tetrachloride were investigated by an *in situ* single-pass perfusion technique. The serum concentrations of theophylline after i.v. administration of aminophylline (10 mg/kg) in the HC rats were significantly higher than those in normal rats during the experimental period. Moreover, the exsorption of theophylline from blood into the intestinal lumen was significantly increased in the HC rats compared with the normal rats. Treatments with oral activated charcoal reduced the serum theophylline levels in the HC rats. Consequently, gastrointestinal dialysis by oral administration of activated charcoal may be a useful method to remove poisonous drugs from the blood in patients with hepatic failure (including cirrhosis), which decreases the systemic clearance.

Keywords theophylline; hepatic cirrhosis; activated charcoal; gastrointestinal dialysis; exsorption; pharmacokinetics; biliary clearance

Introduction

Recently, it has been noted that the clearance of intravenously administered drugs is accelerated by orally administered activated charcoal.[1,2] The mechanism of this effect was shown in our previous study[3] to be the adsorption onto charcoal of drugs which had been transported from the blood into the gastrointestinal (GI) tract through the GI membrane (exsorption) and/or *via* the biliary tract. Therefore, when GI dialysis by oral administration of activated charcoal is applied for hemopurification in drug intoxication, it is desirable for the drug to be transported in large quantities into the GI lumen.

The clearance of theophylline in man had been shown to be decreased by hepatic cirrhosis,[4] congestive heart failure[5] and coadministration of some drugs.[6] These effects are likely to be due to changes in liver blood flow and metabolism of theophylline since most of the drug (about 90%) is biotransformed by the liver to metabolites.[6] Such conditions which inhibit hepatic biotransformation of theophylline cause the drug to accumulate in the body and are likely to cause theophylline poisoning. There are few reports on the transport of the drug from the blood into the intestinal lumen in a disease state with abnormal liver function to provide basic data for the application of GI dialysis.

The present study was designed to investigate the characteristics of transport of theophylline into the GI lumen and to evaluate the effect of oral activated charcoal on the clearance of the drug in rats with hepatic cirrhosis (HC rats).

Experimental

Materials Aminophylline (Neophylline®) was purchased from Eisai Co., Tokyo. Activated charcoal was obtained from Inuhinode Seiyaku Co. Osaka, and its particle size used in this study was less than 62 μm. All other reagents used were of analytical grade.

Animals Wistar strain male rats, weighing 178—445 g, were used in the present studies. Hepatic cirrhosis in rats was induced by subcutaneous injection of carbon tetrachloride dissolved in an equal volume of olive oil at the dose of 4 ml/kg twice a week for eight successive weeks. The experiments on the HC rats were performed at 48 h after the last treatment. The development of hepatic dysfunction was monitored by measurement of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), total protein and albumin with the RABA Super Kit® (Chugai Pharmaceutical Co., Tokyo).

Exsorption Study Intestinal exsorption experiments were performed by the *in situ* single-pass perfusion technique reported previously.[3] Samples of perfusate, blood and bile were collected periodically.

***In Vivo* Study** The rats were fasted overnight with free access to water. In the case of the treatment with activated charcoal, activated charcoal suspended in water (150 mg/ml) was administered orally at an initial dose of 300 mg at time zero and additional doses of 150 mg at 1, 2, 3, and 4 h after the dose of aminophylline. In the case of the control experiments, water corresponding to the volume of activated charcoal used was administered orally at each dosing time.

Analytical Method Theophylline in the serum, bile and perfusate was determined by high pressure liquid chromatography with 8-chlorotheophylline as an internal standard.[3]

Pharmacokinetic Analysis Apparent intestinal and biliary clearance values were calculated as described previously.[3] The elimination rate constant (k_{el}), the serum half-life ($t_{1/2}$), the apparent volume of distribution (V_d), the total body clearance (Cl_{tot}) and the area under the serum concentration–time curve from zero time to infinity ($AUC_{0-\infty}$) were determined by a nonlinear least-squares regression analysis assuming a one compartment model. The unpaired *t*-test was used to assess the effect of charcoal treatment on the pharmacokinetic parameters. The dose of theophylline was calculated by converting the molecular weight of aminophylline into that of theophylline.

Results and Discussion

Figure 1 shows the results following i.v. administration of aminophylline (10 mg/kg) to the normal and HC rats studied by the *in situ* single-pass perfusion technique. The

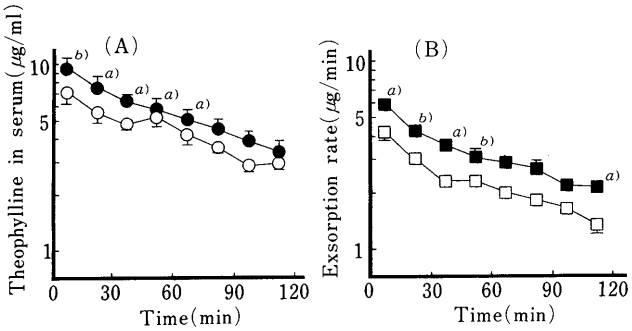

Fig. 1. The Concentration of Theophylline in the Serum and the Exsorption Rate of Theophylline into the Perfusate after i.v. Administration of Aminophylline (10 mg/kg) to Normal Rats (○ □) and Rats with Hepatic Cirrhosis (●, ■) Studied by the *in Situ* Single-Pass Perfusion Method

(A), serum; (B), perfusate. The perfusate was composed of isotonic phosphate buffer, pH 6.0. Each point represents the mean ± S.E.M. of 4 rats. *a)* $p<0.05$, *b)* $p<0.01$.

serum concentrations of theophylline in the HC rats were significantly higher than those in the normal rats during the experimental period. Moreover, the exsorption rate of the drug into the perfusate in the HC rats was larger than that in the normal rats.

The amount of theophylline exsorbed into the intestinal lumen in the HC rats was 13.4% of the dose and significantly larger than the value of 8.75% of the dose in the normal rats in 2 h. On the other hand, the amounts of theophylline excreted into the bile were 0.33% and 0.35% of the dose in the normal and HC rats, respectively, *i.e.*, much less than the amounts of the drug exsorbed into the perfusate. These results suggest that the exsorption from the blood into the intestinal lumen is a much more important transfer route than the biliary excretion in the case of theophylline, particularly in the HC rats.

It is known that most drugs are exsorbed into the GI lumen due to concentration gradients between the blood (a region of a higher drug concentration) and the GI lumen (a region of a lower drug concentration) by passive diffusion. Therefore, the delayed elimination of serum theophylline in the HC rats which resulted in the higher serum level may promote exsorption into the GI lumen to compensate for the poor hepatic metabolism. As another possible explanation for the finding, it may be considered that the permeability of the GI membrane has changed in the disease state.[7] Our results showed that the apparent intestinal clearance of theophylline tended to increase slightly in the HC rats (82.9 ml/h/kg) compared with the normal rats (74.9 ml/h/kg) although a statistically significant difference was not observed between the two groups of rats. Thus, the effect of activated charcoal on pharmacokinetic behavior of theophylline was investigated in the present study only in the HC rats, since hepatic cirrhosis decreased the systemic clearance and moreover caused increased exsorption of the drug as compared with the normal rats.

The pharmacokinetic parameters after i.v. administration of aminophylline (10 mg/kg) in the HC rats are shown in Table I. With oral administration of activated charcoal, $t_{1/2}$ and $AUC_{0-\infty}$ were decreased to 52.4% and 62.6%, respectively, while Cl_{tot} was increased to 171% of the corresponding control. The V_d values were not significantly different between the treated and control rats. Our previous data showed that with the charcoal treatment $t_{1/2}$ and $AUC_{0-\infty}$ were decreased to 61.3% and 63.7%, respectively, while Cl_{tot} was increased to 152% of the corresponding controls after i.v. administration of the drug (10 mg/kg) in normal rats.[8] Comparison of the present study with the previous results showed that the effect of oral administration of activated charcoal tended to be greater in HC rats than in normal rats. This means that the percentage of GI clearance caused by charcoal with respect to total body clearance of the drug will increase as the endogenous clearance decreases if activated charcoal produces a constant GI clearance since the total clearance of a drug during treatment with activated charcoal is the sum of the normal endogenous clearance (by metabolism or renal excretion) and clearance through the GI tract by adsorption on charcoal.[9]

TABLE I. Pharmacokinetic Parameters of Theophylline after i.v. Administration to Rats Suffering from Hepatic Cirrhosis with or without Treatment with Activated Charcoal

Parameter (unit)		Control	Treatment with activated charcoal
C_0	(μg/ml)	12.4±0.58	15.6±1.63
k_{el}	(h^{-1})	0.161±0.01	0.339±0.073[a]
$t_{1/2}$	(h)	4.38±0.28	2.29±0.40[b]
V_d	(ml/kg)	634 ±40.6	518 ±76.7
Cl_{tot}	(ml/h/kg)	103 ±13.7	176 ±52.6
$AUC_{0-\infty}$	(μg·h/ml)	78.9±7.22	52.2±11.5

Each value represents the mean±S.E.M. of 5 rats. *a*) $p<0.05$. *b*) $p<0.01$.

In conclusion, exsorption of theophylline from the blood into the GI tract was greater in the HC rats than in the normal rats. Therefore, oral administration of activated charcoal may be useful to shorten the period of intoxication in a patient with hepatic failure (including cirrhosis) in the case of theophylline poisoning. Moreover, since the endogenous clearance of drug is generally decreased in the state of drug poisoning owing to the renal and/or hepatic dysfunction which may result from the drug poisoning, GI dialysis by oral administration of activated charcoal may play an important role for removal of the poisonous drug from the blood.

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