Transport to Intestinal Lumen and Peritoneal Cavity of Intravenously Administered Aprindine in Rats

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Transfer of aprindine from the blood into the intestinal lumen or into the peritoneal cavity was examined after intravenous administration of the drug at a dose of 5 mg/kg in rats. The amount of the drug transferred from the blood into the intestinal lumen was much greater than into the peritoneal cavity. The average amounts of aprindine transported into the intestinal lumen and the peritoneal cavity were 0.12 and 0.03% of the dose (5 mg/kg) in 120 min, respectively. Thus, a notable difference in the clearance values of the drug was obtained between the intestinal lumen (14.8 ml/h) and the peritoneal cavity (4.94 ml/h). The net water flux showed that secretion predominated in the peritoneal transport while absorption overbalanced secretion in the intestinal transport. It seems likely that a solvent drag effect by water movement did not contribute much to the transport of aprindine from the blood to the intestinal lumen or the peritoneal cavity. The differences in transport across the two membranes could be due to differences in the surface area and other geometrical factors. Differences could also be due to a difference in the pharmacologic effects of the drug which causes a decrease in tissue splanchnic perfusion.

Keywords aprindine; intestinal lumen; peritoneal cavity; intestinal clearance; transfer rate; serum concentration; rat; solvent drag; water movement

Introduction

Aprindine is an antiarrhythmic drug with efficacy in the management of ventricular and supraventricular arrhythmia.¹⁾ The drug exhibits a narrow therapeutic range and a marked interindividual variability in the steady state.¹⁾ Moreover, it has displayed non-linear pharmacokinetic behavior.²⁾ Thus, it is a significant drug in view of overdoses.

In acute overdoses, orally administered activated charcoal has been employed to inhibit the absorption of excess drugs from the gastrointestinal (g.i.) lumen into the blood. Recently, it has been noted that the clearance of drugs which were parenterally administered or were already absorbed into the systemic circulation was accelerated by orally administered activated charcoal.^{3–5)} The g.i. mucous membranes have a large surface area when considered as a whole. In particular, the total absorptive and/or exsorptive area of the small intestine has been calculated to be about 200 m² in an adult human, and is far larger than that of the peritoneal membrane (about 2 m²).⁶⁾ Accordingly, if the g.i. mucous membranes can act as a dialysis membrane, a considerable amount of drug would be expected to enter the g.i. lumen by passive diffusion in drug overdoses. However, g.i. dialysis has not yet been studied as extensively as peritoneal dialysis in spite of involvement of a similar mechanism *i.e.* diffusion according to concentration gradients between the blood (a region of a higher drug concentration) and the g.i. lumen or the peritoneal cavity (a region of a lower drug concentration).

The present study was thus undertaken to compare the removal efficacy of g.i. dialysis with that of peritoneal dialysis, which has been generally established as a valuable means of hemopurification in drug overdoses.

Experimental

Materials Aprindine hydrochloride was kindly supplied by Mitsui Pharmaceuticals, Inc. (Tokyo, Japan), and imipramine hydrochloride was purchased from Nakarai Tesque (Kyoto, Japan). Scintillation fluid (Instagel) was from United Technologies (Packard, Illinois, U.S.A.). All other chemicals used in this study were of analytical grade.

Transfer Experiments Male Wistar rats, weighing 220–290 g, were

fasted overnight with free access to water. Intestinal exsorption experiments were performed using an *in situ* single-pass perfusion technique reported previously.⁷⁾ Lactated Ringer's solution (pH 6.5, 37°C) was perfused at a rate of 1.3 ml/min from the duodenum through the small intestine to the ileocecal junction using a perfusion pump. Aprindine was injected over about 1 min at a dose of 5 mg/kg into the right femoral vein. After injection, blood samples and dialysate were collected periodically. In the case of peritoneal transfer experiments, a small incision was made in the abdomen and 20 ml of lactated Ringer's solution (37°C) was injected into the peritoneal cavity. The dialysate was exchanged for a corresponding volume of new dialysate every 15 min. The procedure for administration of the drug and the collection time of samples were the same as in the *in situ* single-pass perfusion experiments.

Water Movement Water movement experiments were performed in the same manner as in the aprindine transfer experiments above. The rate of water movement from the blood into the g.i. lumen or peritoneal cavity and from the g.i. lumen or peritoneal cavity back to the blood was calculated from changes in concentrations in ³H₂O (0.74 MBq) in the dialysate. Phenol red (10 µg/ml) was used as a nonabsorbable marker. The equations used in the calculation were as follows:

$$\text{Flux}_{i,p \rightarrow b} = \frac{[\text{PhR}]_0}{[\text{PhR}]_t} \left(\frac{[^3\text{H}_2\text{O}]_0 - [^3\text{H}_2\text{O}]_t}{[^3\text{H}_2\text{O}]_0} \right) Q$$

$$\text{Flux}_N = \left(\frac{[\text{PhR}]_0}{[\text{PhR}]_t} - 1 \right) Q$$

$$\text{Flux}_{b \rightarrow i, p} = Q + \text{Flux}_N - \text{Flux}_{i, p \rightarrow b}$$

where $\text{Flux}_{i, p \rightarrow b}$ and $\text{Flux}_{b \rightarrow i, p}$ are water flux from intestinal lumen or peritoneal cavity to the blood and water flux from the blood to intestinal lumen or peritoneal cavity, respectively. Flux_N is net water flux. $[\text{PhR}]_0$ and $[\text{PhR}]_t$ are concentrations of phenol red in the dialysates at time 0 and *t*, respectively. $[^3\text{H}_2\text{O}]_0$ and $[^3\text{H}_2\text{O}]_t$ are concentrations of tritiated water at time 0 and *t*, respectively. *Q* is the flow rate of the perfusate or the volume instilled in the peritoneal cavity per time *t*.

Analytical Methods Aprindine levels in the serum and dialysate were determined by sensitive gas chromatography according to the method of Kawano *et al.*⁸⁾ using imipramine as the internal standard. A Shimadzu GC-RIA gas chromatograph (Kyoto, Japan) equipped with a surface ionization detector and a flexible fused-silica megabore column (DB-17, film thickness 1.0 µm, J & S Scientific, U.S.A.) was used. Helium was used as a carrier and make-up gas. The operating temperatures were set as follows: injection port, 270°C; column, 240°C; detector, 270°C. In the assessment of ³H₂O concentrations, 5 ml of Instagel scintillation fluid was added to 200 µl of dialysate and then radioactivity was determined. Phenol red was determined spectrophotometrically by absorbance at a wavelength of 550 nm after addition of 4 ml of 1 M sodium hydroxide to a 0.5 ml aliquot of dialysate.

Pharmacokinetic Analysis The intestinal and peritoneal clearance values of aprindine were calculated by dividing the overall amount of the

drug transferred into both dialysates in 120 min by the appropriate value for an area under the serum concentration time curve of the drug obtained over the same period of time. The unpaired *t*-test was used to evaluate significant differences.

Results

Transport of Aprindine Figure 1 shows the transfer rate of aprindine from the blood into the g.i. lumen and the peritoneal cavity following intravenous administration at a dose of 5 mg/kg in rats. Aprindine was appreciably transported from the blood into both the intestinal lumen and peritoneal cavity with its transfer rates decreasing as the serum concentrations declined. As shown in Fig. 1, the transfer rate into the intestinal lumen was considerably higher than the rate into the peritoneal cavity. The amount of drug transferred into the intestinal and peritoneal dialysates was 0.12 and 0.03% of the total dose in 120 min, respectively.

To express the ability of each system to remove aprindine, intestinal and peritoneal clearances were calculated. A notable difference in the clearance values of the drug was observed between the intestinal lumen and the peritoneal cavity. The intestinal and peritoneal clearance of the drug were 14.8 and 4.94 ml/h, respectively, the former being significantly higher.

Water Movement Table I shows water movement into the g.i. lumen and peritoneal cavity after intravenous administration of aprindine at a dose of 5 mg/kg. Water movement from the blood into the g.i. lumen was less than that from the blood into the peritoneal cavity. The net water flux showed that secretion predominated in the

Fig. 1. The Transfer Rate of Aprindine from the Blood into the Intestinal Lumen (○, □) and the Peritoneal Cavity (●, ■) after Intravenous Administration at a Dose of 5 mg/kg to Rats

Each point represents the mean $\pm$ S.E.M. of 4 rats. a) $p < 0.05$, b) $p < 0.01$.

TABLE I. Water Flux into the Intestinal Lumen or the Peritoneal Cavity after Intravenous Administration of Aprindine (5 mg/kg) to Rats

	Water flux from blood to intestinal lumen or peritoneal cavity (ml/h)	Water flux from intestinal lumen or peritoneal cavity to blood (ml/h)	Net water flux ^{a)} (ml/h)
Intestinal lumen	27.0 $\pm$ 1.19	31.5 $\pm$ 0.10	-4.51 $\pm$ 1.29
Peritoneal cavity	54.8 $\pm$ 1.71 ^{b)}	47.4 $\pm$ 1.46 ^{b)}	+7.38 $\pm$ 0.67 ^{b)}

Each value represents the mean $\pm$ S.E.M. of 4 rats. a) Positive (+) sign indicates secretion and negative (-) sign indicates absorption. b) $p < 0.01$.

peritoneal cavity, while absorption predominated in the intestinal lumen.

Discussion

Our results indicated that transport of aprindine into the intestine was greater than into the peritoneal cavity. Similar results have also been obtained using procainamide and *N*-acetylprocainamide, which have the same antiarrhythmic effect as aprindine.⁹⁾ We have previously shown that the amounts of both drugs transferred from the blood into the intestinal lumen were much greater than those into the peritoneal cavity. The average amounts of procainamide transferred in 2 h into the intestinal lumen and the peritoneal cavity were 12.7 and 1.7% of the total dose (10 mg/kg), respectively, while the same figures for *N*-acetylprocainamide were 3.5 and 1.4% of the total dose. Accordingly, it seems likely that in general, a smaller percentage of antiarrhythmic drugs are transferred into the peritoneal cavity than into the g.i. lumen. These results may support an early report that peritoneal dialysis is ineffective in enhancing the clearance of these drugs.¹⁰⁾

In general, the rate of transfer across a membrane depends on geometrical factors of the membrane such as its surface area and thickness and the distribution of blood vessels within it or upon the pharmacological effects of a drug. The small intestine has a much larger surface area than the peritoneal membrane, as mentioned in the introduction. As far as area is concerned, the intestine is more suitable as a permeable or exsorbable organ than the peritoneum. The rate of transfer of a drug also depends upon physicochemical factors such as the extent of binding to serum proteins, distribution volume, lipophilicity and molecular size of the drug. The extent of binding of a drug to serum proteins is an important factor in permeation since it is well known that only an unbound drug can permeate through capillary walls into the g.i. tract. The reason why aprindine was exsorbed into the g.i. tract or the peritoneal cavity to a lesser extent than procainamide might be explained by aprindine's extensive binding to a serum protein (94–97%).¹¹⁾ Furthermore, it is known that the apparent volume of distribution is considerably decreased in procainamide overdoses owing to a decrease in tissue splanchnic perfusion caused by hypotension.¹²⁾ Such a decrease in distribution volume in antiarrhythmic drugs may also reduce the transport of aprindine into the peritoneal cavity.

Several studies have demonstrated that the net water flux caused a drag effect on the permeability of some drugs.^{13–17)} For example, Kitazawa *et al.*¹⁵⁾ reported that absorption of sulfanilamide, sulfisoxazole, and metoclopramide increased with increasing transmucosal fluid movement from the lumen to the blood and decreased when the movement of water was directed from the blood to the lumen in rats. They have also reported that exsorption of sulfanilamide after intravenous administration was increased by increasing the tonicity of the perfusate, with the movement of water being directed from the blood to the lumen.¹⁸⁾

During perfusion with lactated Ringer's solution in the present study, the net water fluxes were from the g.i. lumen to the blood and from the blood to the peritoneal cavity (Table I). This indicates that the effect of solvent drag

upon permeability from the blood to the intestinal lumen is less than on permeability from the blood to the peritoneal cavity, if transport from the blood across both membranes is in fact enhanced in each drug by solvent drag. More definitive experiments may be necessary to confirm this solvent drag effect of a drug by water movement.

In conclusion, it was shown that the intestinal lumen exhibits an exsorption/excretion function for aprindine in rats. The present findings confirm previous observations that antiarrhythmic drugs such as procainamide,⁹⁾ *N*-acetylprocainamide⁹⁾ and disopyramide¹⁹⁾ are greatly transferred into the intestinal lumen. Consequently, it is expected that g.i. dialysis may be more useful than the peritoneal dialysis in the removal of antiarrhythmic drugs.

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