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Transport of Paraquat and Mexiletine from the Blood into the Rat Intestinal Lumen and Peritoneal Cavity

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Abstract—Transport of paraquat and mexiletine from the blood into the intestinal lumen and the peritoneal cavity was examined after their intravenous administration (paraquat: 20 mg kg^{-1}, mexiletine: 10 mg kg^{-1}) to rats. The average amounts of paraquat transferred into the intestinal lumen and the peritoneal cavity were 1·39 and 22·8% of the dose in 120 min, respectively. The average amounts of mexiletine transferred into the intestinal lumen and the peritoneal cavity were 6·1 and 2·5% of the dose in 120 min, respectively. The transfer rate of ^3H_2O into the peritoneal cavity after intravenous administration (1·85 MBq) was greater than that into the intestinal lumen. In view of the hydrophilic nature of paraquat cation, a solvent drag effect due to movement of water might contribute to transport of paraquat from the blood to the peritoneal cavity. Differences in transport behaviour across the two membranes could be due to differences in the geometrical factors such as the surface area and the distribution of blood vessels. Differences might also be due to differences in physicochemistry and pharmacological effects of both substances.

Paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) is a widely used herbicide. Poisoning with paraquat is frequently fatal. An antidote having an action specific to the herbicide is not known. Since paraquat is absorbed slowly, a large fraction probably remains in the gastrointestinal lumen for several hours after ingestion (Daniel & Gage 1966; Conning et al 1969). Consequently, decontamination of the gastrointestinal tract is most important. In paraquat poisoning procedures such as gastric lavage or whole bowel irrigation, and subsequently administration of activated charcoal or an ion exchange resin with cathartics (Van Dijk et al 1975; Okonek et al 1976) are used as methods of detoxification.

Recent studies have demonstrated that oral administration of activated charcoal can enhance clearance of a drug which has been parenterally administered or has already been absorbed into the systemic circulation from the gastrointestinal tract (Berlinger et al 1983; Arimori & Nakano 1986, 1987, 1988, 1989). This so-called gastrointestinal dialysis (Levy 1982) has been noted as one of a number of haemopurification methods such as haemoperfusion, haemodialysis, and peritoneal dialysis in poisoning. However, gastrointestinal dialysis by oral administration of activated charcoal has not yet been as extensively evaluated, as a means for removal of drugs, as other haemopurification procedures. We previously reported that transport of procainamide (Arimori et al 1990a), *N*-acetylprocainamide (Arimori et al 1990a) and aprindine (Arimori et al 1991) from the blood into the intestinal lumen was greater than that into the peritoneal cavity. Consequently, we expect that gastrointestinal dialysis by oral administration of activated charcoal may serve as a useful haemopurification method for these organic cations in overdoses.

The present study, therefore, extends our series of investigations on transport of toxic substances into the intestinal lumen and the peritoneal cavity, and was undertaken to determine how much paraquat is removed by gastrointestinal dialysis. An antiarrhythmic drug, mexiletine, was selected as a comparative cation since the transport of some antiarrhythmic drugs into both intestinal lumen and peritoneal cavity has been previously compared by us (Arimori et al 1990a, b, 1991).

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Materials and Methods

Materials

Paraquat dichloride was purchased from Sigma Chemical Co., St Louis, MO, USA. Mexiletine hydrochloride was kindly supplied by Nippon Boehringer Ingelheim Co. (Hyogo, Japan). ^3H_2O was purchased from New England Nuclear, MA, USA. Scintillation fluid (Instagel) was from United Technologies (Packard, IL, USA). All other chemicals used in this study were of analytical grade.

Transport experiments

Male Wistar rats, 200–320 g, were fasted overnight with free access to water. Intestinal and peritoneal transfer experiments were performed as described previously (Arimori et al 1990a, b). The rats were anaesthetized by intraperitoneal injection of ethyl carbamate (urethane) at a dose of 1·2 g kg^{-1}. We selected urethane since it has been reported that this anaesthetic produces splanchnic blood flow similar to that in conscious animals (Hiley et al 1978). Lactated Ringer's solution (pH 6·5, 37°C) was perfused at a rate of 1·3 mL min^{-1} from the duodenum through the small intestine to the ileocaecal junction using a perfusion pump. In the case of peritoneal transfer experiments, 20 mL of lactated Ringer's solution (37°C) was injected into the peritoneal cavity and the dialysate was changed for the corresponding volume of a fresh dialysate every 15 min. Paraquat (20 mg kg^{-1} as the dichloride) or mexiletine (10 mg kg^{-1} as hydrochloride salt) was injected over about 1 min into the right femoral vein. After injection, blood samples, perfusates and dialysates were collected periodically. Water transfer experiments were performed following intravenous administration of ^3H_2O

(1·85 MBq) in the same manner as those of paraquat and mexiletine.

Analytical methods

Paraquat in the serum and perfusate or dialysate was determined by second-order derivative spectroscopy (Nakano & Matsumoto 1989) and mexiletine by HPLC (Hamashima et al 1989). For assessment of ^3H_2O concentrations, 5 mL of Instagel scintillation fluid was added to the serum (100 μL) and dialysate (200 μL) and radioactivity was determined.

Pharmacokinetic analysis

Intestinal and peritoneal clearance values were calculated by dividing the overall amount of each substance transferred into both dialysates in 120 min by the corresponding value for an area under the serum concentration time curve of the compound, obtained over the same period of time. The unpaired *t*-test was used to evaluate significant differences.

Results

Transport of paraquat

Fig. 1 shows concentrations of paraquat in the serum and its transfer rates from the blood into the intestinal lumen and the peritoneal cavity following intravenous administration (20 mg kg^{-1}) to rats. Paraquat was appreciably transported from the blood into both intestinal lumen and peritoneal cavity with its transfer rate decreasing as the serum concentrations declined. The serum levels of paraquat in rats during intestinal perfusion were significantly higher than those during peritoneal dialysis. Moreover, the transfer rates of paraquat into the intestinal lumen were markedly smaller than those into the peritoneal cavity. The average amounts of the herbicide transferred into both intestinal and peritoneal dialysates were 1·39 and 22·8% of the dose in 120 min, respectively. A notable difference was also observed between the mean intestinal clearance value of 0·91 mL h^{-1} and the mean peritoneal clearance value of 20·5 mL h^{-1}.

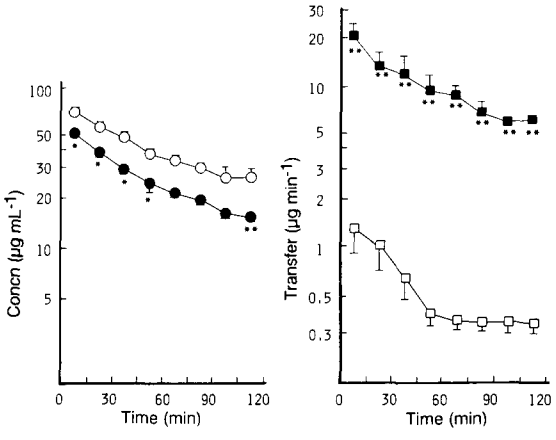

FIG. 1. Concentrations of paraquat in the serum (○) and its transfer rates from the blood into the intestinal lumen (□) during intestinal perfusion, and concentrations in the serum (●) and transfer rates from the blood into the peritoneal cavity (■) during peritoneal dialysis after intravenous administration of paraquat at a dose of 20 mg kg^{-1} to rats. Each point represents the mean ± s.e.m. of four rats. $*P<0·05$, $**P<0·01$.

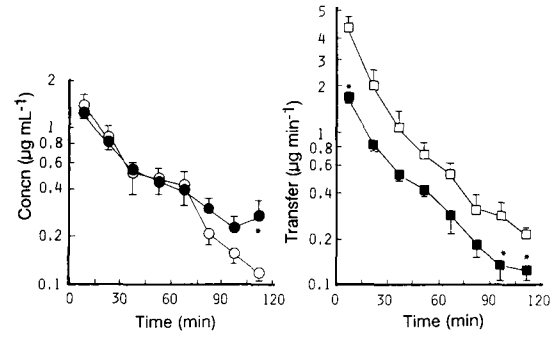

FIG. 2. Concentrations of mexiletine in the serum (○) and its transfer rates from the blood into the intestinal lumen (□) during intestinal perfusion, and concentrations in the serum (●) and transfer rates from the blood into the peritoneal cavity (■) during peritoneal dialysis after intravenous administration of mexiletine at a dose of 10 mg kg^{-1} to rats. Each point represents the mean ± s.e.m. of four rats. $*P<0·05$.

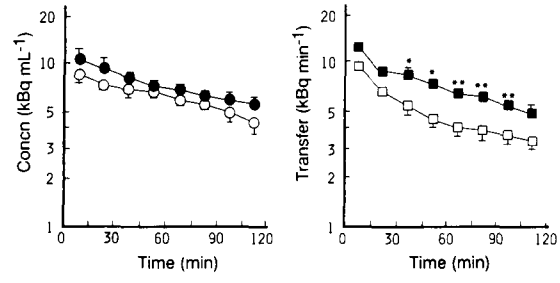

FIG. 3. Concentrations of ^3H_2O in the serum (○) and its transfer rates from the blood into the intestinal lumen (□) during intestinal perfusion and concentrations in the serum (●) and transfer rates from the blood into the peritoneal cavity (■) during peritoneal dialysis after intravenous administration of ^3H_2O (1·85 MBq) to rats. Each point represents the mean ± s.e.m. of four rats. $*P<0·05$, $**P<0·01$.

Transport of mexiletine

Fig. 2 shows concentrations of mexiletine in the serum and its transfer rates from the blood into the intestinal lumen and the peritoneal cavity following intravenous administration (10 mg kg^{-1}) to rats. There was little difference in the serum mexiletine levels between both groups during the first 60 min after starting the experiment, but thereafter the serum levels in rats during the intestinal perfusion tended to be lower than those during the peritoneal dialysis. The transfer rates of mexiletine into the intestinal lumen were significantly greater than those into the peritoneal cavity. The average amounts of the drug transferred into both intestinal and peritoneal dialysates were 6·1 and 2·5% of the dose in 120 min, respectively. The calculated mean intestinal clearance was 155 mL h^{-1} and the mean peritoneal clearance was 71·2 mL h^{-1}.

Transport of water

Fig. 3 shows the transfer rates of water from the blood into the intestinal lumen and the peritoneal cavity following intravenous administration of ^3H_2O at a dose of 1·85 MBq to rats. There was no significant difference in the serum levels of ^3H_2O between the groups, while the transfer rates into the intestinal lumen were significantly smaller than those into the

peritoneal cavity. The average amounts of ^3H_2O transferred into intestinal and peritoneal dialysates were 32·5 and 47·2% of the dose in 120 min, respectively.

Discussion

Our results indicate that there were wide differences in the transport of paraquat and mexiletine between the intestinal lumen and the peritoneal cavity. In general, a rate of transfer across membranes such as the intestinal and peritoneal membranes depends on geometrical parameters of the membrane such as its surface area and thickness, distribution of blood vessels within it, and physicochemical parameters such as the extent of binding to serum proteins, distribution volume and lipophilicity. Surface area of the small intestine (about 200 m^2 in man) is much larger than that of the peritoneal membrane (about 2 m^2 in man) and therefore the intestine would be expected to be a more permeable organ compared with the peritoneum. Accordingly, the fact that the intestinal lumen exhibited a more noticeable transfer function for mexiletine than the peritoneal cavity may be attributed to its large surface area.

The poor transport of mexiletine into the peritoneal cavity may also be explained by a decrease in tissue splanchnic perfusion by the antiarrythmic drug. It has been shown that the apparent volume of distribution of procainamide is considerably decreased during the poisoning owing to a decrease in tissue splanchnic perfusion caused by hypotension (Atkinson et al 1976). Such a decrease in distribution volume would further reduce transport of mexiletine into the peritoneal cavity. Atkinson et al (1976) reported that peritoneal dialysis contributed little to the removal of procainamide and *N*-acetylprocainamide, while haemodialysis could be valuable in removing both substances. In contrast, the phenomenon may facilitate transport of mexiletine more into the gastrointestinal tract than into the peritoneal cavity because of large concentration gradients between the blood and fluids in the gastrointestinal lumen.

In contrast with mexiletine, transfer rates of paraquat from the blood into the intestinal lumen were much smaller than those into the peritoneal cavity (Fig. 1). The poor transport of paraquat across the intestinal membrane may be due to the cationic nature of the herbicide. The biological membrane represents basically a lipid barrier. Consequently, lipid soluble compounds are generally permeable via diffusion through membranes. Paraquat is, however, poorly lipophilic and is present in a permanent positive charge in the systemic circulation (Conning et al 1969). Thus, permeability of the herbicide across the biological membranes seems to be poor. In fact, paraquat is poorly absorbed from the gastrointestinal tract and is rapidly excreted in urine, probably due to its cationic nature (Daniel & Gage 1966; Dijk et al 1975).

However, contrary to our expectations, the transfer rate of paraquat from the blood into the peritoneal cavity was markedly large (Fig. 1). This phenomenon may be due to a unique tissue distribution of paraquat. The peritoneal cavity includes most organs such as liver, lung, kidney and intestine which have abundant blood supplies. Litchfield et al (1973) reported that paraquat was distributed throughout most tissues, with preferential localization in cartilaginous tissue and in the liver in the initial stages after intravenous administration of [^{14}C]paraquat to mice. Thus, the large difference in transfer rates across the two membranes may be due to the quantitative difference in tissue distribution of paraquat. Since paraquat is present in a highly polar form in the systemic circulation, the quantity of paraquat distributed to the peripheral tissue is thought to be only a small fraction. Consequently, it seems that transport into the peritoneal cavity is preferable to that into the intestinal lumen since the peritoneal cavity is in contact with most organs which have high blood flows.

Another possible explanation for the excellent transport of paraquat into the peritoneal cavity may be due to solvent drag. Published studies have demonstrated that the net water flux causes a drag effect on permeability of some drugs (Ochsenfahrt & Winne 1974a, b; Kitazawa et al 1975, 1977; Karino et al 1982a, b). For example, Kitazawa et al (1977) reported that transport of sulphanilamide into the intestinal lumen 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. In the present study, the transfer rates of water were greater in the peritoneal cavity than those in the intestinal lumen after intravenous administration of ^3H_2O to rats (Fig. 3). This result indicates that the peritoneal cavity is subjected to a greater solvent drag than the intestinal lumen. Paraquat is present with a permanent positive charge in the systemic circulation. Therefore, the transfer mechanism of paraquat is suggested to be by passive diffusion through aqueous pores but not through lipid membranes. Thus, it can be assumed that hydrophilic paraquat is susceptible to the solvent drag effect.

Mexiletine is a weak base with a pK_a value of 9·1. Consequently, most of the drug is in an ionized form and only a small part of the drug is expected to be present in an un-ionized form at pH 7·4 according to the classical pH partition theory. However, the transfer rate of mexiletine from the blood into the intestinal lumen was relatively large. There is a possible explanation for this finding. Turnheim & Lauterbach (1980) reported that some organic cations are actively secreted from the blood into the intestinal lumen. Thus, active secretion may contribute to the transport of mexiletine in its cationic form from the blood into the intestinal lumen. Our result shows that the concentrations of mexiletine in the intestinal perfusate were slightly higher than those in the serum. This suggests a possibility that mexiletine is actively secreted from the blood into the lumen. More detailed studies, however, will be needed to elucidate the possibility of active secretion of the drug. An alternative explanation is given by a lower pH value of perfusate (6·5) than that in the blood, facilitating transport toward the perfusate.

In conclusion, we have shown that the intestinal lumen exhibits an excretion function for mexiletine but not for paraquat in rats. Consequently, it is expected that gastrointestinal dialysis may be more useful than peritoneal dialysis in the treatment of mexiletine overdose. On the other hand, we would not expect gastrointestinal dialysis to be effective in removing paraquat from the systemic circulation. However, in the case of paraquat poisoning, a large proportion of paraquat will remain in the intestinal lumen for a long time after ingestion. Orally administered activated charcoal with

cathartics is expected to be effective for the decontamination of the gastrointestinal tract. Gastrointestinal dialysis should exert an adjunctive effect in combination with other purification methods for the removal of paraquat which has been absorbed into the systemic circulation.

Acknowledgement

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