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Study on Transport of Disopyramide into the Intestinal Lumen Aimed at Gastrointestinal Dialysis by Activated Charcoal in Rats

KAZUHIKO ARIMORI AND MASAHIRO NAKANO

Department of Pharmacy, Kumamoto University Hospital, Honjo, Kumamoto 860, Japan

Abstract—The characteristics of exsorption and/or excretion of disopyramide into the gastrointestinal lumen have been investigated after intravenous administration of the drug at doses of 10 and 30 mg kg^{-1} to rats by the in-situ single pass perfusion technique. Disopyramide was appreciably excreted into the bile where its levels were approximately ten-fold higher than those in the serum. The exsorption rate of disopyramide and mono-*N*-dealkyldisopyramide (MND) into the perfusate was increased with an increase in the serum level following an increase from 10 to 30 mg kg^{-1} in the dose of disopyramide. The average amounts of disopyramide exsorbed into the perfusate were 17·0 and 18·4% at the dose of 10 and 30 mg kg^{-1}, respectively, whereas those of MND were less than 1% at both doses of disopyramide. Oral administration of activated charcoal reduced the serum disopyramide levels after intravenous administration of the drug (20 mg kg^{-1}) compared with the control treatment. By oral administration of activated charcoal, $t_{\frac{1}{2}}$ and AUC were decreased to 89 and 82%, respectively, and Cl_{tot} was increased to 122% compared with the corresponding control treatment. V_d was not different between the treated rats and control rats. These results suggest that the oral administration of activated charcoal can enhance the clearance of disopyramide and MND from the blood.

Activated charcoal is generally recognized as an antidote in drug poisoning caused by attempted suicide, accidental ingestion or dosage errors, since it is able to adsorb a wide variety of drugs and toxins on its surface. In acute drug poisoning, activated charcoal should be given as soon as possible to prevent absorption of the drug before it is absorbed from the gastrointestinal (g.i.) tract.

Recent reports indicate that orally administered activated charcoal not only prevents drug absorption from the g.i. tract but also increases clearance of drugs that have already been absorbed and are in the systemic circulation (Berlinger et al 1983; Mahutte et al 1983). This so called g.i. dialysis (Levy 1982) has been noted as one of the haemo-purification methods such as haemodialysis, peritoneal dialysis, and haemoperfusion in drug poisoning. We have previously reported that intravenously administered theophylline (Arimori & Nakano 1985, 1988a), phenobarbitone (Arimori & Nakano 1986a, b) and phenytoin (Arimori & Nakano 1987) were transported from the blood into the small intestinal lumen (exsorption) to a significant extent and into the bile (biliary excretion) to a lesser extent in rats and that drugs can be removed by adsorption onto orally administered activated charcoal. However, some reports have shown little effect on drug clearance following oral administration of activated charcoal possibly due to very large volumes of distribution (Goldberg et al 1985) or the extensive protein binding of some drugs (Arimori & Nakano 1988b). Therefore, it is necessary to have information on the characteristics of transport of drugs from the blood into the g.i. tract if g.i. dialysis by activated charcoal is to be successful in the treatment of drug poisoning.

Disopyramide is an antiarrhythmic drug with efficacy in the management of atrial and ventricular arrhythmias. The drug has a marked intersubject variability in plasma protein binding which is related to its pharmacological effect (Cunningham et al 1977; Giacomini et al 1982). Additionally, when the drug is administered to patients with a lower clearance of the drug such as in severe impaired renal function, caution should be used since more than 50% of the drug is excreted in the urine in the unchanged form (Cunningham et al 1977). Intoxication by an accidental overdose of oral disopyramide gives rise to life-threatening symptoms including apnoea, loss of consciousness, cardiac arrhythmias and loss of spontaneous respiration.

The present study was designed to investigate the characteristics of exsorption and/or excretion of disopyramide into the g.i. tract and to evaluate whether the transported drug could be removed by adsorption onto orally administered activated charcoal in rats.

Correspondence to: M. Nakano, Department of Pharmacy, Kumamoto University Hospital, Honjo, Kumamoto 860, Japan.

Materials and Methods

Materials

Disopyramide phosphate, disopyramide for injection (Rhythmodan-P) and mono-*N*-dealkyldisopyramide (MND) were products of Nippon Roussel Co., Tokyo, Japan. Activated charcoal was a product of Inuhinode Seiyaku Co., Osaka, Japan and the particle size used was less than 62 μm (250 mesh). All other chemicals were of analytical grade.

Exsorption study

Intestinal exsorption experiments were performed by an in-situ single pass perfusion technique reported previously (Arimori & Nakano 1985). Wistar strain male rats, 350–450 g, were anaesthetized by an intraperitoneal injection of ethyl carbamate (1·2 g kg^{-1}). The small intestine was exposed by a midline abdominal incision. The upper duodenum and the

ileocaecal junction were cannulated with a polyethylene tube. The isotonic phosphate buffer solution (0·1 M, pH 6·0), which was maintained at 37°C, was perfused at a rate of approximately 1·3 mL min^{-1} from the duodenum through the small intestine to the ileocaecal junction. Disopyramide phosphate was injected over about 1-3 min into the right femoral vein at doses of 10 or 30 mg kg^{-1}. After injection, the perfusates were collected every 15 min from the ileal outflow and the bile was collected from the cannula introduced into the common bile duct. Exsorption rates were calculated as the amounts exsorbed into the intestinal lumen per min. Blood samples to determine serum drug concentrations were taken from the cannula introduced into the left femoral artery at the midpoint of the perfusate collection time (7·5, 22·5, 37·5, 52·5, 67·5, 82·5, 97·5 and 112·5 min). At the end of the experiments, the urine was collected from the bladder with a syringe.

In-vivo study

Rats (320–370 g) were fasted overnight with free access to water. Each experiment was carried out by a crossover design and an interval of more than two weeks was allowed before the next experiment. Disopyramide phosphate 20 mg kg^{-1}, was administered intravenously via the caudal vein. For the treatment with activated charcoal, a suspension in water (150 mg mL^{-1}) was administered orally via a catheter at an initial dose of 300 mg (2 mL) at time zero and additional doses of 150 mg (1 mL) were given at 1, 2, 3 and 4 h after the intravenous (i.v.) administration of disopyramide phosphate. For the control experiments, water corresponding to the volume of activated charcoal suspension used was administered orally at each dosing time.

Analytical method

Disopyramide and MND in all samples were determined by high pressure liquid chromatography (HPLC) with 4-methylmexiletine as an internal standard with a modification of the method of Carr et al (1976). A 1 mL portion of the perfusate or 50–100 μL portion of each serum, bile or urine was extracted with 2 mL chloroform after addition of 200 μL of the internal standard (10 μg mL^{-1}) and 1 mL of 1 M sodium hydroxide. The mixture was shaken for 10 min and then centrifuged for 10 min. The organic layer was transferred to a clean tube and 200 μL of 0·05 M sulphuric acid was added. After mixing the contents of the tube on a Vortex mixer for 1 min, 10 μL of the aqueous layer was injected into HPLC. Separation was performed with a Shimpack ODS column (5 μm in 4 × 150 mm, Shimadzu, Kyoto, Japan). The mobile phase consisted of acetonitrile and 0·03 M sodium acetate buffer, pH 3·3 (30:70). At a flow rate of 1·0 mL min^{-1}, the eluate was monitored for absorbance at 205 nm.

Pharmacokinetic analysis

Disappearance of disopyramide from the serum followed first-order kinetics. The elimination rate constant (k_{el}) was determined by a linear regression analysis of the elimination curve of serum levels. The serum half-life ($t_{\frac{1}{2}}$) was calculated from the relationship $t_{\frac{1}{2}} = 0{\cdot}693/k_{el}$. An intercept of the ordinate at time zero was used to estimate the initial serum concentration (Co) of disopyramide. The apparent volume of distribution ($V_d = dose/C_o$), the total body clearance ($Cl_{tot} = k_{el} \cdot V_d$), and the area under the serum concentration time curve (AUC) of disopyramide and MND from 0 to 6 h were also calculated by the trapezoidal rule. The paired *t*-test was used to assess the effect of charcoal treatment on the pharmacokinetic parameters.

Results

Transport of disopyramide and MND into the intestinal, biliary and urinary tract

The concentrations of disopyramide in the serum and the bile and the exsorption rate of the drug from the blood into the perfusate across the small intestinal mucosa following i.v. administration of disopyramide to rats were examined by the in-situ single pass perfusion technique at doses of 10 and 30 mg kg^{-1}. Fig. 1 shows the results following i.v. administration of disopyramide to rats. It was observed that the drug was rapidly transported into the bile or the intestinal perfusate after its i.v. administration. Its levels in the bile at both doses were approximately ten-fold higher than those in the serum. Its exsorption rate into the perfusate was increased with an increase in the dose from 10 to 30 mg kg^{-1}.

Fig. 2 shows the concentrations of MND in the bile and its exsorption rate into the perfusate following i.v. administration of disopyramide to rats at the dose of 10 and 30 mg kg^{-1} obtained by the in-situ single pass perfusion technique. It was observed that MND was rapidly transported into the bile or the perfusate after i.v. administration of disopyramide at both doses. Moreover, the concentration of MND in the bile was higher than that in the serum although that in the serum was not measured because it was below the sensitivity of the method for determining the metabolite by small sampling volume under this condition. The exsorption rate of MND into the perfusate also increased with an increase in the dose of disopyramide from 10 to 30 mg kg^{-1}.

The percentages of the dose of disopyramide and MND transported into the urine, intestinal perfusate and bile in 120 min are shown in Fig. 3. Marked amounts of disopyramide were exsorbed from the blood into the intestinal lumen. The average amounts of disopyramide exsorbed into the perfusate were 17·0 and 18·4% at 10 and 30 mg kg^{-1} doses, respectively, and were similar to those excreted into the urine (16 and 22% at the dose of 10 and 30 mg kg^{-1}, respectively). The amounts of disopyramide excreted into the bile were much smaller (1·1 and 1·2% at the dose of 10 and 30 mg kg^{-1}, respectively) than those excreted into the urine or exsorbed into the perfusate at both doses. The amounts of MND excreted into the urine and bile and exsorbed into the perfusate were less than 1% of the dose of disopyramide at 10 and 30 mg kg^{-1}, but the amounts of MND excreted and/or exsorbed after the 30 mg kg^{-1} dose tended to be much more than those of 10 mg kg^{-1}.

Effect of activated charcoal on disopyramide clearance

Fig. 4 shows the time course of disopyramide levels after its i.v. administration at 20 mg kg^{-1} to rats with or without oral activated charcoal. Oral administration of multiple doses of activated charcoal reduced the serum disopyramide levels compared with the control treatment. Its mean serum level at 6 h was significantly decreased from 0·28 to 0·15 μg mL^{-1} by multiple doses of activated charcoal. Pharmacokinetic para-

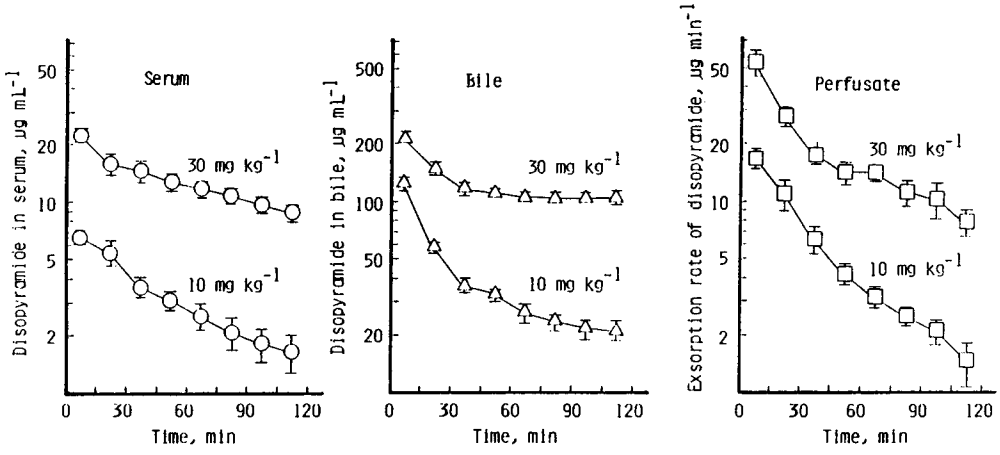

FIG. 1. The concentrations of disopyramide in the serum and bile and the exsorption rate of the drug into the perfusate after i.v. administration of disopyramide (10 and 30 mg kg^{-1}) to rats studied by the in-situ single pass perfusion method. The perfusate was composed of isotonic phosphate buffer, pH 6·0. Each point represents the mean ± s.e.m. of 4 rats.

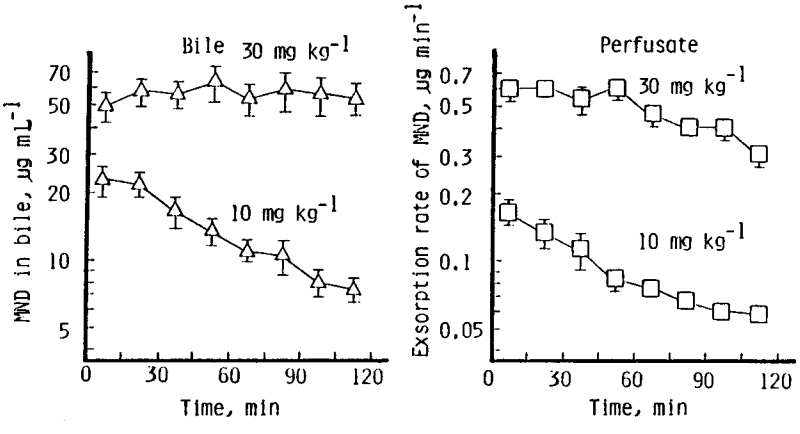

FIG. 2. The concentrations of MND in the bile and the exsorption rate of the drug in the perfusate after i.v. administration of disopyramide (10 and 30 mg kg^{-1}) to rats studied by the in-situ single pass perfusion method. The perfusate was composed of isotonic phosphate buffer, pH 6·0. Each point represents the mean ± s.e.m. of 4 rats.

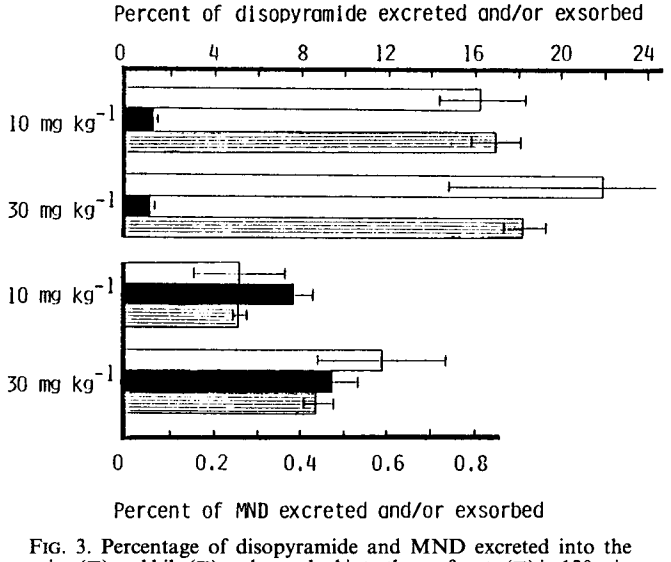

FIG. 3. Percentage of disopyramide and MND excreted into the urine (□) and bile (■) and exsorbed into the perfusate (■) in 120 min after i.v. administration of disopyramide (10 and 30 mg kg^{-1}) to rats studied by the in-situ single pass perfusion method. Each bar represents the mean ± s.e.m. of 4 rats.

meters after 20 mg kg^{-1} doses are shown in Table 1. By oral administration of activated charcoal, $t_{\frac{1}{2}}$ and AUC were decreased to 89 and 82%, respectively, and Cl_{tot} was increased to 122% as compared with the control treatment. V_d values were not significantly different between the treated rats and control rats.

Discussion

The permeability of drugs through the intestinal membrane varies enormously depending upon the extent of serum protein binding, lipophilicity and molecular size of the drug. Only the unbound or free drug can permeate through capillary walls to various organs. Therefore, there seems to be a correlation between the amount of drug exsorbed into the g.i. lumen and the extent of protein binding of drugs which have been investigated in our in-situ single pass perfusion technique (Arimori & Nakano 1985, 1986a, 1987, 1988b). Our previous reports showed that the amounts of frusemide (Arimori & Nakano 1988b) and phenytoin (Arimori & Nakano 1987), both of which have high binding affinity to plasma protein, exsorbed into the intestinal lumen

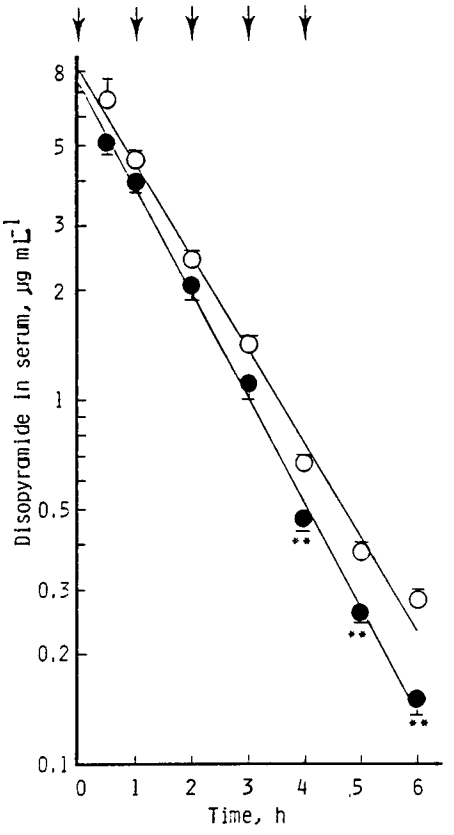

FIG. 4. The serum concentrations of disopyramide after i.v. administration of the drug (20 mg kg^{-1}) to rats with (●) or without (○) treatment with activated charcoal. Each point represents the mean ± s.e.m. of 5 rats. Each arrow indicates the time when activated charcoal was administered. (**)$P < 0.01$.

Table 1. Pharmacokinetic parameters of disopyramide after i.v. administration of the drug at the dose of 20 mg kg^{-1} to rats with or without activated charcoal.

Pharmacokinetic parameters	Control	Treatment with charcoal
$t_{\frac{1}{2}}$ (h)	1·18 ± 0·031	1·05 ± 0·018*
k_{el} (h^{-1})	0·59 ± 0·015	0·66 ± 0·011*
V_d (L kg^{-1})	2·49 ± 0·15	2·73 ± 0·18
Cl_{tot} (L h^{-1} kg^{-1})	1·47 ± 0·073	1·80 ± 0·10*
AUC (μg h mL^{-1})	13·8 ± 0·69	11·3 ± 0·65

Each value represents the mean ± s.e.m. of 5 rats.
* $P < 0.05$

were as small as 0·83% and 1·1% in 120 min, respectively. In contrast, those of theophylline (Arimori & Nakano 1985) and phenobarbitone (Arimori & Nakano 1986a), both of which have low binding affinity, exsorbed were as much as 12% and 6·5% in 120 min, respectively. Marked exsorption of disopyramide into the intestinal lumen via the mucosal membrane was considered to be due to its low molecular weight, high lipid/water partition coefficient, low binding affinity to plasma proteins, and small extent of ionization at pH of the blood (Karim et al 1982). The fact that an appreciable amount of disopyramide was transferred into saliva (Aitio et al 1982) and breast milk (Karim et al 1978) may support our results.

Aitio et al (1982) have reported that the correlations between the salivary and total and free plasma concentrations of disopyramide were relatively good and the ratio of disopyramide concentrations in saliva to those in plasma varied from 0·08 to 1·51 μg mL^{-1} and was highest when the salivary and plasma levels were high. The extent of binding of disopyramide to plasma protein is concentration-dependent at the therapeutic plasma concentration range and shows interindividual variability (Cunningham et al 1977; Giacomini et al 1982). Disopyramide is bound almost exclusively to α_1-acid glycoprotein (AAG) and the concentration of AAG is increased in patients with acute myocardial infarction, chronic renal failure requiring dialysis, and renal transplant recipients (Siddoway & Woosley 1986). Moreover, it has been shown that the unbound fraction of disopyramide is increased as the total plasma concentration is increased even within the therapeutic range (Meffin et al 1979). Since the pharmacological effects of a drug are dependent upon the unbound drug concentration, the variation in the extent of protein binding is of importance in drug poisoning. In our in-situ single pass perfusion study, the amounts of disopyramide and MND exsorbed into the g.i. lumen tended to increase slightly at the dose of 30 mg kg^{-1} compared with those of 10 mg kg^{-1}, although the unbound concentrations of disopyramide were not measured in the present study. These results suggest that disopyramide exsorbed from the blood into the intestinal lumen, which is related to the effect of the g.i. dialysis by oral administration of activated charcoal, would increase in the case of the drug poisoning.

Oral administration of activated charcoal accelerated disopyramide clearance from the blood after i.v. administration of the drug, but the effect was relatively small compared with that on other drugs previously studied in rats, in spite of the marked extent of exsorption. We have previously shown that intravenously administered theophylline (Arimori & Nakano 1985) or phenobarbitone (Arimori & Nakano 1986a), 10 mg kg^{-1}, were exsorbed into the small intestinal lumen to a significant extent (12 and 6·5% of dose in 12 min, respectively) and oral administration of activated charcoal significantly decreased their serum half-life (to 61 and 67% of the control values, respectively) and AUC (both to 64%) and increased the total body clearance (to 152 and 153%, respectively) compared with their respective controls (Arimori & Nakano 1986b). The reason for the small effect on disopyramide may be explained by the higher total body clearance of the drug (1·47 L h^{-1} kg^{-1}) compared with that of theophylline (66·7 mL h^{-1} kg^{-1}) and phenobarbitone (50·2 mL h^{-1} kg^{-1} (Arimori & Nakano 1986b). Park et al (1985) have also reported that activated charcoal has a relatively small effect in increasing digoxin elimination in normal subjects in whom digoxin has a short half life, but has a significant effect in increasing digoxin elimination in renal failure subjects. They suggested that the total clearance of a drug during treatment with activated charcoal is the sum of the normal endogenous clearance and clearance through the g.i. tract by charcoal. In principle, if activated charcoal produces a constant intestinal drug clearance, the percentage of total body drug clearance caused by the charcoal wll increase as the endogenous drug clearance (by metabolism or renal elimination) decreases. Therefore, the increased clear-

ance of disopyramide by orally administered activated charcoal may not be as greatly reflected in the total clearance because the drug has a large endogenous clearance.

Another possible reason for the small effect may be attributed to a relatively large volume of distribution of disopyramide. Goldberg et al (1985) have reported that there was no difference in the clearance of imipramine after i.v. administration in man between the treatment with and without activated charcoal because of the large volume of distribution of the drug. The V_d value of disopyramide is 2·5 L kg^{-1}, which is larger than those of theophylline (0·42 L kg^{-1}) and phenobarbitone (0·61 L kg^{-1}) in rats (Arimori & Nakano 1986b). Therefore, there is relatively little disopyramide present in blood available for the g.i. dialysis across the g.i. wall and subsequent adsorption onto activated charcoal in the lumen.

It was confirmed that the major metabolite of disopyramide, MND was also appreciably transported into the g.i. lumen via the mucosal membrane or bile duct. Some of the disopyramide and MND exsorbed or excreted into the g.i. lumen may be reabsorbed into the blood. MND possesses smaller antiarrhythmic activity than the parent drug in animal studies (Baines et al 1976). In general, it is unlikely that pharmacologically effective concentrations of MND are attained in patients with normal renal and hepatic functions. However, pharmacologically effective MND concentrations may be attained in patients with severe renal impairment or in the overdose of disopyramide. Accordingly, the contribution of MND to the pharmacological effect should be considered since MND as well as disopyramide concentrations are increased in disopyramide poisoning.

In conclusion, it was confirmed that the oral administration of activated charcoal can enhance the clearance of disopyramide which has been parenterally administered or has already been absorbed into the systemic circulation from the g.i. tract in rats. It seems that the g.i. dialysis by activated charcoal may be a useful method for removing excess disopyramide and its metabolites from the blood as one of the haemo-purification methods in the case of drug poisoning accompanied by low endogenous clearance.

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