Comparison of Transport of Procainamide and *N*-Acetylprocainamide from Blood into the Intestinal Lumen with That into the Peritoneal Cavity in Rats

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Transfer of procainamide and its active metabolite, *N*-acetylprocainamide (NAPA) from the blood into the intestinal lumen was compared with that into the peritoneal cavity after i.v. administration of procainamide at the dose of 10 mg/kg to rats. 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 dose (10 mg/kg), respectively, while those of NAPA were 3.5% and 1.4% of dose. The intestinal and peritoneal clearance values of procainamide were 143.5 and 59.4 ml/h, respectively, and those of NAPA were 32.6 and 13.5 ml/h. The difference in transfer rates across the intestinal and peritoneal membranes may be due to difference in the area of permeative surface and the extent of ionization in the dialysate. Consequently, it is expected that the gastrointestinal dialysis by oral administration of activated charcoal may serve as one of the more useful hemopurification methods than the peritoneal dialysis in procainamide and NAPA intoxication.

Keywords procainamide; *N*-acetylprocainamide; intestinal dialysis; peritoneal dialysis; intestinal clearance; peritoneal clearance; transfer rate; rat; intoxication; serum concentration

Introduction

Procainamide is a representative antiarrhythmic drug which exhibits a marked intersubject variation in the daily dose necessary to suppress ventricular arrhythmias.[1] Procainamide is partly biotransformed in the liver and changed into an active metabolite, *N*-acetylprocainamide (NAPA). NAPA has an antiarrhythmic activity comparable to that of procainamide and its biological half-life is about twice longer than that of the parent drug in humans.[2] Accordingly, in the case of procainamide overdose, the toxicity caused by NAPA may become more important than that by procainamide because of its long half-life. Various methods such as peritoneal dialysis,[3] hemoperfusion,[4] hemodialysis[5] and combined hemodialysis-hemoperfusion[6] have been used in severe procainamide and/or NAPA intoxication as methods of hemopurification.

For example, Braden *et al.*[4] have reported that resin hemoperfusion provided excellent NAPA clearance and was clearly superior to hemodialysis in the case of a patient on chronic hemodialysis who developed NAPA intoxication. On the other hand, Villalba-Pimentel *et al.*[3] reported that the peritoneal dialysis was found to be ineffective in enhancing the clearance of procainamide or NAPA. Thus, each hemopurification method has been evaluated and roughly ranked for the treatment of procainamide or NAPA intoxication.

We previously reported that procainamide and NAPA, after i.v. administration of procainamide (10 mg/kg) to rats, were transferred into the small intestinal lumen to a significant extent and into the bile to a lesser extent, and that both drugs can be removed by adsorption onto orally administered activated charcoal.[7] However, full evaluation of the gastrointestinal (g.i.) dialysis by oral administration of activated charcoal has not yet been made as the means for the removal of drugs which have been parenterally administered or have already been absorbed into the systemic circulation from the g.i. tract.

The present study, therefore, was aimed at comparison of the g.i. dialysis with the peritoneal dialysis which has been studied more extensively as the means for hemopurifications in drug intoxication.

Experimental

Materials Procainamide and NAPA were purchased from Sigma Chemical Co., St. Louis, Mo., U.S.A. Amisalin® injection (Daiichi Seiyaku Co., Tokyo, Japan) was used for intravenous injection of procainamide hydrochloride. All other chemicals used in this study were of analytical grade.

Intestinal Dialysis Wistar strain male rats, weighing 220—260 g and fasted overnight with free access to water, were anesthetized by an intraperitoneal injection of ethyl carbamate (1.2 g/kg). Intestinal exsorption experiments were performed by an *in situ* single-pass perfusion technique reported previously.[8] Briefly, the small intestine was exposed by a midline abdominal incision. The upper duodenum and the ileocecal junction were cannulated with polyethylene tubing and the entire small intestine was washed with saline maintained at 37 °C. Lactated Ringer's solution which had been maintained at 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. Procainamide solution (10 mg/ml) was injected at a dose of 10 mg/kg over about 1 min into the right femoral vein. After the injection, the blood and dialysate were collected periodically. Blood samples for the determination of serum drug concentrations were taken from a cannula introduced into the left femoral artery midway during the dialysate collection period.

Peritoneal Dialysis A small incision was made in the abdomen and twenty milliliters of lactated Ringer's solution which had been maintained at 37 °C was injected into the peritoneal cavity. The dialysate was exchanged for the corresponding volume of a new dialysate every 15 min. The procedure for administration of the drug and the collection time of samples were the same as the *in situ* single-pass perfusion technique.

Analytical Method Procainamide and NAPA in the serum, the bile juice and the dialysate were determined by high-pressure liquid chromatography as reported previously.[7]

Calculation of Intestinal and Peritoneal Clearance The apparent intestinal and peritoneal clearance values of procainamide and NAPA were calculated by dividing the overall amount of the drugs transferred into both dialysates in 120 min by the appropriate value for an area under the serum concentration time curve of the two drugs obtained over the same period of time.

Results and Discussion

Figure 1 shows the transfer rate of procainamide and NAPA from the blood into the intestinal lumen and that into the peritoneal cavity following i.v. administration of procainamide to rats at a dose of 10 mg/kg. An appreciable amount of both drugs was transported from the blood into the intestinal lumen and the peritoneal cavity, but the transfer rate into the intestinal lumen was considerably higher. This suggests that the intestine dem-

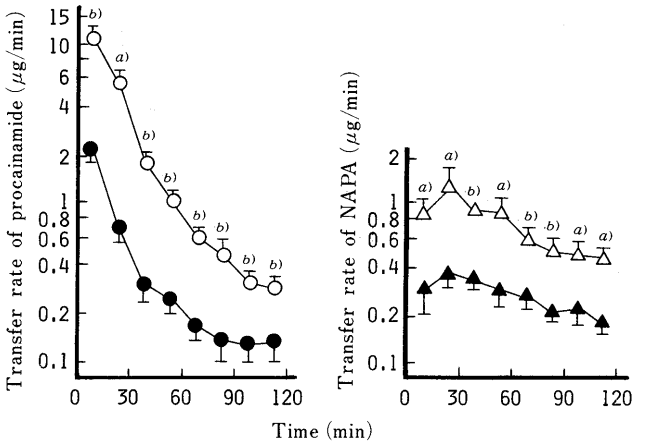

Fig. 1. The Transfer Rate of Procainamide (○, ●) and NAPA (△, ▲) from the Blood into the Intestinal Lumen (○, △) and the Peritoneal Cavity (●, ▲) after i.v. Administration of Procainamide (10 mg/kg) to Rats

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

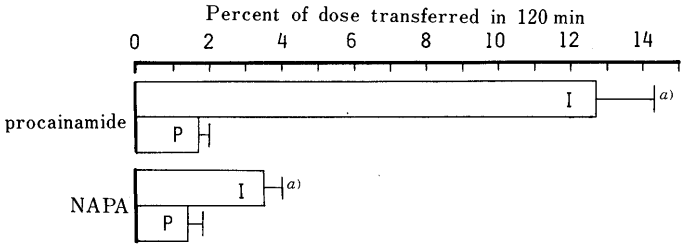

Fig. 2. The Amounts of Procainamide and NAPA Transferred into the Intestinal (I) and Peritoneal (P) Dialysate within 120 min after i.v. Administration of Procainamide (10 mg/kg) to Rats

Each bar represents the mean ± S.E.M of 4 rats. *a*) $p<0.01$.

onstrates a greater distribution/excretion function of procainamide and NAPA than the peritoneal cavity.

To express the ability of a system to remove the drug, the intestinal and peritoneal clearance was calculated. A notable difference in the clearance values of the two drugs was observed between the intestinal lumen and the peritoneal cavity: the values of procainamide were 143.5 and 59.4 ml/h, respectively, and those of NAPA were 32.6 and 13.5 ml/h.

The amounts of procainamide and NAPA transferred in 2 h from the blood into the two sites studied are shown in Fig. 2; as shown, less of both drugs was transferred into the peritoneal cavity. The average amounts of procainamide transferred into the intestinal lumen and peritoneal cavity in 2 h were 12.7% and 1.7% of dose, respectively, while those of NAPA were 3.5% and 1.4% of dose. These results may support an early report that the peritoneal dialysis was ineffective in enhancing the clearance of these drugs.[3] However, their transfer rates across the intestinal membrane per surface area appeared to be lower than those across the peritoneal membrane since the surface area of the small intestine is approximately 100 times larger than the latter membrane.[9]

A possible explanation for the differences in transfer across the two membranes may be due to a possible difference in the area of the permeative surface. The rate of transfer across a membrane depends on the geometrical factors of the membrane such as its area and thickness and the distribution of blood vessels within it. The small intestine represents a larger surface (about 200 m^2 in an adult human) than the peritoneal membrane (about 2 m^2).[9] Accordingly, as far as area is concerned, the intestine is more suitable as a permeable or exsorbable organ than the peritoneum if the intestinal membrane is fully operable as a dialyzable membrane. Furthermore, it is known that the apparent volume of distribution is considerably decreased in procainamide overdoses owing to the decrease of tissue splanchnic perfusion caused by hypotension.[5] This decrease in distribution volumes in procainamide and NAPA may reduce the transport of both drugs into the peritoneal cavity. In contrast, the phenomenon may facilitate the transport of both drugs more into the g.i. tract than into the peritoneal cavity because of large concentration gradients between blood and fluids in the g.i. lumen. In fact, Atkinson *et al.*[5] reported that peritoneal dialysis contributed little to the removal of procainamide and NAPA, while hemodialysis could be valuable in removing both substances.

Another possible explanation for the finding is that the degree of their ionization may affect the permeability of both drugs since the unionized form would be expected to permeate freely through capillary walls to the g.i. tract. It has been shown that the saliva to plasma concentration ratio for both drugs was fairly consistent with the calculated value according to the pH-partition theory, and was increased with decrease in salivary pH value.[10,11] Procainamide is a weak base with a pK_a value of 9.4.[11] The pH value of the lactated Ringer's solution used in this study was 6.5 and about 0.13% of procainamide was thought to be present in an unionized form according to the Henderson–Hasselbalch equation.[12,13] The pH value of the intestinal dialysate had changed from 6.5 to 6.9, while that of the peritoneal dialysate went from 6.5 to 7.4 in each 15 min experimental period. Consequently, the unionized form of procainamide, which would allow reabsorption by diffusion through the membrane, would be approximately three-fold greater in the peritoneal dialysate than that in the intestinal dialysate after the dialysis (0.99% in the peritoneal dialysate at pH 7.4 *vs.* 0.32% in the intestinal dialysate at pH 6.9).

In the peritoneal dialysis, although acidification of the dialysate should increase the peritoneal clearance of procainamide and NAPA, this approach may be hazardous in clinical practice. The g.i. lumen has a large surface when the oral cavity, the esophagus, the stomach and the small and large intestine are considered. Moreover, the stomach has a more favorable environment for the transfer of the drugs than the small intestine since pH in the stomach is in an acidic region. Thus, a considerable amount of procainamide and NAPA are expected to be transferred into the overall g.i. lumen due to the concentration gradient between the blood and the fluid here.

In conclusion, it was shown that the intestinal lumen exhibits a noticeable exsorption/excretion function for both procainamide and NAPA in rats. Consequently, it is expected that the g.i. dialysis by oral administration of activated charcoal may be one of the more useful hemopurification methods than the peritoneal dialysis in procainamide and NAPA intoxication.

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