TRANSPORT OF THEOPHYLLINE FROM BLOOD TO THE INTESTINAL LUMEN FOLLOWING i.v. ADMINISTRATION TO RATS

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The exsorption of theophylline into the small intestinal lumen after intravenous administration of aminophylline was studied by in situ single-pass perfusion technique. As the concentrations of the drug in the serum and the bile juice were decreased, the exsorption rate of the drug into the perfusate decreased obeying the apparent first-order kinetics. The half-lives of the drug concentrations in the serum and the bile juice were 2.13 and 2.58 h for pH 6.0 isotonic phosphate buffer, and were 2.71 and 2.32 h for pH 8.0 isotonic phosphate buffer, respectively. The amounts of theophylline excreted in the perfusate and the bile juice were 12.08% and 0.17% of dose for pH 6.0 isotonic phosphate buffer, and were 13.81% and 0.20% of dose for pH 8.0 isotonic phosphate buffer. These results demonstrated that a considerable amount of theophylline was exsorbed into the intestinal lumen. The mechanism by which oral activated charcoal enhanced clearance of theophylline administered intravenously may be adsorption of the drug transported into the gastrointestinal tract by the charcoal.

**Keywords** — theophylline; exsorption; bile juice; in situ single-pass perfusion technique; intravenous administration; serum concentration; exsorption rate; intestinal lumen; biliary excretion

INTRODUCTION

Theophylline is one of the frequently used drugs in the treatment of asthma. Since it has a narrow therapeutic range and its toxicity can be severe including life-threatening arrhythmias or seizures, theophylline in blood in toxic concentrations has to be removed. Recently, it has been shown that the clearance of intravenously administered or orally taken theophylline is accelerated by orally administered activated charcoal. The possible mechanism has been postulated to be adsorption of the drug secreted into the gastrointestinal tract, but it has not been clarified yet. Transport (exsorption) of i.v. administered drug (sulfisomezole) to intestinal lumen has been noted as a part of absorption study in as early as 1963, and other studies on exsorption have also been carried out as a part of absorption studies. For example, exsorption of i.v. administered sulfaguanidine and sulfamethoxine, sulfanilic acid and sulfaguanidine, sulfanilic acid, p-aminobenzoic acid, Evans blue, and sulfanilamide into intestine was examined to prove change in membrane permeability in the presence of bile salts, tetracycline, taurocholate and monoolein mixed micelle and sodium dodecylsulfate in the perfusate, after systemic anaphylaxis and with increase in body temperature, respectively. On the other hand, effects of i.v. dose and perfusate tonicity on exsorption of i.v. administered sulfanilamide were examined in detail. However, drugs examined so far are limited to ion or twitterion such as sulfonamides, sulfanilic acid, p-aminobenzoic acid and Evans blue, and exsorption of commonly used drugs such as theophylline or phenobarbital has not yet been examined.

The present study was undertaken to elucidate the characteristics of exsorption and/or excretion of theophylline into the small intestinal and the biliary tracts to find relative importance of exsorption and biliary excretion in the trans-
port of theophylline from blood into GI tract.

MATERIALS AND METHODS

Materials — Aminophylline (Neophylline) was purchased from Eisai Co., Tokyo, and all other chemicals used in this study were of analytical grade.

Animal Treatment — Wistar strain male rats, weighing 240–280 g fasted overnight with free access to water, were anesthetized by an intraperitoneal injection of ethyl carbamate (1.2 g/kg). The small intestine was exposed by a midline abdominal incision. Both of the openings were cannulated with silicone tubings. The bile juice was collected separately every 15 min from the common bile duct which was cannulated with a polyethylene tubing. The blood sample to determine the serum concentration was collected from the left femoral vein, which was cannulated with a polyethylene tubing, at the middle time of the sampling period of the perfusates. Both the upper duodenum and the ileocecal junction were opened and the entire small intestine was washed with saline maintained at 37 °C. The cannulae were then connected to the perfusion apparatus.

Exsorption Procedures — Intestinal exsorption experiments were conducted by in situ single-pass perfusion technique. Isotonic phosphate buffers (0.1 M, pH 6.0 and 8.0) which had been maintained at 37 °C were perfused at the rate of approximately 20 ml/15 min through the small intestine using a glass pump (GM-24, Tokyo Rikakikai). Aminophylline at the concentration of 25 mg/ml was injected in about two minutes into the right femoral vein with a dose of 10 mg/kg. After injection, samples of the perfusate were collected every 15 min from the ileal outflow in 25 ml volumetric flask. The perfusate was diluted by the buffer to 25 ml prior to assay.

Analytical Methods — Theophylline in the perfusate was determined by high pressure liquid chromatography with 8-chlorotheophylline as the internal standard. A 2 ml portion of the sample was extracted with 5 ml of chloroform containing the internal standard after addition of 1 ml of 1 N HCl. Separation was performed with a LiChrosorbt RP-18 column (4.6 i.d. × 250 mm). The mobile phase consisted of pH 4.0 acetate buffer and methanol (3:2). At a flow rate of 1.0 ml/min, it was detected using absorbance at 272 nm. The concentrations of theophylline in the serum and the bile juice were measured by a homogeneous immunoassay technique (Ames TDA, Ames Co.) after addition of human serum.

RESULTS AND DISCUSSION

Fig. 1 shows the concentrations of theophylline in the serum and the bile juice, and also shows the exsorption rate of theophylline into the perfusate composed of pH 6.0 and 8.0 isotonic phosphate buffers following intravenous administration of aminophylline to rats at the dose of 10 mg/kg. As the concentrations of the drug in the serum and the bile juice decreased, the ex-

![Graph showing the concentrations of theophylline in serum and bile juice with pH 6.0 and 8.0 buffers.](image)

**FIG. 1.** The Concentrations of Theophylline in the Serum and the Bile Juice and the Exsorption Rate of Theophylline into the Perfusate Composed of pH 6.0 or pH 8.0 Isotonic Phosphate Buffer Following i.v. Administration of Aminophylline (10 mg/kg) to Rats

*Key:* ○ serum, ---△ bile juice.
sorption rate of the drug into the perfusate decreased obeying the apparent first-order kinetics. Moreover, it was shown that the time course of theophylline level in the bile juice was very close to that in the serum. The average half-life in the serum level obtained with the least squares method was in approximate agreement with that in the bile juice. The half-lives of the drug concentrations in the serum and the bile juice were 2.13 and 2.58 h for pH 6.0 isotonic phosphate buffer, and were 2.71 and 2.32 h for pH 8.0 isotonic phosphate buffer, respectively. These results suggest that theophylline may be excreted into bile tract in proportion to the serum level. The exsorption rates of the drug into the perfusates were not very different between pH 6.0 and 8.0 isotonic phosphate buffers. The half-lives of the drug exsorption into the perfusates were 0.86 and 0.94 h for pH 6.0 and 8.0 isotonic phosphate buffers respectively. As theophylline is present mostly in the unionized form in both of the perfusates ($pK_a = 8.75$), the exsorption into the lumen may be only slightly affected by change in pH from 6 to 8.

The amounts of theophylline transported into the perfusate and the bile juice in 120 min are shown in Fig. 2. The dose of theophylline was calculated by converting molecular weight of aminophylline into that of theophylline. As shown in Fig. 2, a considerable amount of theophylline was exsorbed into the intestinal lumen. The average amounts of the drug exsorbed into the perfusate were 12.08% and 13.81% of dose for pH 6.0 and 8.0 isotonic phosphate buffers, respectively. On the other hand, the amount of the drug excreted into bile was much smaller than the amount of the drug exsorbed into the perfusate. The average amounts of theophylline excreted into the bile juice were 0.17% and 0.20% of dose for pH 6.0 and 8.0 isotonic phosphate buffers, respectively. These results suggest that the transport of theophylline through mucosal membrane into the intestinal lumen is appreciable. Kitazawa et al. have also reported that the excretion of sulfanilamide in the bile juice, which is only about 0.5% of dose in 3 h, was much smaller than the excretion of the drug into the luminal perfusate (17% in 3 h). On the other hand, Takada et al. have shown that bromphenol blue was secreted about a half of the dose into the bile juice within 30 min. Their observations confirmed the earlier observation that the excretion into the bile juice depends considerably on the chemical characteristics of the drug.

Some parts of theophylline either exsorbed or excreted into the intestinal lumen may be reabsorbed into blood. In the presence of activated charcoal in the lumen, however, exsorption can be accelerated due to sink condition by adsorption of the exsorbed drug by activated charcoal and furthermore reabsorption can be reduced due to little availability of unadsorbed drug in the lumen. We have observed that absorption of orally administered theophylline was reduced in the presence of activated charcoal. Based on these expectations, it may be considered that the mechanism by which activated charcoal enhances clearance of theophylline administered intravenously may be adsorption of the drug exsorbed into the gastrointestinal tract by the charcoal.

In conclusion, the present study demonstrated that theophylline is exsorbed considerably into

![Diagram](image-url)
the small intestinal lumen, and also excreted only a little into the bile juice in rats.

REFERENCES


