THE EFFECTS OF THE ADMINISTRATION ROUTES ON THE BILARY EXCRETION OF ANTIBIOTICS

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The effects of the administration routes on the biliary excretion of gentamicin and cefazolin were investigated in male white rabbits. The administration routes studied were intravenous, intramuscular injection and injection into portal vein.

In both antibiotics, total excretion into bile was the highest when drug was administered by the injection into portal vein. In case of gentamicin, the bile level above MIC (against {\textit{P. aeruginosa}}) could be obtained only by the administration into portal vein.

These results indicate that the administration into portal vein is useful clinically, for the drug delivery to biliary tract, especially in drugs like aminoglycoside antibiotics which have an extremely low rate of transfer to the bile.

Keywords — administration route; bile concentration; plasma concentration; gentamicin; cefazolin; male white rabbit

INTRODUCTION

For the administration of antibiotics in patient with biliary tract infection, selection of antibiotics with excellent transfer to the tissue of biliary tract is desirable, along with the identification of the causative organism. Among factors influencing the transfer of antibiotics to the bile, molecular weight and plasma protein binding are well known to be important factors. Species and age difference of experimental animals are also known to be major factors. Clinically, as a measure to facilitate the transfer of antibiotics to the bile during biliary tract infection, additional use of cholangiogues and proteolytic enzymes is generally tried. However, the results are not always as satisfactory as one would expect.

We have conducted a series of studies on the changes of absorption, distribution and metabolism of antibiotics after the administration of various routes. As the results of these experiments, the excretion of antibiotics into bile was found to follow a considerably different pattern depending on the route of administration.

In the present study, basic experiments were carried out using male albino rabbits to compare excretion of several antibiotics into bile following intravenous injection, intramuscular injection and injection into portal vein. Gentamicin sulfate, one of the representative aminoglycoside antibiotics with extremely low rate of transfer to the bile and cefazolin with relatively favorable rate of transfer to bile were used in this study.

MATERIALS AND METHODS

Materials — Antibiotics used were gentamicin sulfate (GM, Shionogi Pharmaceutical Co., Ltd.) and sodium cefazolin (CEZ, Fujisawa Pharmaceutical Industry Ltd.). All other reagents and solvents were commercial products of reagent grade and were used without further purification.

In Vivo Absorption Study — Male white rabbits weighing 2.8—3.2 kg were used. The rabbits were housed in individual cages and allowed to
become accustomed to the laboratory conditions for at least 10 d. The animals were maintained on commercial pellets (CR-2, CLEA Japan Inc.) in the animal laboratory of the institute. Room temperature was maintained at 22±1.5°C. The animals were allowed free access to food and water until use. The study was performed between 10:00 a.m. and 3:00 p.m. Sodium pentobarbitone was administered (30 mg/kg; i.v.) to allow rapid bile duct canulations to be performed. Anaesthesia was maintained by the administration of further pentobarbitone as required. To avoid the fall of body temperature during the experiments, electric lamp was placed over the animal and the rectal temperature was kept at 37°C. After the anaesthesia, the animal was placed on an operation board spinely. After an abdominal incision, the common bile duct was cannulated with a polyethylene tube (PE-50, Clay Adams, U.S.A.). A single dose of 5 mg/kg of GM or 20 mg/kg of CEZ was administered intravenously, intramuscularly and into the portal vein. In case of intravenous and intramuscular administration, saline solution of a drug (0.3 ml/kg) was injected into the marginal ear vein and thigh muscle. Drug solution was given at a rate of 1.0 ml/min. Bile samples were collected at 30 min intervals for 3 h. Blood samples (0.5 ml) were taken from the marginal ear vein at the designated intervals. The bile, after estimation of weight, was taken into stoppered glass tube and kept at 4°C until assays were carried out. Blood sample was taken into 1 ml glass tube and centrifuged at 3000 rpm for 5 min. The plasma layer was taken into stoppered glass tube and kept at 4°C until assays were carried out.

Analysis of Antibiotics — The concentration of antibiotics in the bile and plasma were routinely measured by microbiological assay using Micrococcus luteus ATCC 9341 as the test organism. The penicillin cup diffusion method was used for the determination.

FIG. 1. Levels of GM in Plasma and Bile
Each value represents the mean ± S.E. of 6—11 animals.

—○— intravenous administration, —— ▲ —— intramuscular administration, ——●— injection into portal vein. The dose of GM was 5 mg/kg.
RESULTS

GM

Concentration-time curves in plasma and bile after intravenous injection, intramuscular injection and injection into portal vein of 5 mg/kg GM are shown in Fig. 1. The plasma concentration of GM reached 29.0 \( \mu \)g/ml, 10 min after injection into portal vein, followed by a monoexponential decrease with half-life of 25 min. As shown in this figure, the curve was similar to that obtained by intravenous injection. In case of intramuscular injection, the peak plasma concentration was reached 30 min after injection, followed by a gradual decrease, with a rather a long half-life of about 150 min. The maximum bile concentration was obtained at 60 min in any dosage forms. However, among three dosage forms, maximum bile concentration was the highest after injection into portal vein. At 60 min after injection, the concentration in the bile was about 1.8 times as high as that after intramuscular injection. The total recovery (8 h) in bile was 1.80±0.85\% (n=11) after injection into portal vein, 0.75±0.40\% (n=6) after intravenous injection and 0.23±0.13\% (n=8) after intramuscular injection.

CEZ

Fig. 2 shows the concentration-time curves of CEZ in plasma and bile after administration of 20 mg/kg by three dosage forms. At 15 min after the injection into the portal vein, the plasma concentration of CEZ reached 43.1 \( \mu \)g/ml, followed by a decrease and became undetectable 3 h later. After intravenous injection, the plasma level of CEZ rose higher than injection into portal vein, followed by monoexponential decrease and disappeared 3 h later. After intravenous injection and injection into portal vein, bile concentration of CEZ was much higher than that in plasma. After intramuscular injection, the bile level was 3 times greater than the plasma level. Among the three routes of adminis-

**FIG. 2. Levels of CEZ in Plasma and Bile**

Each value represents the mean ± S.E. of 5 – 7 animals. The symbols are the same as shown in Fig. 1. The dose of CEZ was 20 mg/kg.
turation, the bile level of CEZ, as shown in figure, was the highest after injection into portal vein. The total recovery (8 h) was 8.4 ± 2.8% (n = 7) after injection into portal vein, 5.7 ± 2.3% (n = 5) after intravenous injection and 1.2 ± 0.4% (n = 5) after intramuscular injection.

**DISCUSSION**

As to the drug with efficient transfer to bile, the concentration in tissues around the intrahepatic bile duct is assumed to be high. Consequently, it appears to be possible to facilitate the transfer of the drug to bile by raising the intrahepatic drug concentration. In the present study, in order to confirm this, we have administered the drug directly into the portal vein to evaluate the difference in the drug excretion into bile from administration by other routes.

In the present study, after the administration of GM into portal vein, the maximum bile concentration of 4.1 ± 0.7 μg/ml was obtained and this bile concentration is above MIC against *P. aeruginosa* (MIC of GM against *P. aeruginosa* is 1.75 – 3.55 μg/ml). On the contrary, we could not obtain effective bile concentration after intravenous and intramuscular administration. These results indicate that the most efficient GM transfer to bile can be accomplished by the direct administration into portal vein. This is affirmed by the highest recovery in bile after administration into portal vein. In case of CEZ, unlike GM, effective bile concentration could be obtained even after intramuscular administration. However, like the case of GM, even higher excretion of CEZ into bile was achieved by the administration into portal vein.

According to these results, for the antibiotics, such as GM, which are having an extremely low level of transfer to bile by intravenous or intramuscular administration, administration into portal vein appears to be useful clinically, as in the case of biliary tract infection. Direct administration into portal vein, however, are difficult in technics and may possibly cause acute hepatic damage because of a rapid rise of the drug in the liver. So, careful evaluation must be needed.

It is well known that drugs absorbed from the intestinal tract at first pass through the portal vein. By utilizing it, we are attempting to raise the rate of transfer of the drug into bile by ensuring effective intestinal absorption of these antibiotics. The data are now being evaluated and the results will be reported in the near future.

**REFERENCES**


