**AMPICILLIN PRODRUGS INTERACT WITH P-GLYCOPROTEIN: IN VITRO STUDY ON SUCCESSFUL PRODRUGS USING CACO-2 CELLS**

Sachie Tanaami, Sayaka Sakaguchi, Takashi Mizuma, and Masahiro Hayashi

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji 192-0392, Japan

**[Purpose]** Prodrugs have been developed to overcome the faults of active drugs. Nevertheless, the absorption process of prodrugs has not been characterized in detail. Therefore, we have previously characterized transport and metabolism of an ampicillin (ABPC) prodrug, lenampicillin (LAPC), using Caco-2 cell. LAPC has a high permeability by passive transport. However, total transport clearance from the basal (B) to apical (A) sides was larger than that from A to B sides, suggesting that LAPC is a substrate for efflux transporter such as P-glycoprotein (P-gp). Further, verapamil and cyclosporine A, substrates for P-gp, inhibited the transport of LAPC. In this study, in addition to LAPC, we have studied on the interactions of other ABPC prodrugs, bacampicillin (BAPC) and talampicillin (TAPC), with P-gp.

**[Materials and Methods]** Transport experiments of rhodamine 123, a substrate for P-gp, across Caco-2 monolayers were conducted in the presence and absence of LAPC, BAPC, TAPC or ABPC.

**[Results and Discussion]** LAPC, BAPC and TAPC inhibited transport of rhodamine 123 from the B to A sides. The order of inhibitory effects was BAPC > LAPC > TAPC. In contrast, ABPC did not inhibit the transport. These results indicate that promoiety of prodrugs plays a role in changing interaction with P-gp. In conclusion, the ABPC prodrugs have high permeability by passive transport, and thus, these prodrugs are superior to ABPC in the first membrane permeation process. However, after the permeation, ABPC that is produced from the prodrugs is superior to the prodrugs in the A to B transport, since it is not a substrate of P-gp.

---

**CHANGES OF EXCRETORY PATHWAY OF DRUGS BY LIVER DYSFUNCTION**

Hirotoshi Okumura, Miki Katoh, Keiichi Minami, Miki Nakajima and Tsuyoshi Yokoi

Graduate School of Medical Science, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

Drugs are eliminated by urinary and biliary excretion. Changes in the excretory pathway of drugs by liver dysfunction are still unclear. The purpose of the present study was to clarify the relationship between changes of the excretory pathways and the degree of hepatic dysfunction in rat. In addition, DNA microarray was performed to analyze the changes of hepatic transporter gene expression caused by liver dysfunction. Sprague-Dawley rats were intraperitoneally administered with carbon tetrachloride (CCl₄) at a dose of 640 mg/kg for 45 days once every two days. Liver dysfunction was assessed by serum AST and ALT levels. Then, CCl₄-treated rats were intravenously administered with cefmetazole (CMZ) at a dose of 100 mg/kg at 24 hrs after the final CCl₄ treatment. The 24-hr recovery of CMZ in urine and feces was obtained. Serum was also collected at 7 points up to 180 min following the CMZ treatment. CMZ is known to be excreted as an unchanged form. CMZ was mainly excreted in urine in liver dysfunctional rats but in feces in control rats. Depending on the AST and ALT levels, urinary CMZ excretion was increased while fecal CMZ excretion was decreased. The AUC value of CMZ in severe liver dysfunctional rats was approximately 2-fold higher than that of control rats. By the DNA microarray using hepatic RNA, basolateral SLC transporters such as Ntcp, Oct1, and Oatp2 were decreased and basolateral ABC transporters such as Mrp3 and Mrp4 were increased, suggesting that the alteration of transporters in the sinusoidal membrane might be related to hepatoprotection. On the other hand, apical Mrp2 and Bsep were decreased but Mdr1 was increased by the CCl₄ treatment. The change of hepatic transporter genes by liver dysfunction may affect the excretory pattern of CMZ. In conclusion, we clarified that urinary and fecal excretions of CMZ in rats were changed by CCl₄ induced liver dysfunction.