1-B1-10-1

EFFECTS OF P-GLYCOPROTEIN POLYMORPHISM ON PHENYTOIN ABSORPTION
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[Purpose]…P-glycoprotein (P-gp) is a drug efflux pump in many organs, including the intestine and liver. Two SNPs of P-gp gene (G2677T and C3435T) would affect function and expression of P-gp. Effect of P-gp polymorphism on drug disposition are controversial in the literature. It is difficult to predict pharmacokinetics from P-gp genotypes. Phenytoin is a substrate of P-gp. Persistent low phenytoin levels in plasma and P-gp overexpression in brain in several refractory epilepsy patients were reported. P-gp polymorphism may affect bioavailability of phenytoin and its efficacy. Our objective is to investigate how SNPs (C3435T and G2677T) may affect absolute bioavailability of phenytoin.

[Methods]…We selected two groups of 10 volunteers with haplotypes of G/G 2677 and C/C 3435 by PCR-RFLP. Each volunteer was orally given 300 mg of phenytoin and two weeks later intravenously infused with 210 mg of phenytoin at a rate for the same Tmax as the oral route (assuming oral bioavailability is 70%). The design was to result a similar Cmax in oral and intravenous phases with consideration of non-linear metabolism of phenytoin. Series of blood samples were sampled for 72 hours. Concentrations of phenytoin in plasma are analyzed with HPLC.

[Results and Discussion]…We found that the mean absolute bioavailability of phenytoin in T/T 2677 T/T 3435 subjects (91%) is only slightly higher than in G/G 2677 C/C 3435 subjects (82%).

[Conclusions]…The study ruled out the possibility that genetic polymorphism of P-gp may affect phenytoin efficacy through a decreased absorption. Possible effect of P-gp SNP on phenytoin efficacy in refractory epilepsy patients is probably due to effects in CNS.

1-B1-10-2

INFLUENCE OF PROTON PUMP INHIBITORS ON THE PHARMACOKINETICS OF TACROLIMUS IN ADULT LIVING-DONOR LIVER TRANSPLANT PATIENTS: A COMPARATIVE STUDY
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[Purpose] To investigate the effects of proton pump inhibitors (PPIs) on the pharmacokinetics of tacrolimus, pharmacogenomic analyses were carried out considering the cytochrome P450 (CYP) 2C19 and CYP3A5 genotypes of transplant patients (native intestine) and their corresponding donors (graft liver).

[Methods] The concentration/dose (C/D) ratio of tacrolimus [(ng/mL)/(mg/day)] was examined in adult living-donor transplant patients treated with or without PPIs on postoperative days 22-28. [Results and Discussion] The C/D ratio of tacrolimus coadministered with omeprazole was significantly higher in patients carrying two variants for intestinal CYP2C19 than wild-type homozygotes and heterozygotes (P=0.01). Conversely, intestinal and graft liver CYP2C19 polymorphism little influenced the interaction between tacrolimus and lansoprazole, but CYP3A5*1 non-carriers showed higher tacrolimus C/D ratio than CYP3A5*1 carriers. Meanwhile, there were no differences between the control group and rabeprazole group in the C/D ratio of tacrolimus for CYP2C19 wild-type homozygotes or heterozygotes (P=0.85; graft liver, P=0.52) and for patients carrying two variants (native intestine, P=0.68; graft liver, P=0.51), and similar tendency was observed for CYP3A5*1 carriers and non-carriers. [Conclusions] Our findings suggest a safer dosing of tacrolimus coadministered with rabeprazole early on after liver transplantation regardless of the CYP2C19 and CYP3A5 genotypes of transplant patients and their donors. [Footnote] Current Address (Keiko Hosohata): Department of Pharmacology, School of Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi, Japan.