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Delay of metabolism rate of ciclosporin by simvastatin in 7 Chinese healthy men

XU Feng[1], WU Zhao-Hui, ZHANG Zhong-Yi, ZOU Heng-Qin (*Department of Clinical Pharmacology, Zhujiang Hospital, First Military Medical University, Guangzhou 510282, China*)

KEY WORDS cyclosporine; simvastatin; pharmacokinetics

AIM: To study the effects of simvastatin (Sim) on pharmacokinetics of ciclosporin (Cic). **METHODS:** Seven healthy young volunteers took Cic 100 mg alone or in combination with Sim 10 mg in a randomized crossover study. The Cic concentrations in blood were determined by specific fluorescence polarization immunoassay. Data were analyzed with 3P87 program. **RESULTS:** The blood concentration-time curve was fitted to open 2-compartment model, and the pharmacokinetic parameters of Cic alone and Cic + Sim were: C_{max} (646 ± 94) and (698 ± 340) $\mu g \cdot L^{-1}$; T_{max} (1.12 ± 0.13) and (1.13 ± 0.21) h; AUC (2.3 ± 0.4) and (2.6 ± 1.2) $mg \cdot h \cdot L^{-1}$; $T_{\frac{1}{2}\beta}$ (12 ± 6) and (23 ± 8) h ($P < 0.05$). **CONCLUSION:** Sim delays the metabolism rate of Cic when they are given simutaneously.

Since the introduction of ciclosporin (Cic) in solid organ transplantation, a dramatic improvement in short-term graft survival rates has been observed[1]. But renal transplantation recipients on a Cic-containing immunosuppressive regimen showed adverse changes in plasma lipids[2-4]. Hence antihyperlipidemia drugs were prescribed in renal transplantation recipients. Simvastatin (Sim) was most frequently used to lower hyperlipidemia[5]. But there was no report about pharmacokinetic interaction between Sim and Cic. This study investigated the alteration of pharmacokinetics of Cic in healthy volunteers.

MATERIALS AND METHODS

Drugs Cic capsule (50 mg/capsule), Sino-American Huadong Pharmaceutical Co (lot 970103). Sim tablet (10 mg/tablet), Merck Sharp & Dohme (China) Ltd (lot 96058).

Subjects In accordance with the Declaration of Helsinki, 7 healthy male volunteers of Han nationality with written informed consent, having been informed about the possible side effects of the drugs and passed the physical examination, were accepted in this study. Their ages were 21 - 32 a ($24 \pm s$ 3 a), weights were 59 - 63 kg ($61 \pm s$ 1 kg), and their blood, urine, liver, kidney, and electrocardiogram were normal. At least 2 wk before the study, all were kept from medication, tobacco, and alcohol.

Protocol After 12-h fasting, the volunteers received either a single oral dose of Cic capsule (100 mg) or Cic capsule (100 mg) + Sim tablet (10 mg) according to a self-controlled, randomized crossover study design. The washout period was set to be 1 wk (The Guide Principle of Clinical Study of the New Medicine, Ministry of Public Health, People's Republic of China. Beijing, 1993: 166). A uniform diet was supplied after 2 h and 150 mL of water was drunk every 2 h. Physical labor was refrained on that day.

Blood sampling and Cic assay Whole blood samples were collected into the heparinized tubes at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h after the medication. Cic levels were determined by the specific monoclonal fluorescence polarization immunoassay (FPIA) with TDx[6].

Pharmacokinetic analysis The concentration-time curves were analyzed with 3P87 program (Section of Mathematics Pharmacology, the Chinese Pharmacological Society) on a Compae personal computer to determine the compartment models and the pharmacokinetic parameters. All data were analyzed with self-control paired t test.

RESULTS

The whole blood Cic concentration-time curves were fitted to a first order absorption and an open 2-compartment model. Tab 1 summarized the pharmacokinetic data of the Cic capsule in the same 7 volunteers.

[1] Correspondence to Assoc Prof XU Feng.
Phn 86-20-8433-9888, ext 88401. Fax 86-20-8441-3811.
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Tab 1. Pharmacokinetic parameters of Cic 100 mg or Cic + Sim 10 mg in 7 young men.
$\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$ *vs* Cic.

	Cic	Cic + Sim
$T_{\frac{1}{2}ka}$/h	0.24 ± 0.22	0.12 ± 0.07[a]
$T_{\frac{1}{2}\alpha}$/h	1.4 ± 0.7	1.5 ± 0.6[a]
$T_{\frac{1}{2}\beta}$/h	12 ± 6	23 ± 8[b]
K_{10}/h^{-1}	0.4 ± 0.3	0.22 ± 0.10[a]
C_{max}/μg·L^{-1}	646 ± 94	698 ± 340[a]
T_{max}/h	1.12 ± 0.22	1.13 ± 0.21[a]
AUC/mg·h·L^{-1}	2.3 ± 0.4	2.6 ± 1.2[a]

DISCUSSION

Sim was chemically modified by the synthetic addition of 1 methyl group on the alkyl side chain of lovastatin, which rendered it the most potent cholesterol lowering agent in the HMGCoA reductase inhibitors. In the liver, Sim was hydrolyzed to its active form[7]. HMGCoA reductase inhibitor therapy has been reported to improve lipid abnormalities in primary and secondary hyperlipidemia but was associated with severe side effects including rhabdomyolysis in patients on Cic therapy[8,9]. However, a study showed that low-dose (10 mg) Sim can be safely and effectively used to treat hyperlipidemia *in renal transplant recipients with Cic without* major side effects and whole blood through Cic levels remained stable in normal range[10].

Both lovastatin and Cic are metabolized by CYP3A4 in liver[11]. It was not clear that whether Sim was metabolized by CYP3A4. If Sim was metabolized by CYP3A4, Cic and Sim would competitively bind CYP3A4 when they were given simultaneously. In this study, we found that $T_{\frac{1}{2}\beta}$ of Cic was prolonged significantly ($P < 0.05$). And AUC were increased by about 10 % after concomitant use with Sim, though there was no significant difference ($P > 0.05$). Therefore we concluded that Sim could delay Cic metabolism rate when they were given simultaneously.

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西伐他汀延缓 7 位中国健康男子环孢素药物代谢

徐 峰[1]，吴朝晖，张忠义，邹恒琴
(第一军医大学珠江医院临床药理科，广州 510282，中国)

关键词 环孢素；西伐他汀；药物动力学

目的：研究西伐他汀对环孢素药物动力学的影响. **方法**：男性汉族健康志愿者 7 人随机交叉口服单剂量环孢素 100 mg 和同时口服西伐他汀 10 mg 后，采用特异性荧光偏振免疫法测定环孢素全血药物浓度. **结果**：血药浓度—时间曲线拟合表明该药体内过程符合二室开放模型，合用西伐他汀前后环孢素的主要药代动力学参数：C_{max} (646 ± 94) 和 (698 ± 340) μg·L^{-1}；T_{max} (1.12 ± 0.13) 和 (1.13 ± 0.21) h；AUC (2.3 ± 0.4) 和 (2.6 ± 1.2) mg·h·L^{-1}；$T_{\frac{1}{2}\beta}$ (12 ± 6) 和 (23 ± 8) h ($P < 0.05$). **结论**：环孢素与西伐他汀同时应用时，后者可延迟环孢素的代谢.