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Short communication

Effects of simvastatin on the pharmacokinetics of diltiazem and its main metabolite, desacetyldiltiazem, after oral and intravenous administration in rats: possible role of P-glycoprotein and CYP3A4 inhibition by simvastatin

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Abstract:
The purpose of this study was to investigate the possible effects of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, simvastatin, on the pharmacokinetics of diltiazem and its main metabolite, desacetyldiltiazem, in rats. HMG-CoA reductase inhibitors and diltiazem are sometimes prescribed as a combination therapy for the prevention or treatment of cardiovascular diseases. The effect of simvastatin on P-glycoprotein (P-gp) and cytochrome P450 (CYP) 3A4 activity was evaluated. Simvastatin inhibited CYP3A4 enzyme activity in a concentration-dependent manner with a 50% inhibition concentration (IC_{50}) of 3.0 μM. In addition, simvastatin significantly enhanced the cellular accumulation of rhodamine-123 in MCF-7/ADR cells overexpressing P-gp. The pharmacokinetic parameters of diltiazem and desacetyldiltiazem were determined after oral and intravenous administration of diltiazem to rats in the presence and absence of simvastatin (0.3 and 1.0 mg/kg). The areas under the plasma concentration-time curve (AUC) and the peak concentration (C_{max}) of diltiazem were significantly ($p < 0.05$, 1.0 mg/kg) increased by 45.2% and 35.2%, respectively, in the presence of simvastatin compared to control. Consequently, the absolute bioavailability (AB) values of diltiazem in the presence of simvastatin (1.0 mg/kg) were significantly ($p < 0.05$) higher (44.8%) than that of the control group. Moreover, the relative bioavailability (RB) of diltiazem was 1.21- to 1.45-fold greater than that in the control group. The metabolite-parent AUC ratio (MR) in the presence of simvastatin (1.0 mg/kg) significantly decreased compared to the control group. This result implied that simvastatin effectively inhibited the metabolism of diltiazem.
The increase in diltiazem oral bioavailability might be attributable to enhanced absorption in the small intestine *via* the inhibition of P-gp and to reduced first-pass metabolism of diltiazem *via* the inhibition of the CYP3A subfamily in the small intestine and/or in the liver rather than renal elimination of diltiazem by simvastatin.

Key words:
diltiazem, desacetyldiltiazem, simvastatin, CYP3A, P-gp, pharmacokinetics, bioavailability, rats