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Effects of Resveratrol on the Pharmacokinetics of Diltiazem and Its Major Metabolite, desacetyldiltiazem in Rats

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This study was to investigatethe effect of resveratrol on the pharmacokinetics of diltiazem and one of its metabolites, desacetyldiltiazem in rats. Pharmacokinetic parameters of diltiazem and desacetyldiltiazem were determined after oral administration of diltiazem (15 mg/kg) in rats with resveratrol (3.0, 10 and 20 mg/kg). Compared with the control group (given diltiazem alone), the area under the plasma concentration-time curve (AUC) and the peak concentration (C_{max}) of diltiazem in rats with resveratrol were significantly higher than that in the control group ($p<0.05$). The relative bioavailability (RB%) of diltiazem in rats with resveratrol was increased by 1.36- to 1.68-fold. The terminal half-life ($t_{1/2}$), elimination rate constant (K_{el}) and time to reach the peak concentration (T_{max}) of diltiazem were not altered significantly with resveratrol . The AUC of desacetyldiltiazem was increased significantly ($p<0.05$) in rats with resveratro, at doses of 10 and 20 mg/kg, but metabolite-parent ratio (MR) of desacetyldiltiazem was decreased significantly ($p<0.05$), implying that resveratrol, could be effective to inhibit the CYP 3A4-mediated metabolism and P-gp efflux pump of diltiazem. There were no apparent changes of $t_{1/2}$, K_{el} and T_{max} of desacetyldiltiazem with resveratrol. Collectively, the resveratrolsignificantly altered pharmacokinetics of diltiazem, which can be attributed to increased intestinal absorption as well as reduced first-pass metabolism. Based on these results, dose modification should be taken into consideration when diltiazem is used concomitantly with resveratrol or resveratrol-containing dietary supplements in clinical setting.

Key words: diltiazem, desacetyldiltiazem, pharmacokinetics, resveratrol, CYP3A4, rat