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Short communication

Effects of the antioxidant baicalein on the pharmacokinetics of nimodipine in rats: a possible role of P-glycoprotein and CYP3A4 inhibition by baicalein

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Abstract:
The reduced bioavailability of nimodipine after oral administration might not only be due to the metabolizing enzyme cytochrome P450 3A4(CYP3A4) but also to the P-glycoprotein efflux transporter in the small intestine. The aim of this study was to investigate the effects of baicalein on the pharmacokinetics of nimodipine in rats. The effect of baicalein on P-glycoprotein and CYP3A4 activity was evaluated. A single dose of nimodipine was administered intravenously (3 mg/kg) and orally (12 mg/kg) to rats in the presence and absence of baicalein (0.4, 2 and 8 mg/kg). Baicalein inhibited CYP3A4 enzyme activity in a concentration-dependent manner, with a 50% inhibition concentration (IC_{50}) of 9.2 μM. In addition, baicalein significantly enhanced the cellular accumulation of rhodamine-123 in MCF-7/ADR cells overexpressing P-glycoprotein. Baicalein significantly altered the pharmacokinetics of orally administered nimodipine. Compared to the oral control group given nimodipine alone, the area under the plasma concentration-time curve ($AUC_{0-\infty}$) and the peak plasma concentration (C_{max}) of nimodipine significantly increased ($p < 0.05$ for 2 mg/kg; $p < 0.01$ for 8 mg/kg). Consequently, the absolute bioavailability of nimodipine in the presence of baicalein (2 and 8 mg/kg) was 31.0–35.3%, which was significantly enhanced ($p < 0.05$ for 2 mg/kg; $p < 0.01$ for 8 mg/kg) compared to the oral control group (22.3%). Moreover, the relative bioavailability of nimodipine was 1.39- to 1.58-fold greater than that of the control group. The pharmacokinetics of intravenous nimodipine were not affected by baicalein in contrast to those of oral nimodipine. Baicalein significantly enhanced the oral bioavailability of nimodipine, which may be mainly due to inhibition of the CYP3A4-mediated metabolism of nimodipine in the small intestine and/or in the liver and the inhibition of the P-glycoprotein efflux pump in the small intestine by baicalein. The increase in oral bioavailability of nimodipine in the presence of baicalein should be taken into consideration as a potential drug interaction between nimodipine and baicalein.

Key words:
nimodipine, baicalein, pharmacokinetics, bioavailability, P-glycoprotein, CYP3A4