INHIBITORY EFFECT OF THE FIRST GENERATION H1 RECEPTOR ANTAGONISTS ON CYTOCHROME P450 IN HUMAN LIVER MICROSOME.
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The first generation H1 receptor antagonist (antihistamines) has been widely used all over the world as the treatment drug for allergic symptoms for more than 5 decades. Most of these drugs are generally available as an over the counter drugs without prescription. However, its metabolic properties in human had not been characterized. Although some of the investigators have reported the drug-drug interaction with the antihistamines recently, these reports were limited to few drugs. This study was designed to evaluate the effects of the antihistamines on cytochrome P450 enzyme activities by using human liver microsomes. We examined drug-drug interaction mediated by CYP2D6 using six of the commonly employed antihistamines, such as carboxamine maleate, clemastine fumarate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, chlorpheniramine maleate and triprolidine hydrochloride. All of the antihistamines had the inhibitory effects on the bufuralol 1'-hydroxylation, a specific CYP2D6 activity, competitively by Lineweaver-Burk plots analysis. Clemastine was the most potent inhibitor for CYP2D6 with apparent Ki value of 0.3 µM. Diphenhydramine, diphenylpyraline, chlorpheniramine and triprolidine inhibited the activity in similar potency with the Ki value of approximately 10 µM. The inhibitory potency of carboxamine was weaker with Ki value less than 25 µM. These data indicated that the antihistamines, even the drug available over the counter inhibit CYP2D6 activity in vitro in human liver microsomes.

INTESTINAL DRUG-DRUG INTERACTIONS OF ORALLY ADMINISTERED DRUGS IN CYNOGLOSSUS MONKEYS
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The contribution of the intestine to first-pass effect is being focused since the localization of drug metabolizing enzymes and efflux drug transporters has been demonstrated in this tissue. In the present studies, we evaluated the extent of cytochrome P450 (CYP) 3A and P-glycoprotein (P-gp) inhibitions at the intestine using midazolam (MDZ) and fexofenadine (FEX), typical substrates for CYP3A and P-gp, respectively, in cynomolgus monkeys. When MDZ or FEX was administered intravenously, these plasma concentration-time profiles were not influenced by coadministering ketoconazole (KTZ) orally (20 mg/kg). On the other hand, when MDZ or FEX was administered orally at doses of 1 mg/kg or 5 mg/kg, respectively, with concomitant oral dose of KTZ (20 mg/kg), significant increases were observed in the area under the curves of MDZ or FEX plasma concentrations (22-fold in MDZ and 3-fold in FEX). Furthermore, following the oral dosing of erythromycin, a mechanism-based inhibitor, twice a day for three days, the plasma concentration of MDZ after oral dosing increased significantly. These results were substantially comparable to those in humans, suggesting that in vivo studies in monkeys might allow a more precise prediction of intestinal drug-drug interactions in humans.