Increase in the systemic exposure of drug metabolites in rat arising from CYP inhibition

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We have reported that the systemic exposure of primary metabolites of midazolam increased dramatically when CYP enzymes were inhibited in rats. In this study, addition to MDZ, various CYP substrate drugs were used to investigate the effect of CYP inhibition on the systemic exposure of drug metabolites. Midazolam, Tamoxifen, Verpamil and Diazepam were used as CYP substrate drugs. After oral pretreatment with 1-aminobenzotriazole (ABT), a CYP inhibitor, each drug was intravenously injected to rats and the plasma concentration profiles of parent drugs and their primary metabolites (M1) were observed. ABT-pretreatment significantly delayed the elimination of the parent drugs. At the same time, plasma AUC of their M1 increased dramatically (2.3 to 5.1-fold) despite the fact that CYP metabolism was inhibited. To understand the reasons of this phenomenon, the systemic clearance of M1 (CL_{sys}) were measured. $CL_{sys,}$ of M1 of all drugs were found to be decreased by ABT-pretreatment, suggesting that the metabolism to the secondary metabolites (M2) were also inhibited and that is one of the reasons for increased plasma AUC of M1. Then, exposed amounts of M1 in the systemic circulation were calculated by multiplying their AUC by CL_{sys} obtained under normal and CYP inhibited conditions. Except the case of Diazepam, amounts of M1 exposed to the systemic circulation were found to be increased by ABT-pretreatment (1.9 to 2.4-fold). It was considered that the inhibition of the subsequent metabolism of M1 to M2 in the hepatocytes enhanced the amounts of M1 released from the hepatocytes to the blood circulation. *In vitro* experiments with rat liver microsomes supported this hypothesis. There findings suggest the possibility to cause the metabolite-derived side effects when the metabolic enzymes are inhibited and the necessity to check the variation of the PK profile of drug metabolites carefully.