NONLINEAR FIRST PASS METABOLISM OF MIDAZOLAM IN RAT
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It is known that CYP3A existed in both small intestine and liver may affect the bioavailability of an orally admininstered drug metabolized by the enzyme. When the unbound drug concentration in the intestinal mucosa or liver exceeds the Km value of CYP3A, the saturation of CYP3A activity is occurred and the bioavailability of the drug is increased. In order to examine the nonlinearity of first pass metabolism in small intestine and liver, the dose dependency of pharmacokinetics of midazolam (MDZ) was examined in the male SD rats (8w). Area under the curve (AUC) was determined from the plasma concentration profiles after administration of MDZ, and the value of clearance (CL) was calculated from dose/AUC. CL after iv administration was almost constant in the range of the dose examined (2.5-10mg/kg). On the other hand, the CL after intrajejunal administration has decreased in a dose dependent manner. Increasing the dose from 5mg/kg to 30mg/kg, CL was decreased to about 15%. After intraportal administration of MDZ, CL was also decreased in a dose dependent manner. Increasing the dose from 2.5mg/kg to 20mg/kg, CL was decreased to about 25%. Pharmacokinetic analysis of these data indicated that saturation of metabolism might have occurred both in small intestine and liver. These results consisted with our previous in vitro studies using rat microsomes. Present results indicated the nonlinear first pass metabolism might be occurred especially in rats and when extrapolating bioavailability of drugs from rats to human, this phenomena might be considered.

PHARMACOKINETICS AND METABOLITE PROFILES OF 14C-DIAZEPAM IN HUMAN PLASMA ANALYZED BY AMS AND LC/MS/MS IN A MICRODOSING STUDY
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A microdosing study using 14C-labeled diazepam, the same compound used in the CREAM trial study in 2005, was performed to evaluate the feasibility of microdosing and subsequent analysis of pharmacokinetics and metabolite profiles in clinical studies. 14C-labeled diazepam (100µg, 200nCi/body) was intravenously administered to four healthy male volunteers at CMAX, Australia. Plasma samples were collected up to 96 hours after administration. Total radioactivities and unchanged drug concentrations were determined by AMS and HPLC-AMS, respectively. The unchanged drug concentration in plasma was also analyzed by LC/MS/MS. The total and unchanged drug concentrations showed good shape for each volunteer, and are consistent with results of the CREAM study. There was a good correlation of unchanged drug concentration between LC/MS/MS and AMS. The metabolite profiles were measured by HPLC-AMS and compared to those of the CREAM study. These results showed that the microdosing study coupled with AMS analysis was reproducible and sufficient to analyze and elucidate PK data and metabolite profiling.