QUANTITATIVE ANALYSIS OF THE FIRST-PASS METABOLISM IN THE SMALL INTESTINE AFTER ORAL DRUG ADMINISTRATION
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First-pass metabolism of orally administrated drugs that occurs in the intestinal epithelial cells is now recognized as one of the main factors for determining the oral bioavailability of some drugs. In this study, we have tried to evaluate quantitatively the intestinal first-pass metabolism of drugs by using in situ single-pass perfusion study in rat. Under anesthesia condition, rat jejunum was perfused with the solution containing verapamil or propranolol to determine the absorbed and metabolized amount. Blood samples were routinely taken from the portal vein and the systemic circulation during the perfusion. First-pass metabolism in the intestine was calculated from the difference between the amount of the drug disappeared from the intestinal lumen and that appeared into the portal vein. In addition, in vitro metabolic assays in the intestinal microsomes of rat, dog, monkey and human (prepared by XenoTech LLC) were performed to consider the in vitro/in vivo correlations. From in situ single-pass perfusion study, the intestinal extraction ratios (Eg) of verapamil and propranolol were calculated as 0.9 and 0.6, respectively, suggesting the high metabolic extraction of both drugs in rat intestine. In vitro metabolic clearance of verapamil in the intestinal microsomes was in the order of monkey>> human>rat>dog. In the case of propranolol, in vitro intestinal metabolic clearance was quite low in all animals and human. In order to make clear the reason of these in vitro/in vivo differences in the intestinal metabolic activity, further studies will be performed with the inhibitors of metabolic enzymes.

IMPROVEMENT OF ORAL ABSORPTION BEHAVIOR OF POORLY WATER-SOLUBLE DRUG USING SMEDDS: PHARMACOKINETIC ANALYSIS AND PREDICTION BASED ON GITA MODEL (II)
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Based on Gastrointestinal-Transit-Absorption (GITA) model, we succeeded in predicting the mean plasma concentration-time curve of griseofulvin, classified into Class II of the biopharmaceutics classification system (BCS), orally administered as powder into rats. Individual absorption behavior was also successfully described by analytical method utilizing GITA model. However, the large intra- and inter-individual difference caused by variable in-vivo dissolution behavior makes it difficult to predict the individual plasma concentration-time curve accurately. In this study, therefore, we tried to diminish the variability in in-vivo dissolution behavior by preparing the self-microemulsifying drug delivery system (SMEDDS), composed of Capryol 90, Cremophor EL and Carbitol. The bioavailability of griseofulvin was increased and the inter-individual difference was attenuated by orally dosing griseofulvin as SMEDDS formulation. Furthermore, it was found that the gastric emptying after oral administration of SMEDDS formulation was slower than that after oral dosing of aqueous or PEG solution. The release of griseofulvin from microemulsion was also investigated, and it was suggested that bile and lipase could enhance the release from microemulsion. Based on these results, we tried to predict the plasma concentration-time curve of griseofulvin after oral administration as SMEDDS formulation into rats by using GITA model in which the release process from microemulsion was introduced. The in-vivo release profile and the segmental contribution to absorption of griseofulvin were also evaluated.