INVESTIGATION OF UNIQUE PHARMACOKINETICS IN CYNOMOLGI (1) - PROBLEM IN ESTIMATION OF HUMAN BIOAVAILABILITY AND ITS SOLUTION -
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Evaluation of pharmacokinetics for compounds in animal species is important in drug discovery stage to assure promising candidate in clinical stage. Species differences in pharmacokinetics are often observed, however the factors contributing to such differences especially between cynomolgus and other species have not yet been fully clarified. In the present study, we analyzed pharmacokinetic profile of novel compounds (Drugs A, B and C) with similar pharmacological property and the commercially available drugs in both cynomolgus and rats. Observed absolute oral bioavailability (BA) of Drug A was much lower in cynomolgus than that in rats, whereas that of Drugs B and C was almost similar between the two species. The BA of each compound cannot be accounted for by hepatic first-pass effect, indicating that intestinal absorption and/or intestinal metabolism affect BA. We have also analyzed plasma concentration profiles of several commercially available drugs including midazolam, metabolized in human intestine, etoposide and digoxin, P-glycoprotein substrates, and theophylline, well-absorbed and poor-metabolized, after iv and po administration. In cynomolgus midazolam and etoposide also showed poor BA which could not be explained by hepatic first-pass elimination. Therefore, to clarify the reason of such poor BA and its species difference, it is necessary to directly evaluate the mechanism(s) involved in intestinal absorption in these species.

INVESTIGATION OF UNIQUE PHARMACOKINETICS IN CYNOMOLGI (2) - INTESTINAL ABSORPTION MECHANISM OF MIDAZOLAM IN CYNOMOLGI AND RATS
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Oral bioavailability (BA) of certain therapeutic agents, such as midazolam, is known to be lower in cynomolgus, even if those agents exhibit much higher BA in other species including human. It has been suggested that minimal intestinal absorption of midazolam could cause its lower BA in cynomolgus. In the present study, we aimed to clarify the intestinal absorption mechanism of midazolam and its species difference between cynomolgus and rats. We evaluated apical-to-basal and basal-to-apical transport of midazolam, and formation of 1-OH and 4′-OH metabolites in small intestinal tissues using Ussing-type chamber in cynomolgus and rats. Contrary to rats, metabolic clearances of midazolam in monkey intestines were higher than transport clearances. In cynomolgus, the duodenum metabolic clearance in the direction of apical-to-basal transport was higher than that in the direction of basal-to-apical transport, although no vectorial transport was observed, implying that inhomogeneous metabolic activity for midazolam exists in monkey intestines. Higher concentration of midazolam in donor side chamber increased transport clearance of midazolam in cynomolgus, but decreased that in rats. The nonlinear kinetics of midazolam transport and inhomogeneous metabolism in intestinal tissues could be explained by the mathematical model which assumes the extensive metabolism during the uptake of midazolam from apical cell-surface. Thus, extensive and inhomogeneous distribution of metabolic activity for midazolam in small intestinal tissues may reduce intestinal absorption of midazolam in cynomolgus. A certain type of saturable transport system would be involved in the intestinal absorption in rat intestine.