INVESTIGATION OF UNIQUE PHARMACOKINETICS IN CYNOMOLGI (3) - ESTIMATION OF INTESTINAL FIRST-PASS EFFECT IN CYNOMOLGI -

Midori Ono¹, Nobuyuki Amano¹, Tomohiro Nishimura², Yoshiyuki Kubo², Yukio Kato², Akira Tsuji² and Tetsuo Miwa¹
¹Discovery Research Center, Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd., Osaka, 532-8686 and ²Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan

The aim of this study is to clarify the contribution of intestinal first-pass effect to species difference in oral bioavailability (BA). We compared BA of several compounds that are under development, and midazolam, a reference compound that is supposed to be subjected to intestinal metabolism. We first performed in vitro metabolism study using hepatic microsomes prepared from both cynomolgi and rats, and calculated intrinsic clearance, which were then converted into predicted value for hepatic availability (Fₕ) in vivo. The Fₕ of each compound thus estimated from in vitro studies was then compared with BA that was experimentally obtained in a series of this study. Midazolam exhibited much lower BA than the estimated Fₕ in cynomolgi, whereas little difference between BA and Fₕ was observed in rats, indicating that intestinal first-pass effect leads to difference between BA and Fₕ in cynomolgi. The absolute value for Fₕ x Fₐ estimated in Ussing-type chamber for midazolam in cynomolgi was much lower than that in rats and can mostly explain the difference between BA and Fₖ. In conclusion, Ussing-type chamber method would be a useful approach not only to understand the mechanism(s) involved in intestinal absorption of therapeutic agents, but also to quantitatively estimate intestinal first-pass effect. Our results indicate that intestinal metabolism is an important factor to explain the species difference in oral BA. Based on the result of midazolam, this approach was applied to explain the intestinal first-pass effect for novel compounds that are under development.

INVESTIGATION OF UNIQUE PHARMACOKINETICS IN CYNOMOLGI (4) - LIMITED INTESTINAL ABSORPTION OF ETOPOSIDE IN CYNOMOLGI AND RATS

Yukio Kato¹, Tomohiro Nishimura¹, Yoshiyuki Kubo¹, Nobuyuki Amano², Midori Ono², Tetsuo Miwa² and Akira Tsuji¹
¹Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, ²Discovery Research Center, Pharmaceutical Research Division, Takeda Pharmaceutical Co. Ltd., Osaka 532-8686

In the present study, we aimed to clarify the mechanism of the species difference in oral bioavailability including cynomolgi that exhibit lower oral bioavailability for a certain type of drugs than in human. According to our pharmacokinetic analysis of the commercially available drugs that showed limited bioavailability in cynomolgi after oral administration, we chose etoposide as a model drug, since such poor bioavailability could not be explained by hepatic first-pass elimination. We divided the small intestine to three segments and measured the permeability of etoposide in each segment in cynomolgi and rats by Ussing-type chamber. Permeabilities of digoxin, theophylline and FITC-dextran (FD-4) were also examined as a reference for P-gp function, rapid absorption and slow absorption, respectively. Additionally, we investigated P-gp expression level in cynomolgi and rat small intestines by western blot analysis. Contrary to the high permeation of theophylline, apical-to-basal permeability of etoposide was comparable to FD-4 in all segments of cynomolgi and rats, indicating that such minimal intestinal permeability results in the limited bioavailability of etoposide both in cynomolgi and rats. Despite of the P-gp expression no clear vectorial transports of etoposide and digoxin were observed in cynomolgi, although obvious vectorial transports of them were observed in all segments of rat small intestine. Kinetic analysis revealed the species difference of the intestinal absorption mechanism of etoposide. Apical uptake was found to be rate-limiting step of etoposide absorption in cynomolgus, whereas apical-to-basal transport was limited by back efflux to luminal side probably via P-gp from inside the cells in rats.