

PREDICTION OF *IN VIVO* INTESTINAL HYDROLYSIS AND ABSORPTION OF PRODRUG FROM *IN VITRO* DATA

Keiichirou Tanaka, Toshimitu Soejima, Takaaki Nozawa, Teruko Imai
School of Pharmacy, Kumamoto University, 5-1 Oe-honmachi, Kumamoto, 862-0973,
Japan, 087p2022st.kumamoto-u.ac.jp

ABSTRACT

Prodrug, a pharmacologically inactive derivative of an active parent drug, is useful to improve bioavailability of therapeutic agent. Prodrugs are mostly ester derivatives which are converted to parent drugs by hydrolases that widely exist in the body including intestine. Hydrolysis of prodrug in the intestinal epithelial cells let its bioavailability down due to efflux of parent drug into intestinal lumen (Fig.1). Prodrug orally absorbed as an intact prodrug results in a high bioavailability. In the present study, we tried to decide a reliable indication of intestinal hydrolysis capacity from the correlation between *in vitro* hydrolysis data and *in situ* single-pass perfusion data in rat jejunum.

All prodrugs tested in *in situ* perfusion experiment showed the high membrane permeability coefficient (P_{eff}) which indicate 100% absorbance in human. *In situ* hydrolytic clearance (CL_{deg}) of prodrugs was same order of *in vitro* intrinsic clearance ($CL_{int, deg}$) determined in 9000g supernatant of rat jejunum homogenate (Isovaleryl-propranolol>> Temocapril> Ethylhexofenadine> Butyl-*p*-aminobenzoate> Ethyl-*p*-aminobenzoate> Oseltamivir). The sigmoidal correlation was observed between *in situ* hydrolysis rate and $\text{Log}(CL_{int, deg})$. We have suggested that $100\mu\text{L}/\text{min}/\text{mg}$ S9 protein of $CL_{int, deg}$ is limitation of complete hydrolysis in a process of intestinal absorption. The proposed correlation is useful for the prediction of *in vivo* intestinal hydrolysis and absorption of prodrug from *in vitro* data.

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