ANALYSIS OF FACTORS AFFECTING PROPRANOLOL PHARMACOKINETICS IN RAT AND HUMAN USING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL

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Propranolol is known to be a highly-extracted drug in the liver, and to receive extensive first-pass effect. Dose range has been discussed, which caused a non-linear pharmacokinetics (PK) of orally administered propranolol. Some reported non-linear PK, comparing bioavailabilities (BA) between sustained release dosage forms and conventional tablets (lower BA was obtained after sustained release dosing), because of a saturable first-pass effect (dose: 40-160mg). Others reported linear PK between BA and dose of propranolol (dose: 40-120mg). In this study, we attempt to examine metabolic kinetics of propranolol using rat and human microsomes to estimate Michaelis-Menten parameters. By using those parameters, we simulated blood drug levels after propranolol administrations using a general physiologically-based pharmacokinetic (PBPK) model, and analyzed factors influencing PK. The drug was assumed to be metabolized solely by the liver. The metabolic PK parameters used in the model were experimentally obtained, and other physiological parameters were quoted from literatures. The metabolic activity of propranolol in the rat microsomes was much higher than that obtained from the human microsomes within the clinically observed plasma levels (below 1.0μg/mL). The simulated propranolol levels per unit dose tended to increase at higher dosing depending on the Km values. To assess factors affecting PK, fluctuations of AUC and Cmax (tmax) in response to the change of its PK parameters were investigated.

COMPARISON OF IN-VITRO DISSOLUTION PROFILES OF GENERIC DILTIAZEM FORMULATIONS WITH INNOVATOR ONES AIMED TO DEVELOP AN IN-VITRO IN-VIVO CORRELATION (IVIVC)

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A well-validated in-vitro in-vivo correlation (IVIVC) facilitates formulation development, since it enables to predict bioavailability profiles of the formulations from the in-vitro drug release data. Especially, BCS* Class I drugs classified by the solubility and permeability characteristics achieve excellent in-vitro in-vivo correlation. The purpose of this study is to characterize the in-vitro in-vivo correlation of diltiazem hydrochloride (a BCS* Class I drug) formulations. Eight marketed diltiazem hydrochloride formulations (30 mg sustained release uncoated tablets and 100 mg sustained release capsules) of innovator product; Herbesser (Tanabe Seiyaku, Osaka, Japan) and three brands of generic products; Clarute (Sawai pharmaceuticals, Osaka, Japan), Coroherser (Nichi-iko Pharmaceuticals, Toyama, Japan) and Pazeadin (Taiyo Yakuhin, Aichi, Japan) were used. The in-vitro dissolution rate profiles of these diltiazem hydrochloride formulations were determined using the JP paddle method at 50 rpm with 900 mL of either water or a test solution (pH 1.2, pH 4.0, or pH 6.8). The in-vivo drug absorption rates were calculated by the deconvolution of plasma concentration profiles of oral doses using the profile of intravenous dose as the weighting function. All plasma concentration data were quoted from the DI-leaflets. The dissolution profiles of the tested formulations were slightly different. A single IVIVC was obtained in the tested formulations. Simulation of in-vivo plasma profiles of diltiazem hydrochloride using the obtained IVIVC is a useful approach to compare the innovator formulations and the generic ones.

*BCS: Biopharmaceutics Classification System