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NON-LINEAR PHARMACOKINETICS IN ANIMALS: CLARIFICATION OF MECHANISM AND EXTRAPOLATION TO HUMANS
Takeshi Fukuda1, Ken-ichi Numoya1, Tetsu Kondo1, Takeo Umemura1, Yoshiyuki Yamaizaki1, Ichiro Matsumoto1, Yasuyuki Miyata1, Mikio Ogawa1, Ryoko Yamamoto2, and Miki Hisa Takano2
1Pharmacokinetic Research Laboratories, Ono Pharmaceutical Co., Ltd., 17-2 Wadai, Tsukuba 300-4247, Japan; 2Department of Pharmaceutics and Therapeutics, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8553, Japan

When plasma concentrations are predicted to increase disproportionally with dose, Phase I clinical study requires more steps than usual in terms of side-effects. Therefore, when nonlinearity was observed in animals, its mechanism should be elucidated, and the possibility of nonlinearity in humans should be estimated before Phase I study. When compound X was orally administered to rats, the plasma concentrations increased more than a linear fashion with dose. To clarify the mechanism of the nonlinearity, the hepatic (E_U) and intestinal (E_I) extraction ratios of compound X were determined by methods such as mesenteric blood collecting method in situ and intraperitoneal administration. As a result, the E_U and E_I were 19% and 75%, respectively. The fractional metabolism of compound X in the intestine decreased as dose increased. These results indicate that the non-linear pharmacokinetics in rats was derived mostly from the saturable intestinal first-pass metabolism. An in vitro metabolism study of compound X was next carried out using human intestinal microsomes to estimate the possibility of nonlinearity in humans. The obtained K_m (19.5 μmol/L) was similar to the predicted concentration of compound X in intestine when 20 mg of compound X was orally dosed to humans, suggesting that the intestinal first-pass metabolism was saturated at a dose of 20 mg or more. The prediction was supported by the results from clinical pharmacokinetic studies. Therefore, the methods used in this study would be helpful for compounds with the same problem in estimating the possible nonlinearity in humans.

30PE-20

APPLICATION OF POTENT SOLUBILIZERS TO THE EXPLORATORY STUDY OF TOXICITY AND EFFICACY FOR POORLY SOLUBLE DRUGS (III)
Koji Takada1, Ayoji Furuichi1, Takeo Fujita1,2
1ADME Research Inc. 1-12-8, Senta-1gashin, Minoh-shi, Osaka, 562-0035, Japan and 2Celeste co.17-4-3F, Kyobashi 1-Chome, Chuo-ku, Tokyo 104-0031, Japan.

【Purpose】In the case of poorly water-soluble compounds, it is hard to assess their toxicity and efficacy in vivo due to the insufficient blood exposure by oral administration. In this study, oral exposure test of poorly water-soluble compounds was carried out with potent solubilizers (Wellsolve, Wellsolve-F™) to develop a rational method for exploratory toxicity and efficacy study. 【Method】Albendazol, Troglozilate and Danazol were used as model compounds with poor water-solubility. These drugs were orally administered to SD rats as: (1) 0.5% methyl cellulose (MC) suspension, (2) Wellsolve™ (WS) vehicle (WS:DMSO=90:10) or (3) Wellsolve-F™ (WS-F) vehicle (WS:F: DMSO=90:10). Two different doses were used for each drug (10 and 300 mg/kg for Albendazol and Danazol, 10 and 100 mg/kg for Troglozilate). After administration of drugs, blood samples were collected from the jugular vein to observe blood concentration-time curve. 【Results and Discussion】When MC suspension of Albendazol were orally administered, AUC[0-24] was 579 ng · hr/mL for 10 mg/kg dose and 2704 ng · hr/mL for 300 mg/kg, indicating that the blood exposure of Albendazol increased only 4.7 times regardless of 30 times increase in dose. On the other hand, when WS vehicle were used for administration, AUC[0-24] was 714 and 11925 ng · hr/mL (10 and 300 mg/kg), respectively. Absorption enhancement effect of WS was more distinct at high dose and at 30 mg/kg dose, blood exposure was 4 times higher than that obtained by MC suspension. WS-F gave the similar result with WS for AUC although the Cmax was significantly lower. Both WS and WS-F showed the similar effects on the absorption of Troglozitate and Danazol, confirming the superiority of these solubilizers to use in toxicity and efficacy study in animals.