30PE-21

SIMULTANEOUS SIMULATION OF METABOLISM-BASED DRUG INTERACTION OF ORAL AND IV DOSE OF DULOXETINE (CYP1A2 SUBSTRATE) WITH FLUVOXAMINE (CYP1A2 INHIBITOR) BY USE OF DYNAMO-PK ANALYSIS METHOD
Katsumi Iga, Akiko Kiriyama and Akino Honbo
Doshisha Women's College of Liberal Arts

Fluvoxamine (FLV: a potent CYP1A2 inhibitor) is known to cause common-metabolism based drug-drug interaction against various drugs administered orally. Previously, by use of Dynamo-PK analysis method, we analyzed how greatly the magnitude of drug interaction is influenced by the hepatic extraction ratio (Eh) of a rapidly-eliminating substrate drug (melatonin) as well as the Ki of FLV. In the present study, we carried out a simultaneous simulation of drug interaction of oral dose and iv infusion of duloxetine (DUL) in presence and absence of FLV, by use of the same method and the reported clinical study data (Lobo et al., 2008). Functional analysis of drug interaction was also carried out, focusing on Eh of a hypothetical substrate with FLV. Plasma DUL levels following a oral dose and iv infusion of DUL in presence and absence of FLV were well simulated. Magnitude of the interaction as designated by RAUCs obtained in the simulation versus the clinical study for oral dose and iv infusion were 4.6 versus 2.7, and 5.6 versus 2.7, respectively. Functional analysis of drug interaction demonstrated that Eh of a hypothetical substrate drug affected the interaction greatly: unlike the iv administration route, the oral administration route increased RAUC dramatically with Eh at Eh > 0.9. Development of a new Dynamo-PK analysis method which can afford us the analysis of drug interaction of metabolites, is under the way.

30PE-22

INTERACTIONS OF JM-1232(-) WITH HUMAN CYTOCHROME P450 ENZYMES
Takako Ohkura1, Kazuyo Yokohata1, Teruyo Mori1, Koji Tayai1, Anne Matthews2, Danny S. Paul2, Michael Hall2
1Department of Preclinical Development II, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., 2-2-18, Imazu-naka, Tsurumi-ku, Osaka, 538-0042, Japan. 2Department of In Vitro Metabolism, Huntingdon Life Sciences Ltd., Woolley Road, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, United Kingdom.

JM-1232(-) is under development for use as an anaesthetic and sedative. The potential of JM-1232(-) to interact with human hepatic cytochromes P450 (CYPs) both as substrate and inhibitor was investigated. (A) [14C]JM-1232(-) was incubated: 1) at concentrations of 1, 3 and 30 µM with Supersomes® expressing each of CYPs 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (50 pmol/ml) for 60 min, 2) at a concentration of 10 µM with pooled human liver microsomes (0.5 mg/ml) in the presence of selective chemical inhibitors (1, 10, 100 µM) of each CYP for 30 min, and 3) with pooled human liver microsomes (0.5 mg/ml) in the presence of inhibitory antibodies (2.3-2.7 µg/ml) of each CYP. (B) JM-1232(-) (25 µM) was incubated with pooled human liver microsomes in the presence of substrates selective for each CYP, both with and without a 30-min pre-incubation period. Results from incubations with pooled human liver microsomes showed that JM-1232(-) was metabolised to several metabolite fractions, two of which were quantified. Most metabolism of JM-1232(-) in incubations with Supersomes® was seen with CYP3A4 ≈ CYP2C19 ≈ CYP2D6 and little or none with the other three CYPs. The greatest extent of inhibition of JM-1232(-) metabolism by pooled human liver microsomes was by selective inhibitors of CYP3A4/5 > CYP2C19 ≈ CYP2D6. Inhibition of JM-1232(-) metabolism by pooled human liver microsomes was seen with inhibitory antibodies of CYP3A4, only. There was no notable inhibition by JM-1232(-) of any of the CYP activities examined (maximum 16% inhibition, of CYP2D6 activity) and there was no evidence for time-dependent inhibition of any CYP. In conclusion, the human Phase I metabolism of JM-1232(-) is principally catalysed by CYPs 3A4/5, 2C19 and 2D6, and it is likely that CYP3A4 is the major enzyme. JM-1232(-) is not a significant inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4/5 at 25 µM, a concentration considered to be high relative to the anticipated human Cmax.