P353 Prediction of human-specific metabolites of compound X using chimeric mice with humanized liver

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Characterization of drug metabolites in human plasma is crucial for understanding their contributions to drug efficacy and toxicity. The purpose of this study was to assess whether chimeric mice with humanized liver adequately predict the formation of human-specific metabolites of compound X. After a single oral administration of compound X to healthy volunteers, plasma concentrations of compound X and its metabolites were determined using LC-MS/MS. Compound X was primarily metabolized via hydrolysis of the amide bond to M1, and the ratio between the mean area under the curve of M1 to that of the unchanged drug (AUC_{M1}/AUC_{UD}) was 324% in human plasma. Furthermore, M1 was metabolized to oxidized metabolites (M2, M3, M4, and M5) and the AUC_{met}/AUC_{UD} ratio for each was 1.5%, 6.6%, 5.8% and 6.0%, respectively. These oxidized metabolites of M1 were not detected in rats, dogs, or monkeys, indicating that they were human-specific. Next, a single oral dose of ^{14}C-labeled compound X (20 mg/kg) was administered to PXB mice with humanized liver (PhoenixBio, Co., Ltd, Hiroshima, Japan) and control mice (SCID mice). Metabolic profiling of plasma samples collected at 1 and 6 h after administration was conducted using Radio-LC-MS/MS. At 1 h after administration, compound X and M1 were detected as major components in plasma of PXB mice, accounting for 25% and 42% of the total peak area determined by the radiochromatogram, respectively. The ratio of the plasma concentration of M1 to the unchanged drug (Cp_{M1}/Cp_{UD}) was 173%. M4 and M5 were also detected in plasma of PXB mice, accounting for 0.7% and 1.4% of the total peak areas, respectively (Cp_{M4}/Cp_{UD} and Cp_{M5}/Cp_{UD} were 2.9% and 5.7%, respectively). Although they were not found to be radioactive, trace levels of M2 and M3 were detected via LC-MS/MS in the plasma of PXB mice. At 6 h after administration, M4 was detected in the plasma of PXB mice, accounting for 0.5% of the total peak area (Cp_{M4}/Cp_{UD} was 36%), M5 was detected at trace levels via LC-MS/MS, and M2 and M3 were not detected at all, even by LC-MS/MS. In contrast, no human-specific metabolites (M2, M3, M4, or M5) were detected in the plasma of SCID mice, even though M1 was detected and accounted for 20% of the total peak area. The rank order of plasma exposure of human-specific metabolites in PXB mice (M4 and M5 >> M2 and M3) was different from that in humans (M3, M4, and M5 > M2). Therefore, PXB mice could not fully predict plasma exposure of human-specific metabolites in humans. These results suggested that PXB mice could be useful as an *in vivo* model for qualitative prediction of human-specific metabolites in human plasma.