27O-ISMS11 Prediction of Human Pharmacokinetics Using Chimeric Mice with Humanized Liver

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Prediction of human pharmacokinetics (PK) is important for drug discovery. Predictions of human PK have primarily been conducted using *in vitro-in vivo* extrapolation and allometric scaling methods. However, these methods are often prone to failure due to discrepancies between *in vitro* and *in vivo* data, and interspecies differences in drug metabolism and PK. Chimeric mice with humanized liver have been developed. In these mice, the mouse liver is repopulated with mostly human hepatocytes, which express human drug-metabolizing enzymes and transporters. Thus, these mice are regarded as reliable animal models for mimicking human drug metabolism and PK. We evaluated the prediction of human PK using chimeric mice with humanized liver. We predicted total clearance (CL_t) and volume of distribution at steady state (Vd_{ss}) for various compounds metabolized by P450 and non-P450 enzymes based on single-species allometric scaling using chimeric mice with humanized liver, and observed excellent predictability. We predicted human intravenous plasma concentration-time profiles using the complex Dedrick plot, and also observed good predictability. Using similar methods, we evaluated the prediction of human CL_t and Vd_{ss} for hepatic drug transporter substrates, and found excellent predictability. These results suggest that chimeric mice with humanized liver are useful for predicting human PK. [Reference] Sanoh S et al., Predictability of plasma concentration–time curves in humans using single-species allometric scaling of chimeric mice with humanized liver. Xenobiotica, 45(7): 605-614 (2015)