HUMAN-SPECIFIC METABOLITE IN DICLOFENAC-TREATED CHIMERIC PXB MICE WITH HIGHLY HUMANIZED LIVER

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[Purpose] FDA issued the Guidance of Safety Testing of Drug Metabolites (STDM) in February 2008. This guidance may require to evaluate whether metabolites either are identified only in humans or are present at disproportionately higher levels in humans than in any of the animal species used during standard nonclinical toxicology testing. Diclofenac is a non-steroidal anti-inflammatory, primarily used for the treatment of arthritis. A previous study showed that diclofenac forms a human-specific metabolite, 3'-hydroxy-4'-methoxy diclofenac in vivo, although the metabolite were not detected in vitro metabolism. We studied the metabolism of diclofenac on chimeric PXB mice, possessing highly humanized livers. This animal model has been shown to exhibit human-type drug metabolism in response to various drugs and, therefore, is attracting much attention for studies on metabolic profiling of newly developed drugs.

[Methods] Homogenized liver and plasma from control mice and chimeric PXB mice treated with diclofenac were subjected to LC/MS. [Results and Discussion] Using LC/MS, we detected 3'-hydroxy-4'-methoxy diclofenac as being present in the livers and plasma of PXB mice treated with diclofenac while absent from the corresponding control mouse. [Conclusions] We found out human-specific metabolite in plasma and liver, administrated to chimeric PXB mice, possessing highly humanized livers. This result shows that chimeric PXB mice is greatly helpful animal model in order to predict human metabolism in vivo.

AN IMPROVED METHOD TO ASSESS INTERNAL RADIATION EXPOSURE IN HUMANS USING IN VIVO AND IN VITRO ANIMAL PHARMACOKINETIC DATA

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[Purpose] Before conducting a human microdosing study, distribution study of the radiolabeled compound in pigmented animals should be carried out to assess the internal radiation exposure in humans. Previous methods for the radiation exposure assessment such as MILD methods consider organ/body weight ratio but ignore the species difference in the clearance. We propose a new method to estimate the internal radiation exposure more correctly in humans using both the animal distribution data in vivo and the intrinsic clearance data in vitro in animals and humans as the scaling factor.

[Methods] Distribution of ¹⁴C-labelled tolubutamide and acetoaminophene was determined in the pigmented rats. Radiation exposures in humans were estimated by OLINDA ver. 1.1 software (Organ Level INternal Dose Assessment code, Vanderbilt Univ, 2007) by fitting the time-radioactivity level data of these compounds. In vitro intrinsic clearance data were obtained using liver subcellular fractions from rats and humans in the presence of cofactors.

[Results and Discussion] The ¹⁴C-radiolabeled compounds were eliminated almost completely from rats within a week. An in vitro intrinsic clearance value of tolubutamide in pooled human liver microsomes was similar to that in rat liver microsomes.

[Conclusions] Based on the traditional concept of animal-human-in vitro-in vivo parallelogram in the risk assessment system, the present study first introduced the in vitro clearance data as the scaling factors into the assessment of the human radiation exposure. Estimated human radiation exposure in the microdosing studies was quite low compared with the permitted annual dose limit for the radiation exposure in normal humans.