INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDY (5)
 IDENTIFICATION OF HUMAN METABOLITES BY A COMBINATORIAL USE OF AMS AND LC/MS/MS
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[Aim]To evaluate pharmacokinetics (PK), metabolism and drug interaction of 14C-acetoaminophen (14C-AA) in human volunteers after a single oral microdose (MD) (100 µg/200 nCi/body) by AMS and LC/MS/MS. 
[Methods] Tissue distribution of radioactivity in male pigmented rats and isolation of metabolites in urine after therapeutic oral administration of AA were conducted before the MD clinical study. Drugs were administered to two groups (n=6, per group) of human volunteers (first group (14C-AA only) and second group (1g probenecid (PB) one hour after dosing of 14C-AA). The single oral MD of 14C-AA was 100 µg/200 nCi/body. Blood, urine and feces samples were collected up to 48 h, 168 h and 168 h respectively. The samples were then pretreated. After fractionation of HPLC, Radioactivity of a parent drug (AA), sulphate (AA-Sul) and glucronic acid (AA-Glu)) is measured by AMS. The structure of metabolites is analyzed by two LC/MS/MS systems using high sensitive LTQ Orbitrap and Qtrap 5500.
[Results and Discussion]The human radiation dose calculated was 4.09E-04 mSv/MBq (0.015 mSv/µCi) from the tissue distribution of radioactivity in male pigmented rats. The retention times (min, the isolated metabolites) were (1.87, AA-Glu), (3.90,AA-3OSul), (4.91,AA-Sul), (7.66,AA-3Cys), (8.94,AA) and (13.81,AA-3MC) by UPLC (HSS T3 column). In 24th JSSX Annual Meeting we discuss the followings, 1) mass balance, 2) the linearity of AUC and Cmax between MD and TD, 3) the drug interaction between AA and PB, and 4) metabolites in the MD study.

INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (6) – USE OF 14C-LABELLED COMPOUNDS TO ANALYZE HUMAN PHARMACOKINETICS OF PARENT DRUGS AND THEIR METABOLITES
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[Purpose] The aims of the study are 1) to validate the processes from manufacturing to administration of 14C-labeled compounds in a domestic clinical environment, and 2) to develop a method to analyze the pharmacokinetics in microdosing (MD) clinical studies. [Methods] Acetaminophen (AA) and tolbutamide (TB) were chosen as model drugs and two separate MD clinical studies were scheduled with 14C-labeled AA and TB. Accelerator mass spectrometry (AMS) was used for 14C detection. All the feces and urine were collected throughout the study periods and plasma samples were collected at 9 time points during 0-48 hours. [Results and Discussion] In both MD clinical studies, it was found that administration of 100 µg of drug (per person) as a single oral dose contains 7400Bq of radioactivity. The radiation risks are much lower than generally accepted risks such as international flight and X-ray medical examination. 14C-labeled compounds can be manufactured under current Good Manufacturing Practice and the final dosage preparation can be verified at the pharmacy at the study site. Total amount of radioactivity and concentration is under the limit of the domestic law. [Conclusions] MD clinical studies with 14C-labeled compound can be conducted under conditions meeting quality assured environmental standards.