



Research on the effects of chemical substances on children, elderly people, and those with gene disorders

**Title of Research:**

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**Quantitative prediction of the pharmacokinetics of chemical substances by the use of mathematical model with considering the age-dependent functional changes of metabolic enzymes and transporters**

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**Summary of Research:**

To predict the influence of age on the pharmacokinetics of chemical substances, we performed a human clinical cocktail semi-microdosing study for investigating the age-dependent functional changes of metabolism and transport of compounds with healthy adults and aged persons. As a result, pharmacokinetics of some probe drugs for CYP (cytochrome P450) 3A and OATP (organic anion transporting polypeptide) transporters were changed in aged persons. This suggests that functions of intestinal and hepatic CYP3A/OATPs might be altered in aged persons. Moreover, we measured the plasma and urine concentration of trimethylamine N-oxide (TMAO) to investigate whether this can be used as a renal OCT2 functional probe endogenous compound. Although TMAO is taken up into kidney mainly via OCT2 in mice, since the contribution of renal secretion mediated by OCT2 to the overall renal clearance is fairly minor in humans, TMAO cannot be used as a sensitive probe for renal OCT2 in humans.

**Timeline:**

March 1, 2016 -

**Topics:**

2016 ICCA-LRI Workshop (poster) "Quantitative prediction of the pharmacokinetics of chemical substances by the use of mathematical model with considering the age-dependent functional changes of metabolic enzymes and transporters"

**Publications:**

Takeshi Miyake, Tadahaya Mizuno, Hiroyuki Kusuhara "Organic cation transporter (OCT) is responsible for the renal influx and clearance of trimethylamine N-oxide (TMAO)", 31<sup>st</sup> Japan Society of the Study of Xenobiotics (JSSX) Annual meeting, Nagano, 2016.10