Substantially increased plasma coproporphyrin-I concentrations associated with *OATP1B1*15* allele in Japanese general population

Suzuki Y[1], Sasamoto Y[1], Koyama T[2], Yoshijima C[1], Ohno K[1]

[1]Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University, Japan

[2]Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine, Japan

Background: Coproporphyrin-I (CP-I) in plasma is a sensitive and specific endogenous probe for phenotyping organic anion transporting polypeptides 1B (OATP1B, encoded by SLCO1B). A few small-scale studies suggested that plasma CP-I concentration is affected by OATP1B1 polymorphism, but detailed studies are lacking. In this large-scale study, we measured plasma CP-I concentrations in 391 subjects from the Japanese general population, and evaluated the relationship between plasma CP-I concentrations and OATP1B1 polymorphisms to further assess the utility of plasma CP-I concentrations as an endogenous OATP1B probe. Methods: We analyzed the data of 500 randomly selected subjects who received health check in Kyoto Prefectural University of Medicine, and selected 391 participants who met the following inclusion criteria: body mass index (BMI) lower than 30 kg/m^2, estimated glomerular filtration rate (eGFR) higher than 60 mL/min/1.73 m^2, total bilirubin lower than 1.5 mg/dL, and alanine aminotransaminase (ALT) lower than 100 IU/L. Participants were stratified into six polymorphism groups from genome-wide association study data: *OATP1B1*1b/*1b*, *OATP1B1*1a/*1b*, *OATP1B1*1a/*1a*, *OATP1B1*1b/*15*, *OATP1B1*1a/*15* and *OATP1B1*15/*15*. Plasma CP-I concentrations were measured by validated UHPLC-MS/MS method. Results: Plasma CP-I concentrations were in ascending rank order in subjects with *OATP1B1*1b/*1b* (n = 103), **1a/*1b* (n = 122), **1a/*1a* (n = 40), **1b/*15* (n = 74), **1a/*15* (n = 41) and **15/*15* (n = 11), with significant differences among *OATP1B1*1b/*1b*, **1b/*15* and **15/*15*, and among *OATP1B1*1a/*1a*, **1a/*15* and **15/*15*. Post-hoc analysis revealed significant increases in plasma CP-I concentrations for *OATP1B1*1b/*15* and **15/*15* compared to *OATP1B1*1b/*1b*, and for *OATP1B1*15/*15* compared to *OATP1B1*1a/*1a*. Especially, substantial increase was observed in *OATP1B1*15/*15* subjects. Conclusions: These findings confirm the utility of plasma CP-I concentrations as an endogenous biomarker for phenotyping of OATP1B activity. Plasma CP-I concentration is potentially useful for the study of drug-drug interaction via OATP1B or individual dose adjustment of OATP1B substrates.

Keywords: coproporphyrin-I; OATP1B1; polymorphism; *OATP1B1*15*.