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Symposium

## [S-12] S-12: TDM for central nervous system drugs

Chairs: Kiyofumi Yamada, Japan / Philip Nicholaou Patsalos, UK

Tue. Sep 26, 2017 10:30 AM - 12:00 PM Room E (1F)

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### [S-12-5] Neonatal PBPK modeling of morphine disposition with OCT1 transporter developmental expression

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Keywords: Neonates, Ontogeny, OCT1 transporter, PBPK modeling, Morphine

#### Background

Morphine is widely used for pain management in neonates and small infants. However, clinicians still struggle with finding the right dose, due to inadequate knowledge of factors influencing the large variability in morphine concentration and response. We previously reported that the Organic Cation Transporter 1 (OCT1) genotype can partially explain the variability in morphine clearance (Fukuda *et al.*, *Pharmacogenomics*, 2013). The aim of this study was to develop a physiologically-based pharmacokinetic (PBPK) model to predict morphine clearance in neonates and small infants, by integrating age-dependent anatomical and physiological changes including developmental expression of OCT1 protein.

#### Methods

Morphine specific information was collected from the literature: physicochemical parameters; *in-vitro* kinetic parameters for OCT1 and UGT2B7; and *in-vivo* renal clearance. Pediatric liver tissue samples were provided by 32 donors, aged from 1-day postnatal to 12 years. OCT1 protein expression was determined by Western blotting of crude membrane fractions isolated from the liver samples. The morphine compound file was evaluated with Simcyp Simulator software by comparing predicted concentration-time profiles with observed ones in clinical studies for adults and older children aged 6-16 years, before being integrated with OCT1 developmental protein expression.

#### Results

The developed PBPK model of morphine, incorporated with pediatric physiological information, showed age- and OCT1-genotype dependent morphine clearance in pediatric patients aged 6-16 years. Observed clearance estimates were within a 2-fold range of median predictions for each OCT1 genotype in 10 age cohorts (yearly age increments). The *in-vitro* study showed that OCT1 protein expression was detectable in liver samples from subjects 1 day old, and increased with age. The PBPK model, integrated with the ontogeny profile of the OCT1 protein, predicted developmental changes in allometrically-scaled morphine clearance estimates. The predicted clearances were comparable to observations by McRorie *et al.* (1992), but slightly lower than those by Anand *et al.* (2008).

#### Conclusions

This is the first study to demonstrate the developmental changes in morphine clearance in neonates and small infants using PBPK modeling with incorporated OCT1 developmental protein expression. The small difference between observations and PBPK simulations would be addressed through the investigation of physiological conditions of *in-house* neonatal patients receiving morphine.

