[PR1-104] Novel genetic variants of ABCC3, OCT1, Race and Sex explain Inter-Individual Variability in Morphine's Pharmacokinetics and Postoperative Analgesia and Adverse Effects in Children

Olbrecht V, Venkatasubramanian R, Niu J, Mizuno T, Fukuda T, Chidambaran V, Esslinger H, Vinks A, Sadhasivam S
Cincinnati Children's Hospital , Cincinnati , OH, USA

Introduction: Large inter-individual variability in morphine pharmacokinetics may contribute to the unpredictable variability in morphine analgesia and adverse effects. Caucasian children have more adverse effects and slower morphine clearance than African American children and this may be due to differences in morphine's metabolic pathway (Figure 1). Girls have more postoperative adverse effects than boys with higher doses of morphine. The purpose of this study was to examine the influence of race, sex and genetics on morphine's pharmacokinetics in children to better understand clinical variations in opioid response.
Methods: Serial plasma samples from 228 children and adolescents undergoing outpatient tonsillectomy were collected during and after surgery up to 40 minutes following intraoperative morphine administration. A maximum of 4 plasma samples were collected per child. Morphine, morphine-3-glucoronide (M-3G) and morphine-6-glucoronide (M-6G) levels were measured using a validated and sensitive LC-MS/MS assay. A 2-compartmental pharmacokinetic NONMEM® model incorporating metabolite compartments to predict metabolite levels was developed. Influences of weight, race, sex, OCT1 genotype and ABCC3 genotype on morphine clearance and metabolite formation were analyzed.
Results: Our morphine PK model had 509 plasma samples with detectable morphine levels. M-3G and M-6G levels were above detection in 411 and 169 samples respectively and were below detection levels at the initial time of collection suggesting a delay in metabolite formation or metabolite transport into plasma. This observed delay in the plasma metabolites was modeled by incorporating delay in metabolite formation using additional compartments. Children with ABCC3 rs4793665 homozygous C/C genotype had about 40% higher M-6G formation rate than the wild-type and heterozygous genotypes resulting in increased M-6G transport into the plasma; 13% higher M-3G formation was also consistently observed in the homozygous C/C genotype. OCT1 homozygous genotypes (n=12) were found to have significantly lower morphine clearance (~24%) (Figure 2 A, B). Though not statistically significant, lower morphine clearance was observed in Caucasians (~5%) and girls (~6%) (Figure2 C, D).
Conclusion: Our large pediatric pharmacokinetic and pharmacogenetic study demonstrates that besides body weight, OCT1 and ABCC3 homozygous genotypes play a significant role in the pharmacokinetics of morphine and its metabolites. A small difference in morphine clearance between girls and boys alone seems not substantial enough to explain higher morphine adverse effects in girls than boys. Higher frequencies of the ABCC3 rs4793665 C/C and OCT1 homozygous genotypes were observed in the Caucasian population. This finding partially explains lower morphine clearance and higher incidences of adverse effects with morphine in Caucasians as compared to African Americans.

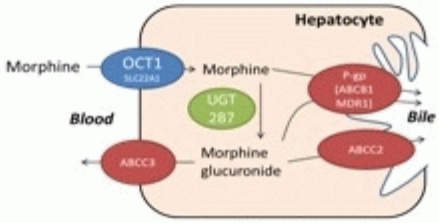

Figure 1 Interaction of transporters and hepatic handling of morphine and its metabolite

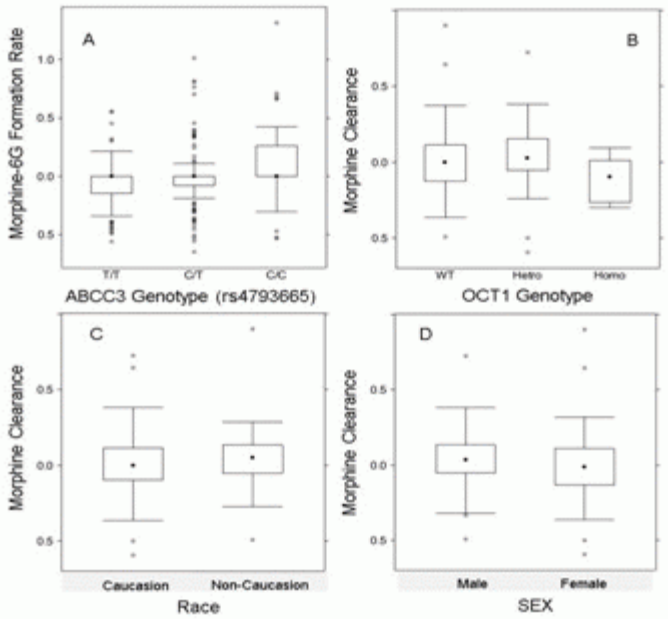

Figure 2. Morphine clearance and Morphine-6-Glucuronide formation rate: Effects of A. OCT1 genotype, B. ABCC3 rs4793665 genotype, C. Race and D. Sex