Novel Genetic Variants of Organic Cation Transporter 1 Explain Differential Clearance of Morphine in Children and Unequal Burden of Perioperative Pain and Opioid Adverse Effects

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Background:
Unpredictable inter-individual variability in analgesic response and adverse effects to morphine is a clinical, economic and public health problem. Caucasian children undergoing surgery are at high risk of opioid-related adverse effects while African-American children have a higher incidence of inadequate pain control with morphine due to relatively slower morphine clearance in Caucasian children (1, 2). Common genetic polymorphisms of the primary metabolic enzyme of morphine, uridine diphosphate glucuronyl transferase 2B7 (UGT2B7), did not explain this difference (2). Organic cation transporter 1 (OCT1) plays a significant role in liver cell uptake of morphine from the blood and has the potential to influence the pharmacokinetics of morphine (Figure 1). In this study, we evaluated the effects of common OCT1 genetic variants on morphine metabolism and clearance in children.

Methods:
A prospective, genotype blinded study was conducted in 146 children undergoing outpatient adenotonsillectomy. Serial venous samples were obtained for morphine and morphine glucuronide pharmacokinetic analysis before and 5 minutes, 10-15 minutes and 30-45 minutes after an intraoperative intravenous morphine dose. Subjects were genotyped for OCT1 variants (R61C, G401S, 420del, G465R) and classified into 3 groups (wild-type, heterozygote and homozygote) based on the presence of non-synonymous OCT1 variants; subjects lacking any of the defective OCT1 variants were defined as wild-type. A population pharmacokinetic two-compartment model using non-linear mixed effects and post-hoc Bayesian estimates was used along with OCT1 genotypes as covariates.

Results:
Three hundred twenty-nine morphine concentration measurements and 146 morphine concentration-time profiles were obtained from the 146 subjects. OCT1 genetic variants observed were 85 wild-type (*1/*1), 52 heterozygotes (*1/*2-5) and 9 homozygotes (*2-5/*2-5). Weight-standardized morphine clearances in homozygotes for defective OCT1 alleles were found to be significantly lower than heterozygote carriers of the defective allele (p<0.05, Figure 2) and there was a decreasing trend in morphine clearance in heterozygotes. Allelic frequency of OCT1 differed between both races, with a higher frequency of wild-type in African-American children than in Caucasian children.

References:

Conclusion:
- In addition to weight, OCT1 genotype is an important factor in intravenous morphine pharmacokinetics in children.
- Homozygous OCT1 genotype is more common in Caucasians (17%) who have decreased morphine clearance and higher opioid adverse effects compared to African-American children.
- OCT1 genotyping has the potential to maximize pain relief while minimizing side effects.