Genotypes are associated with Respiratory Depression, PONV and Morphine’s Pharmacokinetic Variations in Children

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Methods
After obtaining IRB approval and informed consents, 316 children ages 6 to 15 years, ASA physical status 1 or 2 scheduled for tonsillectomy who received standard anesthetic, surgical and postoperative care were recruited. Clinical data collected included: postoperative pain scores, total opioid use, incidence of postoperative nausea and vomiting (PONV) and respiratory depression (RD). Common genotypes of the OCT1 gene in each patient were identified using the Illumina Omni5 GWAS array.

Background:
Large inter-individual variability in morphine pharmacokinetics could contribute to variability in morphine analgesia and adverse events. Organic cation transporter 1 (OCT1) is a transporter in the liver which transports morphine from the bloodstream into hepatocytes (Figure 1). We have previously shown that genetic variation resulting in defective OCT1 expression is associated with lower morphine clearance in Caucasian children as compared to African American children (1,2). The aim of this study is to identify the association between common OCT1 genotypes affecting morphine’s pharmacokinetics and clinically important postoperative opioid-related outcomes.

Results
The OCT1 rs72552763 GAT deletion was associated with a significantly higher incidence of RD (OR 9.6, p=0.007; Figure 2a). The OCT1 rs12208357 TT genotype was associated with a higher incidence of PONV (OR 2.3 compared to CT genotype and OR 4.6 compared to CC genotype, p=0.037; Figure 2b). Moreover, the OCT1 rs12208357 TT genotype was associated with PONV leading to prolonged PACU stay (OR 3.3, p=0.031; Figure 2c). The same OCT1 genotypes were associated with lower morphine clearance in our earlier pharmacokinetic studies in children providing biological validation for these findings (1,2).

Discussion
Children with certain OCT1 genotypes are at higher risk for postoperative RD and PONV leading to prolonged hospital stay. These associations are explained by underlying pharmacokinetic clearance variations of intravenous morphine in children. It is interesting to note that these defective OCT1 variants are more frequent in Caucasian children than African-American children, explaining racial differences in morphine’s pharmacokinetic clearance and postoperative outcomes that our found clinically (3,4).

References