Introduction
Approximately 6 million children undergo painful surgery in the U.S. each year. In 2013, the FDA issued its strongest warning against codeine use in children undergoing tonsillectomy.
- Use associated with deaths and anoxic injuries
- Related to CYP2D6 variations and concomitant variable codeine metabolism
- Oxycodone is stronger than codeine.
  - Partly metabolized by CYP2D6 to oxymorphone
  - Oxymorphone is 14-fold more potent than oxycodone
  - Oxymorphone’s contribution to clinical analgesia will be higher in ultrarapid (30%) than poor metabolizers (5%).
- Recently, oxycodone has been shown NOT to be a safe alternative to codeine for breastfeeding infants and nursing mothers.
- Currently, there is no evidence to demonstrate that oxycodone is safer than codeine in children.

The aim of this prospective observational study was to determine the impact of genetic polymorphism of CYP2D6 on pharmacokinetics of oxycodone and oxymorphone in children taking oxycodone following painful surgery.

Methods:
- 33 children enrolled age 2-17
- A single dose of oxycodone was administered postoperatively.
- Eight serial blood samples for oxycodone, oxymorphone and other metabolite PK analysis were collected at 0,30, and 60 minutes and 2, 4, 6, 8, 12 and 24 hours following the dose of oxycodone.
- CYP2D6 status was determined.
- Children were monitored for oxycodone-related adverse events.

Results
- The impact of CYP2D6 genetic polymorphism on the oxycodone pharmacokinetics was evaluated by observing the variation of exposure markers (C_{max}, D, AUC_{0-24} and AUC_{CYP2D6}) with respect to the CYP2D6 total activity score.
- As shown in Figure, CYP2D6 activity score had clear impact on oxymorphone AUC_{0-24}/D, though a similar impact on oxycodone AUC_{0-24}/D was not observed.
- Importantly, the oxymorphone exposure relative to oxycodone exposure was consistently dependent on the CYP2D6 phenotype with higher activity phenotypes (EM) having higher oxymorphone exposures than PMs and IMs.

DISCUSSION
- This first pediatric study supports that CYP2D6 genotypes play a significant role in the pharmacokinetics of oxycodone and oxymorphone.
- Specifically, children identified as being extensive metabolizers of oxycodone had greater exposure to oxymorphone than poor and intermediate metabolizers, potentially increasing contribution of analgesia and adverse effects of oxymorphone in EMs and UMs.
- Pharmacokinomics provides a general framework for the integration of pharmacogenetics with pharmacokinetics into clinical practice for gene-based prescribing.
- By expressing a patient’s CYP2D6 phenotype pharmacokinetically and associated clinical dose adjustments, clinicians can potentially improve the safety and efficacy of oxycodone.
- Future studies are warranted to further quantify the influence of pharmacogenetic variability on oxycodone pharmacokinetics and oxycodone-related clinical outcomes.
- Personalized oxycodone dosing for an individual child may improve pain control following surgery while limiting dangerous adverse side effects.

REFERENCES:
2. FDA Public Health Advisory: Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects In Nursing Babies.