Introduction: Oxycodone is among the most commonly prescribed opioids for postoperative pain. Studies have demonstrated marked variation in the pharmacokinetics (PK) of oxycodone among the pediatric population (1,2) which may be due to genetic variation of its metabolism. Although 80% of oxycodone breakdown occurs by cytochrome P450 3A4 into an inactive metabolite, up to 11% occurs through CYP2D6 into oxymorphine. Oxymorphine has 40 times the affinity and 8 times the potency of oxycodone upon Mu-opioid receptors. Therefore, the CYP2D6 ultra-rapid metabolizer genotype (UM) may confer risk for serious side effects in commonly prescribed doses. Additionally, developmental changes in the activity of intestinal drug-metabolizing enzymes and transporters could potentially alter the bioavailability of oxycodone. This suggests the need to rationalize oxycodone dosing regimens in neonates, infants, and children. Understanding oral oxycodone pharmacokinetics (PK) and pharmacogenomics (PG) favors the safe and effective use of this analgesic in a wide variety of pediatric surgical patients. The aim of this study is to characterize the population PK and PG of oxycodone and its metabolites (oxymorphine, noroxymorphine and noroxycodone).

Methods: This prospective cohort, single-center trial was approved by the hospital investigational review board. A total of 40 opioid-naïve children, aged 0-5 years, scheduled for in-patient surgery, have been consented. Blood samples were collected for the assay of oxycodone and its main metabolites, as well as for CYP3A4 and CYP2D6 genotyping. Oxycodone, oxymorphine, noroxymorphine and noroxycodone levels at 10 time points were assayed using liquid chromatography- mass spectrometry (UPLC/MS/MS) and single-dose pharmacokinetics parameters were determined. CYP2D6 genotyping on the Affy/Metrix DMET Plus panel augmented with three extra primers was used to identify ultra-rapid metabolizers.

Results: Concentration data revealed a substantial interpatient PK variability likely due to age and genetic differences. All patients were wild-type normal metabolizers for CYP3A4, but there are significant differences in oxycodone plasma concentrations when analyzed in the context of the CYP2D6 phenotype. All poor and intermediate metabolizers (n=2 and 3, respectively) were found in the slow absorption/lower Cmax group (n=21). Three out of four ultra-rapid metabolizers were found in the fast absorption / higher Cmax group.

Summary: A trend appears to exist with age contributing to the variability of PK of oxycodone. This justifies the need for its consideration in the dosing optimization of Oxycodone based on individual genetics and age.

Figure 1: Differences in onset of absorption and magnitude of oxycodone plasma concentrations.

Figure 2: Differences in onset of absorption and magnitude of oxycodone and its metabolites concentrations relative to age group.