Original Article

Association of *CYP2D6* genotype predicted phenotypes with oxycodone requirements and side effects in children undergoing surgery

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Background: Oxycodone is a commonly used oral opioid in children for treating postoperative pain. Highly polymorphic gene *CYP2D6* metabolizes oxycodone into its more potent metabolite, oxymorphone. We hypothesized that altered activity due to *CYP2D6* polymorphisms will influence oxycodone requirements {relative oxycodone use [oxycodone morphine equivalents (MEq)/total MEq] to maintain analgesia} (primary outcome) and risk for oxycodone induced side-effects such as respiratory depression (RD) and emesis (secondary outcomes). We also explored the influence of genotype availability and provider guidance on oral opioid prescription patterns.

Methods: Patients who underwent Nuss procedure and spine fusion with *CYP2D6* genotyping results available preoperatively were included. Data on demographics, genotypes, oral opioids, pain scores, RD and emesis were collected. Univariate and multivariable regression for comparison of *CYP2D6* genotype predicted poor, ultrarapid, intermediate metabolizers (PM, UM and IM) phenotype with normal metabolizers (NM) for outcomes were performed. Stratified logistic regression was conducted in low (oxycodone/total MEq <0.5) and high (and oxycodone/total MEq >0.5) oxycodone use groups for RD and emesis, with application of firth correction due to quasi-complete separations. Breslow-Day test was used to evaluate odds ratios for prescribing genotype directed opioid between control group (2012-15) (where providers were alerted to genotyping results availability but not directed to use them while prescribing) and genotype directed groups (2016-18) (where providers were directed to use the genotyping results available to them while prescribing oxycodone after surgery).

Results: Of 193 subjects (age 15.9±0.25 years, 28.5% female, 93.78% White; 101 NM, 76 IM, 10 PM and 6 UM), 77.72% underwent pectus surgery. *CYP2D6* phenotype was associated with oxycodone MEq/total

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MEq requirements (P<0.001). Both PM and UM phenotypes had lower oxycodone requirements compared to NM [–0.316 (SE 0.098), P=0.005 and –0.432 (SE 0.113), P<0.001 respectively]. *CYP2D6* phenotype was associated with RD in high use oxycodone group (P=0.018) but not low use oxycodone groups (P=0.634). No phenotype association was found for emesis. Oxycodone was prescribed to 91.24% of NM/IM *vs.* 66.67% of PM/UM (P=0.129) in control group and 94.64% of NM/IM *vs.* 28.57% of PM/UM (P<0.001) in the genotype-directed group. PM/UM phenotypes in genotype directed group had a lower chance of being prescribed oxycodone (effect size =–2.775; SE 1.566; P=0.076).

Conclusions: Our findings suggest *CYP2D6* genotypes are associated with oxycodone requirements for analgesia and may influence risk for RD. Genotype availability and guidance likely influence oral opioid prescription pattern after surgery. Our findings are limited by small sample size for UM/PM groups.

Keywords: *CYP2D6*; oxycodone; pharmacogenetics; analgesia; opioid adverse effects; postoperative pain

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Introduction

Children undergo 3.9 million surgeries every year in the United States. Safe and effective postoperative analgesia is critical to successful recovery after invasive surgery in children (1,2). Despite efforts to minimize opioid use for postoperative analgesia, opioids still play a major role in postoperative pain control. Postoperative pain management remains sub-optimal as 40% of patients suffer moderate-to-severe acute pain after surgery, and 40% experience opioid side-effects (3,4). In recent times, there has been a shift in analgesic utilization towards oxycodone (5). Annual prescription prevalence for oxycodone is 2,116 per 100,000 patients, making it the most widely prescribed oral opioid in children in the United States (6), despite its high interindividual response variability and higher risk for opioid dependence (7). Superior oral bioavailability, increased central nervous system permeability, controlled-release formulation and advertised favorable side-effect profile compared to morphine have contributed to oxycodone's commercial success (8-10).

Lalovic *et al.*, demonstrated that 45%±21% of oxycodone is N-demethylated by cytochrome P450 enzymes (*CYP3A4/5)* to noroxycodone, noroxymorphone, alpha- and beta-noroxycodol; 11%±6% of oxycodone is O-demethylated via *CYP2D6* to oxymorphone, alpha- and beta-oxymorphol; 8%±6% of oxycodone is 6-keto-reuced to alpha- and beta-oxycodol (11,12) (*Figure 1*). Since oxycodone's metabolism is mostly dependent on the cytochrome P450 (CYP) family of liver enzymes including *CYP2D6* and *CYP3A4/5* (9,11), patients with CYP allelic variations could present with unpredictable level of analgesia and side-effects. *CYP2D6* is a known polymorphic gene with >130 alleles of defined phenotypes [poor metabolizers (PM), intermediate metabolizers (IM), normal metabolizers (NM) or ultra-rapid metabolizers (UM)]. Different phenotypes are the result of enzyme activity conferred by allelic variations (13). Altered activity *CYP2D6* phenotypes have been implicated in poor analgesic responses, increased side effects and even mortality from oral opioids such as codeine (14,15).

Unlike codeine which is a prodrug and only its *CYP2D6* metabolite is active, oxycodone is an active parent drug. However, it is metabolized by *CYP2D6* to oxymorphone which has a 10–60-fold higher μ-opioid receptor affinity (16), and similar abuse liability (17). Oxymorphone/oxycodone ratios were shown in pharmacokinetic (PK) studies to be lower in *CYP2D6* PM compared to NM/IM (18). Despite the knowledge of CYP2D6 variations and their influences on oxycodone exposure (19,20), the impact of the polymorphic *CYP2D6* on oxycodone clinical effects is not clear (21). Although a handful of studies show *CYP2D6* phenotypes impact oxycodone analgesia (22) and serious adverse effects including mortality (23,24), studies in pediatric populations show conflicting findings (19,22). Per recent Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, "there is insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time for oxycodone" based on *CYP2D6* genotype (19). However, Ramsey *et al.* suggested possible merit in genotype-guided prescription of drugs

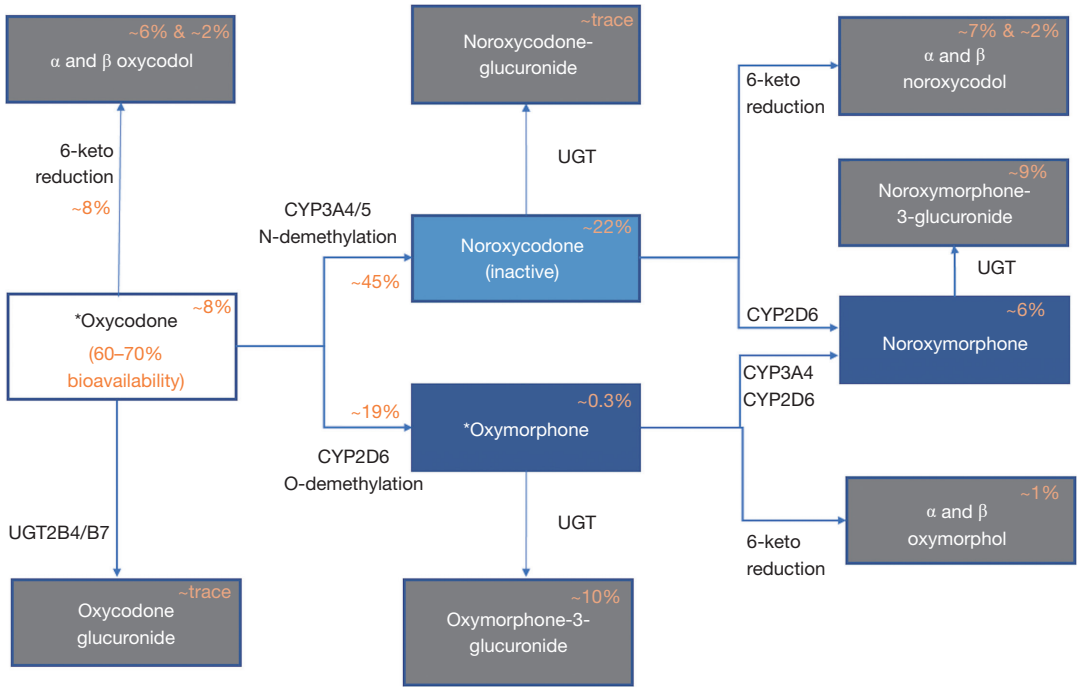

Figure 1 Oxycodone metabolic pathways (reference: www.pharmgkb.com): oxycodone primarily gets metabolized to noroxycodone and oxymorphone and later to noroxymorphone. The drug and its metabolites undergo glucuronidation before elimination. Oxycodol, noroxycodol and oxymorphol are reductive metabolites of oxycodone, noroxycodone and oxymorphone respectively, with each of them having two stereoisomers (α and β). % mentioned next to arrow represents the percentage of drug metabolized by that specific pathway and % mentioned in the boxes represent the percentage of renally eliminated metabolite compared to the parent drug. The dark blue boxes represent the *CYP2D6* pathway metabolites and light blue the *CYP3A* metabolic pathway. *, active metabolite. CYP, cytochrome P450; UGT, uridine 5'-diphospho-glucuronosyltransferase or UDP-glucuronosyltransferase.

metabolized by *CYP2D6*, including oxycodone due to its high annual use amongst United States' pediatric patients (2,116 per 100,000 patients; 95% CI: 2,097–2,135) (6).

In this study, we aimed to determine associations between *CYP2D6* genotype-predicted phenotypes with oxycodone requirements for analgesia, risk of respiratory depression (RD) and emesis in post-surgical children. We hypothesized that compared to NM, PM and UM will have different oxycodone requirements to maintain analgesia. Also, RD and emesis would be associated with phenotype in high oxycodone use groups but not in low oxycodone use groups. In addition, we explored whether genotype availability and provider guidance would influence oral opioid prescription patterns. We present the following article in accordance with the STREGA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-58/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Cincinnati Childrens (Protocol# 2013-0853) and informed consent was obtained from all individual participants for the prospective part of the study (2012–2015) and was waived for the retrospective data review (2016–2018). Retrospective chart review of data from two cohorts undergoing Nuss procedure or posterior spine fusion (for idiopathic scoliosis) between 2012 and 2018 was conducted. The first cohort included patients recruited for a prospective preemptive *CYP2D6* genotyping study between 2012–2015. The second cohort consisted of patients who were genotyped for *CYP2D6* preoperatively as part of clinical management between 2016–2018.

Patients in both cohorts had *CYP2D6* genotyping completed and resulted before surgery. Inclusion criteria for chart review: American Society of Anesthesiologists classification 1–3, diagnosis of pectus excavatum or idiopathic scoliosis undergoing Nuss procedure or spine fusion respectively, with *CYP2D6* genotyping results available before or at the time of surgery. Exclusion criteria included presence of obesity (BMI >30 kg/m^2), developmental delays, age <8 years, liver/renal disease (based on patient's preoperative medical history), history of substance abuse/opioid use preoperatively.

All patients underwent surgery using standardized anesthesia protocols (general endotracheal anesthesia using total intravenous anesthesia/intraoperative neuromonitoring for spine fusion and inhalation anesthesia/muscle relaxant for Nuss procedure). Postoperatively, spine fusion patients received patient-controlled analgesia (morphine or hydromorphone) and were transitioned to oral opioids on postoperative days (POD) one or two. All patients received ondansetron intravenously every 6 hours for emesis prophylaxis. Pectus patients received a thoracic epidural which was continued until POD 2 (2016–2018) and POD 3 (2012–2015). All patients were monitored using continuous electrocardiography (heart rate), thoracic Impedance plethysmography (respiratory rate), pulse oximetry (oxygen saturation) and intermittent blood pressure measurement on the floor after surgery. All subjects were offered oral opioids every four hours (either oxycodone 0.1–0.2 mg/kg or hydromorphone 0.04–0.08 mg/kg). Opioid *CYP2D6* Panel result approved by institutional Genetic Pharmacology Service was available in electronic medical records (EMR) (Epic Systems, Verona, WI, USA) for clinical use. An EPIC alert notified the clinician that a pharmacogenetic (PGx) test result was available for the medication. Before 2016 (during the preemptive genotyping study), pain physicians were provided education about the genotyping alerts on EPIC, but not directed to use the genotyping results available to them while prescribing oxycodone after surgery. Between 2016–2018, patients were clinically genotyped and postoperative pain team was directed to administer *CYP2D6* non-dependent oral opioid (hydromorphone/morphine instead of oxycodone for *CYP2D6* UM and PM) per the genotype recommendation on genotyping result. For the exploratory aim, patients undergoing surgery between 2012–2015 (cohort 1) were considered the control group and those between 2016–2018 (cohort 2) were the intervention group.

Data collection

Patients for the chart review were identified based on prospectively recruited subjects (2012–2015) and list of patients who underwent pectus surgery (2016–2018), and satisfied criteria. The patient list was provided to EPIC data informatics team to retrieve the data described below. The data was manually verified and missing data retrieved by authors (SM, JM). Data variables and outcomes assessments were focused on POD after discontinuation of regional analgesia for assessing oxycodone effects (POD 2: cohort 2 and POD3: cohort 1).

Patient characteristics: demographics (age, sex, race, weight).

Surgical data: surgery type, date of surgery, diagnosis.

Oral opioid and doses: names of any oral and intravenous opioid administered (oxycodone, hydromorphone, morphine), times for administration and opioid doses were collected.

CYP2D6 inhibitor use: concomitant use of fluoxetine, bupropion, paroxetine, quinidine, terbinafine and duloxetine was documented.

Pain assessment: pain scores [numerical rating scale (25) (NRS: 0–10)] assessed by nursing and documented in EMR were obtained. Pain scores after epidural removal or PCA discontinuation and after oral opioid was started were included for evaluation.

RD: documentation of at least one occurrence of: (I) needing supplemental oxygen (including blow by) or (II) respiratory rate ≤10 for age 6–10 years; RR ≤8–10 for older than 10 years or (III) SpO_2 <90% while spontaneously breathing room air.

Vomiting was scored as a binary variable (yes or no) by reviewing output on the EMR.

Other relevant medications: EMR was evaluated for administration of known strong *CYP2D6* inhibitors (Fluoxetine, Bupropion, Paroxetine, Quinidine, Terbinafine and Duloxetine) and recorded.

Genotyping

DNA was collected from blood/saliva for *CYP2D6* genotyping several days before surgery in all subjects. In both cohorts, genotyping results were available before day of surgery. The Cincinnati Children's Hospital Medical Center (CCHMC) CLIA approved, CAP certified molecular genetics laboratory performed *CYP2D6* genotyping using the TaqMan allelic discrimination system

Table 1 Genotyped *CYP2D6* alleles using the TaqMan allelic discrimination system (Applied Biosystem, Forest City, CA, USA)

Enzyme activity	*CYP2D6* allele (variant reference number)
Full	**1* (N/A), **2* (rs16947), **2A* (hCV32407252), **35* (rs769258)
Reduced	**9* (rs5030656), **10* (rs1065852), **17* (hCV2222771), **41* (hCV34816116)
None	**3* (hCV32407232), **4* (rs3892097), **5* (deleted), **6* (rs5030655), **7* (rs5030867), **8* (rs5030865), **11* (rs5030863), **14* (rs5030865), **15* (hCV32407245), **18* (hCV32407220), **19* (hCV32407233), **20* (hCV72649949), **40* (hCV32407240), **42* (hCV72649935), **44* (hCV32407228)

*CYP2D6*5* allele (full gene deletion) and *CYP2D6* duplication were detected by long-PCR; *, empirical assignment of detected variants into star (*) alleles defined by the Pharmacogene Variation Consortium (https://www.pharmvar.org/gene/CYP2D6). PCR, polymerase chain reaction.

Table 2 *CYP2D6* diplotype mapping to phenotype based on activity scores

CYP2D6 phenotype	Activity score	Examples of *CYP2D6* diplotypes
Ultrarapid metabolizer	>2.25	*1/*1xN, *1/*2xN, *2/*2xN, *1x2/*9
Normal metabolizer	1.25≤x≤2.25	*1/*10, *1/*41, *1/*9, *1/*1, *1/*2, *2x2/*10
Intermediate metabolizer	0<x<1.25	*4/*10, *4/*41, *10/*10, *10/*41, *41/*41, *1/*5
Poor metabolizer	0	*3/*4, *4/*4, *5/*5, *5/*6

*, indicates star alleles based on empirical assignment of detected variants defined by the Pharmacogene Variation Consortium (https://www.pharmvar.org/gene/CYP2D6).

(Applied Biosystem, Forest City, CA, USA) on a low density microarray for all alleles except *CYP2D6*5* allele (full gene deletion) and *CYP2D6* duplication (*Table 1*). Allele designations was performed by the most current and validated Autocaller (1.1) and laboratory designed allele calling tools. A known genotype control was run with each batch to ensure the quality of the allelic calls. *CYP2D6*5* allele (full gene deletion) and *CYP2D6* duplication were detected by long-PCR according to the method described by Løvlie *et al.* (26) These assays allow distinction between the *CYP2D6* gene and the non-functional pseudogenes *CYP2D7* and *CYP2D8* but do not detect allele-specific copy number. Turnaround time for results was 2 business days.

Phenotyping

Based on *CYP2D6* alleles, allelic activity scores and total activity scores (TAS) were determined, and phenotypes (PM, IM, NM and UM) defined, according to latest guidelines (*Table 2*) (27). In subjects using *CYP2D6* strong/moderate inhibitors, we accounted for phenoconversion by multiplying the TAS by inhibitor factor: 0 for strong (e.g., bupropion, fluoxetine) and 0.5 for moderate (e.g., duloxetine) inhibitors, as has been done previously (28,29). For the exploratory aim, we used EMR documented phenotypes (which were based on previous CPIC guidelines) (30).

Outcomes

Primary outcome was oxycodone analgesia which was measured as oxycodone requirements in morphine equivalents (MEq)/kg relative to total MEq/kg use, and secondary outcomes were risk for RD and emesis.

Statistical analysis

Descriptive statistics (mean and standard deviation, or median and interquartile range for continuous variables, and frequencies and percentages for categorical variables) were generated for demographics and other data characteristics, and normality for continuous variables was assessed. Pain experienced over time in the immediate postoperative period is captured well by the area under curve (AUC) which was calculated using trapezoidal rule for area under the curve of pain scores over time period [as in prior studies (2,31)]. AUC% for pain scores <4 (mild pain), were also calculated as %AUC corresponding to pain score <4/10. Although pain AUC was initially the analgesia outcome

measure, considering the opioid drug and dose changes that were made clinically to maintain analgesia, relative use of oxycodone (as the *CYP2D6* dependent opioid) was analyzed post-hoc as primary outcome measure. MEq/kg were calculated for all oral and intravenous opioids. Oxycodone (*CYP2D6* dependent) and *CYP2D6* non-dependent (morphine, hydromorphone) opioid MEq/kg were calculated separately and ratio of oxycodone requirements relative to total MEq/kg obtained. We first determined univariate associations of outcomes with categorical independent variables (sex, race, surgery type, need for opioid change), either two-sample *t*-tests (if normal) or Wilcoxon rank-sum test (if not normal) and continuous independent variables (age, TAS) using Pearson correlation (if both normal), or Spearman correlation (if any nonnormal). We checked for correlation of covariates with *CYP2D6* phenotype. Multivariable linear regression model was used to investigate association of *CYP2D6* genotype predicted phenotype (PM, IM, UM *vs.* NM) with primary. Stratified logistic regression was conducted in low (oxycodone/total MEq <0.5) and high (and oxycodone/total MEq >0.5) oxycodone use groups, with application of firth correction due to quasi-complete separations. Covariates were included in multiple regression models if associated with outcome (P<0.1 on univariate analyses) but not correlated with *CYP2D6* phenotype. For the exploratory aim, we compared control (cohort 1) and EMR directed groups (cohort 2) for first oral opioid medication prescribed (*CYP2D6 vs.* non-*CYP2D6* substrate) using Fisher's exact tests. Breslow-Day test was used to evaluate odds ratios between the groups. P<0.05 was used for denoting statistical significance.

Results

The combined cohort comprised of 193 subjects in all. Average age was 15.9 years (SD 0.25), 55/193 (28.5%) females, 181/193 (93.78%) white, weight 55.26 kg (SD 13.45); 77.72% underwent pectus surgery. The cohort overall had an average *CYP2D6* TAS of 1.435 (SD 0.647) and included 101 NM, 76 IM, 10 PM and 6 UM phenotypes (two IM phenotypes were on *CYP2D6* inhibitors and were phenoconverted to PM). Oxycodone was the most commonly prescribed first oral opioid (N=184; 9 hydromorphone). In 32 subjects, oxycodone was changed to hydromorphone while hydromorphone was switched to oxycodone in 32 subjects. Mean (SD) of AUC of pain for the cohort was 85.98 (3.58). Outcomes and cohort characteristics by *CYP2D6* phenotypes are provided in *Table 3*.

Pain AUC

On comparing AUC by age, surgery, sex and opioid choice, we found female sex and spine surgery had higher AUC, but no differences by opioid choice or age. Median (IQR) of AUC was 111.22 (76.07, 138.17) in females *vs.* 71.10 (41.15, 115.37) in males; P<0.001); spine surgery [median (IQR) 105.59 (73.89, 137.28) compared to 75.4 (41.7, 117.5) in pectus; P=0.008]. oxycodone use [median (IQR) of 82.62 (46.28, 125.95) *vs.* hydromorphone use 78.74 (61.5, 103.76); P=0.773] and age (Spearman correlation coefficient 0.102, P=0.179). In those subjects receiving oxycodone only, average pain AUC was 123.2 (SD 52.8) for UM, 88.9 (SD 51.9) for IM, 84.8 (SD 44.3) for NM and 67.9 (39.9) for PM. *CYP2D6* phenotype was not found to be a significant predictor for pain AUC (P=0.643).

Oxycodone requirements

Of the independent variables evaluated for association with oxycodone/total MEq, surgery type was significant. Oxycodone was used more often in spine surgery compared to pectus surgery [1.0 (95% CI: 0.805–1.000) *vs.* 0.789 (95% CI: 0.636–1.000), P=0.013]. However, surgery type was not included in multiple regression due to being correlated to *CYP2D6* phenotype (P=0.041). Spearman correlation for AUC with oxycodone MEq/total MEq was –0.133 (P=0.079). Multivariate regression results for *CYP2D6* phenotype, adjusted for pain AUC are given in *Table 4*, with *CPY2D6* phenotype being a significant predictor. Compared to NM, least squares means of oxycodone MEq/total MEq were lower for PM [–0.301 (95% CI: –0.496, –0.106), P=0.008] and UM [–0.443 (95% CI: –0.666, –0.221), P<0.001], but not statistically significant for IM *vs.* NM [–0.035 (95% CI: –0.120, 0.049), P=1.00]. Predicted oxycodone MEq/total MEq plotted against *CYP2D6* phenotypes are presented in *Figure 2*. Phenotype was a significant predictor (P<0.001) with both PM and UM phenotypes using lower oxycodone/total MEq doses compared to NM [–0.316 (SE 0.098), P=0.005 and –0.432 (SE 0.113), P<0.001 respectively].

Risk of RD

Univariate analyses identified no variables associated with RD (*Table 3*). Stratified regression showed that *CYP2D6* phenotypes were not associated with RD when oxycodone/total MEq <0.5 (P=0.614) but was associated in the

Table 3 Cohort characteristics by *CYP2D6* phenotype

Independent variables	*CYP2D6* phenotype			
	PM (N=10)	IM (N=76)	NM (N=101)	UM (N=6)
Sex (n, %)				
Female	1 (1.82)	18 (32.73)	34 (61.82)	2 (3.64)
Male	9 (6.52)	58 (42.03)	67 (48.55)	4 (2.90)
Race (n, %)				
Non-white	1 (8.33)	6 (50.00)	5 (41.67)	0 (0.00)
White	9 (4.97)	70 (38.67)	96 (53.04)	6 (3.31)
Surgery type (n, %)				
Pectus	10 (6.67)	63 (42.00)	74 (49.33)	3 (2.00)
Spine	0 (0.00)	13 (30.23)	27 (62.79)	3 (6.98)
Respiratory depression, yes (n, %)	6 (13.95)	11 (25.58)	26 (60.47)	0 (0.00)
Emesis, yes (n, %)	3 (5.88)	20 (39.22)	25 (49.02)	3 (5.88)
Need for oral opioid change, yes (n, %)	4 (8.16)	18 (36.73)	25 (51.02)	2 (4.08)
%AUC above pain score 4/10, yes (n, %)	5 (3.68)	56 (41.18)	70 (51.47)	5 (3.68)
Age (years), median (IQR)	15.4 (14.5, 20.2)	15.7 (14.4, 16.8)	15.4 (14.2, 16.8)	15.4 (13.9, 20.7)
Total activity score, median (IQR)	0.0 (0.0, 0.0)	1.0 (1.0, 1.0)	2.0 (1.5, 2.0)	3.0 (3.0, 3.0)
Pain area under curve, median (IQR)	50.2 (43.5, 74.3)	93.5 (45.8, 127.7)	77.8 (48.0, 119.5)	111.0 (79.7, 138.2)
Oxycodone MEq/total MEq, median (IQR)	0.6 (0.0, 0.7)	0.8 (0.7, 0.9)	0.9 (0.7, 1.0)	0.2 90.0, 0.9)

PM, poor metabolizer; IM, intermediate metabolizer; NM, normal metabolizer; UM, ultrarapid metabolizer; AUC, area under curve for pain scores over time; IQR, interquartile range; MEq, morphine equivalents.

Table 4 Multiple regression models and results of *CYP2D6* phenotype associations with relative oxycodone use outcome

Outcomes	Predictors	Category	Least squares means				P value
			Estimate	SE	Lower CL	Upper CL	
Oxycodone/total MEq	*CYP2D6* phenotype	IM	0.781	0.036	0.709	0.853	<0.001
		PM	0.516	0.097	0.324	0.707	
		UM	0.373	0.109	0.158	0.588	
		NM	0.816	0.030	0.758	0.875	
	Surgery	Spine	0.651	0.053	0.546	0.757	0.233
		Pectus	0.592	0.039	0.514	0.669	

MEq, morphine equivalents; SE, standard error; CL, confidence level; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer; NM, normal metabolizer.

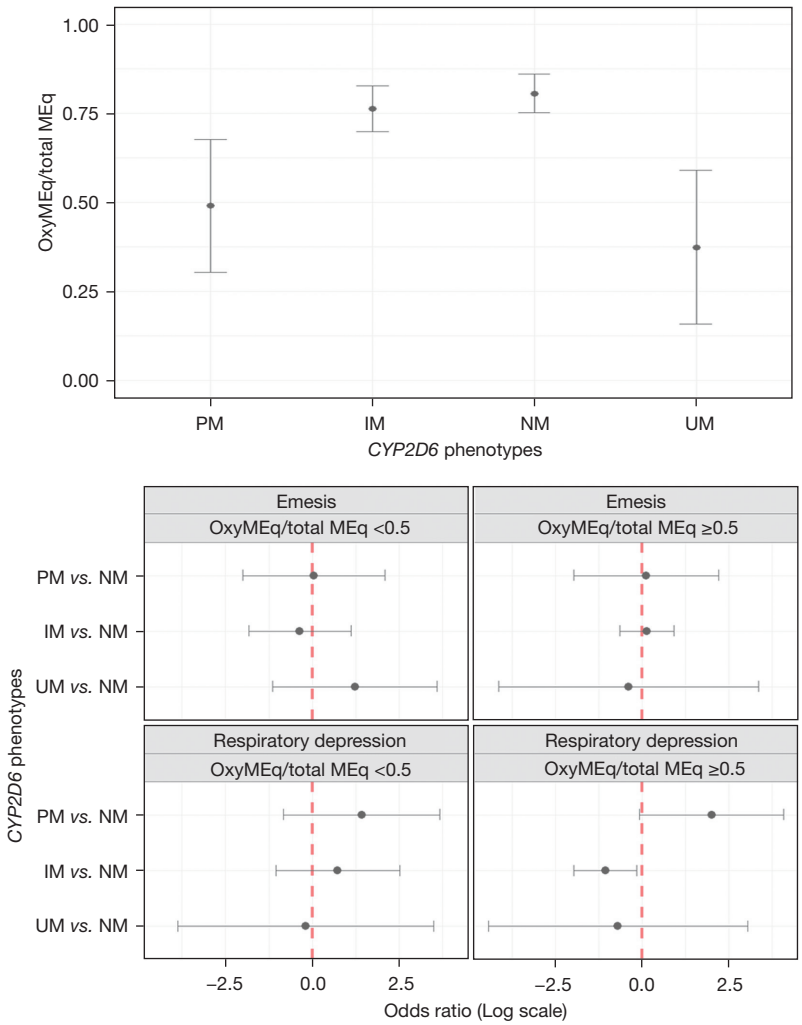

Figure 2 Multivariate regression model based phenotype associations with oxycodone outcomes. In the upper panel, predicted Least square means and 95% CI of oxycodone requirements (OxyMEq/total MEq) are plotted against *CYP2D6* phenotype for maintaining pain control (adjusted for median pain AUC). The lower panel shows predicted odds for risk of emesis and respiratory depression for different phenotypes (PM, IM and UM) versus NM, based on stratified regression in high oxycodone use (≥0.5 oxycodone MEq/total MEq) and low oxycodone use groups. OxyMEq, oxycodone morphine equivalents; PM, poor metabolizer; IM, intermediate metabolizer; NM, normal metabolizer; UM, ultrarapid metabolizer.

oxycodone/total MEq >0.5 group (P=0.018) (*Table 5*). IM had lower odds for RD compared to NM (0.346; 95% CI: 0.140–0.855; P=0.021). While UM had lower odds and PM higher odds for RD compared to NM, they were not statistically significant. Predicted odds for risk of RD for different phenotypes (PM, IM and UM) *vs.* NM are presented in *Figure 2*.

Risk of emesis

Pectus surgery was associated with higher emesis (30.94%) compared to spine surgery (7.5%) (P=0.003) but was not included in multiple regression due to being correlated to *CYP2D6* phenotype (P=0.041). Stratified regression (*Table 5*) did not find *CYP2D6* phenotypes to be associated

Table 5 Multiple regression models and results of *CYP2D6* phenotype associations with respiratory depression and emesis outcomes

Side effects	OxyMEq/total MEq	*CYP2D6* phenotype	OR (lower CL, upper CL)	P value
Respiratory depression	<0.5 (n=40)	IM *vs.* NM	2.088 (0.354, 12.309)	0.614
		PM *vs.* NM	4.142 (0.435, 39.412)	
		UM *vs.* NM	0.829 (0.021, 33.202)	
	≥0.5 (n=151)	IM *vs.* NM	0.346 (0.140, 0.855)	0.018
		PM *vs.* NM	7.408 (0.927, 59.214)	
		UM *vs.* NM	0.494 (0.012, 20.974)	
Emesis	<0.5 (n=40)	IM *vs.* NM	0.699 (0.161, 3.038)	0.634
		PM *vs.* NM	1.044 (0.134, 8.149)	
		UM *vs.* NM	3.409 (0.318, 36.601)	
	≥0.5 (n=151)	IM *vs.* NM	1.144 (0.529, 2.477)	0.981
		PM *vs.* NM	1.120 (0.139, 9.027)	
		UM *vs.* NM	0.671 (0.016, 28.667)	

OxyMEq, oxycodone morphine equivalents; OR, odds ratio; CL, confidence level; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

with risk of emesis. Predicted odds for risk of emesis for different phenotypes (PM, IM and UM) *vs.* NM are presented in *Figure 2*.

Genotype guidance exploratory aim

There were 66 subjects in control (2012–2015 non directed genotype group) and 127 subjects included the genotype directed group (2016–2018). Characteristics of the groups are provided in *Table 6*. In the control group, there was no significant difference in prescribing of *CYP2D6* dependent opioids [91.24% of NM/IM *vs.* 66.67% of PM/UM (P=0.129)]; in the genotype-directed group, there was a significant difference [94.64% of NM/IM *vs.* 28.57% of PM/UM were prescribed *CYP2D6* dependent opioids (P<0.001)]. The Odds for prescribing non-*CYP2D6* opioids to PM/UM compared to NM/IM was 5.2 in the control group and 44.17 in the genotype-directed group (Breslow-Day test, P=0.105). Logistic regression showed that PM/UM phenotypes in genotype directed group had a lower chance of being prescribed *CYP2D6* opioids (effect size =–2.775; SE: 1.566; P=0.076).

Discussion

In this retrospective study, we evaluated whether oxycodone requirements and side effects were associated with *CYP2D6* phenotypes. Genotype predicted *CYP2D6* phenotype was associated with lower oxycodone requirements to achieve analgesia in PM and UM compared to NM and risk for RD in the high oxycodone dose group only. No associations were identified for emesis with any phenotype. We also demonstrated that genotyping directed guidance to prescribe oral opioids, compared to reliance on passive EMR alerts resulted in a lower chance of being prescribed oxycodone in poor and UM, compared to NM and IM phenotypes.

Balyan *et al.* and Stamer *et al.* have demonstrated lower oxymorphone/oxycodone ratios in PM in adults and children (18,21). Since oxymorphone has 10–60-fold increased potency and affinity for mu opioid receptors compared to oxycodone, we expected UM to have lower need for oxycodone to achieve similar analgesia, and this is what we found. However, contrary to expectation, risk for oxycodone side effects were not found to be higher in UM *vs.* NM. Our findings are aligned with previous reports of higher potency of oxymorphone with comparable/fewer side effects, although this was not previously demonstrated in the context of *CYP2D6* phenotypes (32).

To our surprise, we also found lower oxycodone requirements to maintain analgesia in PM compared to NM. This might be due to increased effects of an already active drug. In addition, oxycodone has superior blood-brain barrier (BBB) penetration with concentrations reaching 3-

Table 6 Opioid prescribing, outcomes and characteristics of control and genotype directed group

Independent variables	Control group (N=66)	Genotype guided (N=127)
Age (years), mean (SD)	15.2 (2.6)	16.2 (3.8)
Sex, female (n, %)	34 (51.5%)	21 (16.5%)
Race, White (n, %)	62 (93.9%)	119 (93.7%)
Surgery	Pectus 23; spine 43	Pectus 127
Phenotype distribution		
Poor/ultrarapid metabolizer	1/5	7/1
Intermediate/normal metabolizer	3/57	6/112
TAS, mean (SD)	1.55 (0.64)	1.38 (0.59)
First opioid prescribed, n		
Oxycodone	56	108
Hydromorphone	7	11
Need for medication/dose changes (n, %)	17 (26.9%)	31 (25.8%)
Pain AUC, median (IQR)	97.1 (69.6, 131.3)	72.6 (39.7, 116.3)
Emesis, yes/no (% yes)	8/53 (13.11%)	38/80 (32.20%)
Respiratory depression, yes/no (% yes)	14/46 (23.33%)	24/90 (20.34%)

SD, standard deviation; TAS, total activity score; AUC, area under curve; IQR, inter quartile range.

to 6-fold higher in the brain than in the plasma (10,33,34). While UM phenotype was not associated with RD or emesis, IM was associated with lower risk for RD in high dose oxycodone group, while PM had nominally higher risk. In NM, the oxycodone/oxymorphone plasma and brain concentration ratios are 43:1 and 78:1 respectively, and this increases to 110:1 and 540:1 in PM, and decreases to 32:1 and 57:1 in UM (35). Although previous studies have shown oxycodone to be the major contributor of analgesia after oral and intravenous administration, 83.02% and 94.76% respectively; while oxymorphone only plays a minor role (15.77% and 4.52% after oral and intravenous administration, respectively), our findings suggest both higher oxycodone effects in PM and oxymorphone in UM may have clinically significant effects (36,37). Thus, while the Royal Dutch Pharmacists Association-Pharmacogenetics Working Group (DPWG) have concluded that no change in oxycodone prescribing is required based on *CYP2D6* genotype (38), our study demonstrates that there might be potential differences in phenotype effects, which need further investigation in bigger samples in a prospective randomized controlled study.

However, the effect sizes for phenotypes on outcomes are small. This might be because in order for patients to experience clinically significant disturbance in oxycodone metabolism, both *CYP2D6* and *CYP 3A4/5* pathways may need to be compromised. A "two-hit phenomenon" is supported by Gronlund and colleagues (39) who illustrated that with concomitant administration of *CYP2D6* and *CYP3A4* inhibitors, the AUC of oxycodone concentration increased 2.9-fold with subsequent increases in pain scores, and drowsiness.

Contrary to our findings, Zwisler *et al.* found no difference in total oxycodone consumption between *CYP2D6* PM in a genotype blinded study in post-surgical patients (40). However, the same authors found that antinociceptive effects of oxycodone depended on oxymorphone in experimental pain models with higher pain thresholds after nerve stimulation and lower AUC after cold pressor tests in EM compared to PM (41). It is possible that experimental and clinical pain phenotypes may be differently influenced by *CYP2D6* phenotypes. Furthermore, the findings of our exploratory aim are aligned with the report by Thomas and colleagues who demonstrated that genotype-guided care influenced opioid prescription of oxycodone. In their high risk group (IM/PM and UM), 72% were prescribed an alternative opioid *vs.* 0% in their usual care participants (42).

Limitations of this study include under representation of UM patients in our sample population. As summarized by Gaedigk *et al.*, prevalence of *CYP2D6* phenotypes differ between different race/ethnic populations (13). For example, UM phenotypes are highest in Oceanian (21.2%) followed by Ashkenazi Jewish (11.5%) and Middle Eastern (11.2%) populations. PM phenotypes are highest in Europeans (5.4%) and in the Ashkenazi Jewish population (6%). Our cohort was primarily white and was unable to capture UM phenotypes adequately (14). Given the discrepancy between findings of associations of IM with outcomes, which are difficult to explain, we cannot rule out findings as a result of chance alone. Larger prospective studies are needed to validate the findings of this study. Future studies may also consider methods to preferentially include genotype predicted PM/UMs. Additionally, all patients received similar antiemetics (ondansetron) also metabolized by CYP2D6. Therefore, it is possible that in PM phenotypes, ondansetron may have a superior effectiveness and dampen the incidence of emesis and hence skew our results for oxycodone associated emesis (43). Lastly, other genetic variants can affect oxycodone outcomes (for example, mu opioid receptor variant A118G and ATP binding cassette variants C3435T and G2677T/A), which were not studied here (44). Future studies may also need to evaluate the level of *CYP2D6* DNA methylation since its expression is epigenetically regulated (45).

One confounder for enteric oxycodone is the wide interindividual variation in absorption. In a study by Kokki and colleagues (46) a large variation in the rate and extent of absorption of buccal and enteric oxycodone in children ages 6–93 months was observed. Zwisler *et al.* illustrated that one hour after taking oral oxycodone, plasma concentrations in healthy subjects varied considerably (2.99–104.25 ng/mL in PM and 0.12–72.68 ng/mL in EM) (41). Thus, it is ideal to measure plasma oxycodone concentrations and exposure. Another confounder is the phenomenon of phenoconversion, whereby IMs behave as PM phenotype. This may occur when there is co-administration of oxycodone and *CYP2D6* inhibitors, which has been shown to influence pain management (47). Although the magnitude of phenoconversion in our cohort was small, only 2 subjects were impacted—phenoconverted from IM to PM, drugs used to treat pediatric behavioral disorders are rampant and several of these are *CYP2D6* inhibitors. Hence, this may be an important area for future investigations and generalizability to other surgical populations in a more diverse cohort of children.

Conclusions

In this study we investigated association between *CYP2D6* predicted phenotypes, oxycodone requirements and side-effects. We found relative oxycodone requirements to maintain analgesia were lower in PM and UM compared to NM, leading us to posit these might be due to higher oxycodone and oxymorphone effects in these respective groups. Risk for RD was associated with *CYP2D6* phenotype in high oxycodone but not the low oxycodone use groups. Our findings suggest that at extreme phenotypes, increased parent oxycodone and oxymorphone may influence clinical outcomes but oxymorphone may have a better safety profile. We also found that EMR available *CYP2D6* phenotype information significantly influenced oral opioid prescription pattern.

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Footnote

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