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CYP2D6 pharmacogenetic and oxycodone pharmacokinetic association study in pediatric surgical patients

Aim: Oxycodone is partly metabolized to the active metabolite oxymorphone by hepatic CYP2D6 in the liver. Significant genetic variability in CYP2D6 activity affects oxymorphone formation. This study aimed to associate CYP2D6 genotype and oxycodone's metabolism. **Methods:** 30 children were administered oral oxycodone postoperatively. Plasma levels of oxycodone and oxymorphone, and CYP2D6 genotype were analyzed. CYP2D6 genotype and oxycodone metabolism phenotype were determined based on CYP2D6 total activity score (TAS) and metabolism phenotype: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) or ultrarapid metabolizer (UM). **Results:** Compared with PM/IM subjects, significantly greater oxymorphone exposure was seen in EM subjects ($p = 0.02$ for C_{max} , $p = 0.016$ for AUC_{0-6} and $p = 0.026$ for AUC_{0-24}). Similarly, higher TAS value was found to be associated with greater oxymorphone exposure. Higher conversion of oxycodone to oxymorphone was observed in EM subjects compared with PM/IM subjects ($p = 0.0007$ for C_{max} , $p = 0.001$ for AUC_{0-6} and $p = 0.004$ for AUC_{0-24}). **Conclusion:** CYP2D6 phenotypes explain metabolism of oxycodone in children, and oxymorphone exposure is higher in CYP2D6 EM phenotype. Further studies are needed to predict the occurrence of adverse event and tailor oxycodone dose for a specific CYP2D6 phenotype.

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Pain management in pediatric surgical patients is complicated due to the risk of adverse effects of analgesics and inadequate anesthesia [1,2]. In the USA, approximately 6 million children undergo painful surgeries each year. Opioids are some of the most effective analgesics available and are considered foundational in clinical pain management [3]. Despite this efficacy, adverse events such as respiratory depression and death have been attributed to opioid administration in children [4]. For many years, codeine was thought to be optimum analgesic for children due to oral administration, wide therapeutic index and low probability of respiratory depression, but variable metabolism and con-

cerns on its contribution to these untoward events have caused a critical re-evaluation of this drug's use in the pediatric population [5].

Codeine is an opioid prodrug that is transformed to the active metabolite, morphine, by P-450 enzyme CYP2D6. In CYP2D6 poor metabolizer (PM), codeine is minimally converted to morphine, while in CYP2D6 ultra-rapid metabolizer (UM), very high concentrations of morphine are generated [6]. The variation in pharmacokinetics due to underlying pharmacogenetics results in varying drug effects, ranging from ineffective to toxic [7]. In February 2013, the US FDA issued its strongest warning against the use of codeine in children undergoing tonsillectomy

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Figure 1. Oxycodone metabolism mediated by CYP3A4 and CYP2D6. Majority of circulating oxycodone (~80%) is N-demethylated to inactive metabolite noroxycodone by CYP3A4, while a minor portion is O-demethylated to active metabolite oxymorphone by CYP2D6. Both noroxycodone and oxymorphone are further metabolized to didemethylated metabolite noroxymorphone (a weak analgesic) by activity of CYP2D6 and CYP3A4 respectively.

due to reports of deaths and anoxic injuries related to *CYP2D6* genetic variations and concomitant variable codeine metabolism [8]. In *CYP2D6* UM, excess morphine generation and adverse toxic effects are observed after codeine administration [6]. The FDA and other health organizations, such as WHO and EMA are considering a declaration of contraindication for codeine use in children [9]. Additionally, there is evidence that some nursing mothers are UMs of codeine which has led to unpredictable levels of morphine in breast milk and infant death [10]. Hence, there is a need to find a safer alternative to codeine in children.

Oxycodone is another commonly used but more restricted opioid administered for acute and chronic pain [11]. A μ -opioid receptor agonist, oxycodone is semisynthetic in nature [12] and has 60–80% bioavailability upon oral administration [13,14]. Though it has been in use for over 100 years, minimal information is available regarding the pharmacokinetics and pharmacodynamics of oxycodone in the pediatric population. Oxycodone is metabolized by CYP2D6 to oxymorphone and CYP3A4 to noroxycodone, a metabolite with poor antinociceptive effect [15]. Oxymorphone has 40-times more affinity for μ -opioid receptor and is 14-times more potent than oxycodone in efficacy [16]. Both noroxycodone and oxymorphone are further metabolized to noroxymorphone, which has three-times and ten-times higher affinity for μ -opioid receptor in comparison to oxycodone and noroxycodone, respectively [13]. Since oxycodone, like codeine, is partly metabolized by polymorphic CYP2D6 to an active metabolite, it is expected to have

excessive adverse effects in *CYP2D6* UMs (Figure 1). In fact, oxycodone has recently been shown not to be a safe alternative to codeine for infants of nursing mothers [17]. In *CYP2D6* PM, poor analgesic effect was observed following oxycodone administration [18]. Two case studies, first involving 64 healthy adults with three *CYP2D6* UM individuals and other involving a *CYP2D6* PM patient, have reported variation in oxycodone pharmacology due to variation in *CYP2D6* genotype [19,20]. A better understanding of the genetic influence of *CYP2D6* on the pharmacokinetics of oxycodone could help clarify the role of genetic variability in the safety of children taking oxycodone especially in unmonitored home setting following surgery.

To this end, we hypothesized that genetic variations of *CYP2D6* alleles can alter the pharmacokinetics of oxycodone and its metabolites. The aim of this prospective observational study was to determine the impact of genetic polymorphism of *CYP2D6* on oxycodone pharmacokinetics and clearance in children taking oxycodone following painful surgery.

Methods

Study design

We conducted a prospective observational study that is part of an ongoing Phase IV study to characterize the pharmacokinetics and to evaluate the safety of oxycodone administered to children following a surgical procedure. Approval was obtained from the Cincinnati Children’s Hospital Medical Center Institutional Review Board. Written informed consent was obtained from parents/legal guardians. This study is registered with ClinicalTrials.gov, identifier #NCT01959204.

Participants

Children aged 2–17 years undergoing painful orthopedic, thoracic, urology and colorectal procedures were enrolled as part of the larger study. Subjects of American Society of Anesthesiologists status I or II were either enrolled preoperatively or postoperatively with the expectation that they would require IV access

Table 1. The summary of demographic information.			
Age	n	Age (years)	Weight (kg)
All	30	11.9 ± 4.2	45.6 ± 17.4
2–6 years	5	4.0 ± 1.4	16.8 ± 2.7
7–12 years	8	10.0 ± 1.5	41.7 ± 11.3
13–18 years	17	14.8 ± 1.1	56.0 ± 10.3
Age (year) and bodyweight (kg) of subjects are presented as mean ± standard deviation for all subjects as well as subjects categorized in groups based on age.			

Table 2. Frequency of observed alleles, associated phenotype and TAS.

Allele 1	Allele 2	Phenotype	TAS	n
*4	*41	PM	0.5	1
*1	*4	IM	1	5
*1	*6	IM	1	2
*17	*41	IM	1	1
*2A	*4	IM	1	4
*2A	*5	IM	1	1
*1	*9	EM	1.5	1
*2A	*9	EM	1.5	1
*1	*1	EM	2	5
*1	*2A	EM	2	6
*2A	*2A	EM	2	3

The observed CYP2D6 alleles, phenotype, Total Activity Score (TAS), and number of subjects with specific alleles are included in Table 2.

EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; TAS: Total activity score.

after inpatient surgery and postoperative analgesia with an opiate-level medication. Children were excluded if they were known to have used an inhibitor or inducer of CYP3A4 within 14 days of dosing with oxycodone [21]. Children were excluded if they had a history of smoking, alcohol consumption or drug addiction.

Patients were given oxycodone oral solution (0.1 mg/kg for children aged 2–6 years, 0.08 mg/kg for

ages 7–12 years and 0.07 mg/kg for ages 13–17 years) after being postoperatively cleared to transition to oral pain medication. Safety was assessed for 24 h following oxycodone dose by monitoring and recording adverse events, vital sign measurements and physical examination findings.

Pharmacokinetic sampling

Serial blood samples for pharmacokinetic analysis were collected for the determination of plasma concentrations of oxycodone at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 h following oxycodone administration. Oxycodone and oxymorphone levels in plasma were analyzed by LC–MS/MS (Biologistic Services, CO, USA). The assay's lower limit of quantitation for oxycodone and oxymorphone was 0.02 ng/ml.

Pharmacokinetic analysis

Oxycodone and oxymorphone pharmacokinetics after a single dose of oxycodone oral solution were characterized using noncompartmental analysis using Phoenix Win-Nonlin® (version 6.1, Pharsight, CA, USA). The peak concentration (C_{max}), time to peak concentration (T_{max}), terminal half-life ($T_{1/2}$) and area under the curve (AUC) were calculated for oxycodone and oxymorphone using the plasma concentration–time profiles. Actual postdose sample collection times were utilized to generate individual concentration–time profiles using noncompartmental analysis. Terminal half-lives were typically calculated using the terminal 2–3 time points after carefully examining

Figure 2. Concentration–time profiles of oxycodone (A) and its active metabolite oxymorphone (B) in plasma of pediatric patients (n = 30). Oxycodone was administered orally to children postoperatively; dosing was based on age (0.1 mg/kg for children ages 2–6 years, 0.08 mg/kg for ages 7–12 years, and 0.07 mg/kg for ages 13–17 years). The blood samples were collected till 24 hours.

the individual concentration time profile. The area under the plasma concentration time curve was calculated by the linear up/log down method. In addition to the observed AUC_{0-last} , partial areas under the concentration–time curves were evaluated to calculate the exposure up to 6 h (AUC_{0-6}), 12 h (AUC_{0-12}) and 24 h (AUC_{0-24}). All pharmacokinetic parameters were normalized by the actual oxycodone dose for standardization.

Genotyping

Blood was drawn in the operating room upon placement of intravenous line prior to surgery. DNA was isolated on the same day and frozen at -20°C . Batched genotyping for a panel of *CYP2D6* alleles was performed in a Clinical Laboratory Improvement Amendments approved and Certification Authorization Professional-certified laboratory after clinical data were entered on study participants. *CYP2D6*

Figure 3. Comparison of C_{max} of oxycodone and oxymorphone with oxycodone metabolism phenotype. (A) Dose normalized maximum plasma concentration values of oxycodone in oxymorphone were compared in *CYP2D6* phenotype groups PM/IM ($n = 14$) and EM ($n = 16$). The results are expressed as mean $\pm$ 95% CI. No statistical difference was observed in two groups in oxycodone C_{max} values. The two groups were statistically significant in oxymorphone C_{max} as determined by unpaired Mann–Whitney test. (B) Oxycodone and oxymorphone C_{max} values were plotted with respect to *CYP2D6* total activity score (TAS). A trend line was drawn connecting mean C_{max} of groups with TAS values 1 and 2. The trend line showed higher slope for oxymorphone with high TAS associated with bigger C_{max} . EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

Figure 4. Comparison of oxycodone and oxymorphone AUC₀₋₆ of with oxycodone metabolism phenotype.

(A) Dose normalized integrated exposure of oxycodone and oxymorphone were compared in *CYP2D6* phenotype groups PM/IM ($n = 14$) and EM ($n = 16$). The results are expressed as mean $\pm$ 95% CI. No statistical difference was observed in two groups in oxycodone AUC₀₋₆. A statistically significant difference in oxymorphone AUC₀₋₆ was observed by unpaired Mann–Whitney test. (B) Oxycodone and oxymorphone AUC₀₋₆ were plotted with respect to *CYP2D6* total activity score (TAS). A trend line was drawn connecting mean AUC₀₋₆ of groups with TAS values 1 and 2. The trend line showed higher slope for oxymorphone with high TAS value associated with higher AUC₀₋₆. AUC: Area under the curve; EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

alleles, as defined in the internationally recognized human *CYP450* database [22] included functional alleles *2, *2A and *35, reduced function alleles *9, *10, *17 and *41, and nonfunctional alleles *3, *4, *5, *6, *7, *8, *11, *14, *15, *18, *19, *20, *40, *42 and *44. When these variants were not identified, *1 was assumed. The TaqMan allelic discrimination system (Applied Biosystem, CA, USA) was used to analyze all alleles except *CYP2D6**5 allele (full gene deletion) and *CYP2D6* duplication, which were detected by long-PCR [23].

Predicted oxycodone metabolism phenotypes were designated by two methods: a total activity score (TAS) [24] and the descriptive metabolism phenotype (Table 2). The summed TAS of 1.0 represents both full function + null function alleles and reduced function + reduced function alleles which may represent two distinctive pharmacokinetic groups. Evidence exists not only for reduced expression [22,25] but also for substrate specificity of reduced function *CYP2D6* alleles [26]. Our second method using descriptive metabolism phenotype distinguishes between predicted phenotypes that

contain at least one full function allele and those that do not.

Pharmacogenetic analysis

The pharmacokinetic parameters such as dose-normalized $C_{\max}$, AUC_{0-6} , AUC_{0-24} were plotted with respect to *CYP2D6* genotype groups PM/IM or EM. To establish relationship among dose-normalized $C_{\max}$, AUC_{0-6} , and AUC_{0-24} of oxycodone and oxymorphone with TAS, these parameters were plotted with respect to TAS of 0.5, 1, 1.5 and 2. Extent of conversion of oxycodone

done to oxymorphone with respect to *CYP2D6* genotype group PM/IM or EM was investigated by plotting oxymorphone/oxycodone ratio of $C_{\max}$, AUC_{0-6} , AUC_{0-24} with respect to *CYP2D6* genotype. Similarly, oxymorphone/oxycodone ratio of $C_{\max}$, AUC_{0-6} , AUC_{0-24} was compared with distinct pharmacokinetic groups formed by TAS.

Statistical analysis

Numerical data were presented as mean $\pm$ standard deviation. The statistical difference of pharmacokinetic

Figure 5. Comparison of oxycodone and oxymorphone AUC_{0-24} of with oxycodone metabolism phenotype.

(A) Dose normalized integrated exposure of oxycodone and oxymorphone were compared in *CYP2D6* phenotype groups PM/IM ($n = 14$) and EM ($n = 16$). The results are expressed as mean $\pm$ 95% CI. No statistical difference was observed in two groups in oxycodone AUC_{0-24} . A statistically significant difference in oxymorphone AUC_{0-24} was observed by unpaired Mann–Whitney test. (B) Oxycodone and oxymorphone AUC_{0-24} were plotted with respect to *CYP2D6* total activity score (TAS). A trend line was drawn connecting mean AUC_{0-24} of groups with TAS values 1 and 2. The trend line showed higher slope for oxymorphone with high TAS value associated with higher AUC_{0-24} . AUC: Area under the curve; EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

Figure 6. Comparison of oxycodone and oxymorphone C_{max} ratio with oxycodone metabolism phenotype. (A) The C_{max} ratio of oxymorphone/oxycodone for individual patient were compared based on their CYP2D6 phenotype groups PM/IM ($n = 14$) and EM ($n = 16$). The results are expressed as mean $\pm$ 95% CI. The C_{max} ratios were higher in EM patients compared to PM/IM patients as calculated by unpaired Mann–Whitney test. (B) The oxymorphone and oxycodone C_{max} ratios were plotted with respect to CYP2D6 total activity score (TAS). A trend line was drawn connecting mean C_{max} ratios of groups with TAS values 1 and 2. The trend line showed high TAS value associated with higher C_{max} ratio. EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

parameter in two groups was calculated by performing nonparametric unpaired Mann–Whitney test using GraphPad software® (GraphPad Prism, CA, USA). The p-value of less than 0.05 was considered statistically significant.

Results

Demographic.hics

A total of 30 children between ages 2 and 17 years from three different study sites were enrolled in the study after being postoperatively cleared for oral pain medication. Demographic details for all subjects and grouped as per age are presented in Table 1.

Distribution of genotypes & phenotypes

Table 2 details the list of the observed CYP2D6 genotype, CYP2D6 phenotype and the corresponding counts. Of all the enrolled children, only one was classified as PM with $*4/*41$ genotype. Thirteen children were classified as intermediate metabolizer (IM) with five children with $*1/*4$ genotype and four children with $*2A/*4$ genotype. The remaining 16 children were classified as extensive metabolizers (EMs), with $*1/*1$ ($n = 5$) and $*1/*2A$ ($n = 6$) being the most frequent genotypes.

Oxycodone & metabolite pharmacokinetics and modeling

The concentration–time profiles for oxycodone appeared to have a single phase post- C_{max} (Figure 2A).

Oral absorption of oxycodone typically resulted in 1–2 concentration peaks with a median peak time of about 2 h with no noticeable difference across the three age groups. While fast absorption was observed in most of the subjects, delayed absorption was observed in a few subjects with peak concentrations occurring about 12 h postdosing. Overall, concentration–time profiles of oxymorphone were parallel to the observed oxycodone concentration with oxymorphone concentrations between 1 and 5% of the observed oxycodone concentration. None of the 24 h samples had observable oxymorphone concentrations (Figure 2B). Times to peak concentration for oxymorphone were very similar to that of oxycodone. The mean terminal half-life for oxycodone was 2.7 (± 0.7) h and that for oxymorphone was 3.6 (± 1.9) h. Dose-normalized C_{max} of 2.2 (± 1.5) arbitrary unit (AU) was observed for oxycodone while it was estimated to be 0.054 (± 0.056) AU for oxymorphone. The dose-normalized AUC_{0-24} was estimated to be 10.9 (± 4.5) AU for oxycodone and 0.22 (± 0.14) AU for oxymorphone.

Genetic association: impact of CYP2D6 genetic polymorphism

The impact of CYP2D6 genetic polymorphism on the oxycodone pharmacokinetics was evaluated by observing the variation of exposure markers (C_{max} , AUC_{0-6} and AUC_{0-24}) with respect to the CYP2D6 genotype and CYP2D6 TAS. There was no significant differ-

Figure 7. Comparison of oxycodone and oxymorphone AUC₀₋₆ ratio with oxycodone metabolism phenotype. (A) The AUC₀₋₆ ratio of oxymorphone/oxycodone for individual patient were compared based on their *CYP2D6* phenotype groups PM/IM ($n = 14$) and EM ($n = 16$). The results are expressed as mean $\pm$ 95% CI. The AUC₀₋₆ ratios were higher in EM patients compared to PM/IM patients as calculated by unpaired Mann–Whitney test. (B) The oxymorphone and oxycodone AUC₀₋₆ ratios were plotted with respect to *CYP2D6* total activity score (TAS). A trend line was drawn connecting mean AUC₀₋₆ ratios of groups with TAS values 1 and 2. The trend line showed high TAS value associated with higher AUC₀₋₆ ratio.

AUC: Area under the curve; EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

ence in exposure markers of oxycodone metabolism among PM/IM and EM of *CYP2D6* (Figure 3A for dose-normalized $C_{\max}$, Figure 4A for dose-normalized AUC₀₋₆ and Figure 5A for dose-normalized AUC₀₋₂₄). A similar comparison of oxymorphone exposure among PM/IM and EM showed significantly higher exposure in EM. The p-value of 0.028 was observed for dose-normalized $C_{\max}$ levels (Figure 3A) in PM/IM and EM. Higher dose-normalized AUC₀₋₆ ($p = 0.0162$; Figure 4A) and dose-normalized AUC₀₋₂₄ ($p = 0.026$; Figure 5A) for oxymorphone were seen in EM. As shown in Figure 5B, TAS had clear impact on dose-normalized oxymorphone AUC₀₋₂₄ ($p = 0.0091$ among TAS 1 and 2 groups), though a similar impact on dose-normalized oxycodone AUC₀₋₂₄ was not observed. This is consistent with the current understanding that oxymorphone formation accounts for about 1–5% of oxycodone elimination. Dose-normalized oxymorphone AUC₀₋₂₄ estimates tended to be unreliable because extrapolation after the last dose accounted for >20% of the sample. Similar results were obtained when the impact of TAS on dose-normalized AUC₀₋₆ (Figure 4B) and $C_{\max}$ (Figure 3B) of oxymorphone was evaluated. IMs consistently had lower oxymorphone exposures than EMs as determined by the Mann–Whitney test.

The impact of *CYP2D6* activity was further evaluated using the ratio of oxymorphone-to-oxycodone exposures to normalize the impact of intersubject variation in exposure due to variable bioavailability.

Significantly higher oxymorphone/oxycodone ratio was observed for EM for $C_{\max}$ ($p = 0.0007$; Figure 6A), AUC₀₋₆ ($p = 0.001$; Figure 7A) and AUC₀₋₂₄ ($p = 0.004$; Figure 8A). As observed previously, the oxymorphone exposure relative to oxycodone exposure was consistently dependent on the *CYP2D6* phenotype with higher activity phenotypes having higher oxymorphone exposures (Figures 6B, 7B & 8B).

Discussion

Our study offers early evidence that *CYP2D6* phenotype significantly affects oxycodone metabolism in pediatric surgical patients. Patients with more active *CYP2D6* activity and oxycodone metabolism had higher levels of oxymorphone in comparison to phenotypes with less *CYP2D6* activity.

In an age where personalized medicine is gaining more popularity, there is increasing focus to better understand the pharmacogenetic influence on the response and side effects of opioid medications [27–30]. To this end, the main purpose of this study was to identify the role of pharmacogenetic variability on the pharmacokinetics of oral oxycodone in children undergoing surgery. We have demonstrated that phenotypic activity of *CYP2D6* significantly influenced oxymorphone levels in children taking oxycodone. By normalizing the impact of intersubject variation in exposure due to variable bioavailability of oxycodone, we again showed that oxymorphone exposure was higher with

increased phenotypic activity of *CYP2D6*. Overall, these results suggest that there is variability in oxycodone metabolism as determined by the child's underlying *CYP2D6* genotype. More attention should be paid while administering oxycodone to EM and PM due to possibility of toxic effects or lack of efficacy [31].

Certain populations have higher prevalence of *CYP2D6* UM phenotype (20% in Saudi Arabians [32] and 29% in Ethiopians [33]) compared with 1–7% prevalence in Caucasians [19]. These individuals are likely at higher risk of toxicity from opioids metabolized by *CYP2D6* pathway including oxycodone, codeine, tramadol and hydrocodone, and more vigilance is required when these opioids are administered in these population and *CYP2D6* UMs.

This study included children of different age ranging from 2 to 16 year. Initially, we recruited older children (>6 years). We are trying to recruit younger children (2–6 years) in a larger study. The fractional *CYP2D6* expression at birth is 3.6% of adult value and 50% adult level expression is reached at 1.2 months [34]. Thus, our findings correlating *CYP2D6* phenotype with oxycodone dosing could be extrapolated for young children and even neonates. However, we need to validate our findings from older children in younger children.

In a cross-sectional study in adult cancer patients taking oxycodone, it was observed that while different *CYP2D6* genotypes resulted in varying pharmacokinetics of oxycodone, they did not produce any observ-

able difference in markers of efficacy such as pain score, symptoms of nausea, sedation and cognitive failure [35]. This adult study had many confounders and limitations in terms of robust clinical phenotypes. In another study, in healthy adult volunteers by Zwisler *et al.*, significant difference was observed in pain reduction, pain tolerance, discomfort and oxymorphone/oxycodone ratio between *CYP2D6* EM and PM individuals [36]. This study further corroborates our oxycodone PK and *CYP2D6* association findings in children. This study is clinically important as children tend to experience more adverse effects including deaths and life-threatening respiratory depression from clinical use of opioids compared with adults [4]. In this study, we focused on clinical doses of oxycodone and *CYP2D6* genotype on oxycodone's metabolism in children for the first time.

Recent Clinical Pharmacogenetics Implementation Consortium guidelines [37], cautions against the use of codeine, tramadol, hydrocodone and oxycodone in *CYP2D6* PMs for analgesic efficacy reasons and in UM for toxicity reasons. Further studies are needed to verify if difference in oxycodone pharmacokinetics in children results in varying postoperative response.

One limitation to our pilot study is the small number of extreme *CYP2D6* phenotypes studied, which lead to fewer numbers of phenotypes in our study population. Only one child was classified as a PM and no children were identified as UMs. More patients are

Figure 8. Comparison of oxycodone and oxymorphone AUC₀₋₂₄ ratio with oxycodone metabolism phenotype. (A) The AUC₀₋₂₄ ratio of oxymorphone/oxycodone for individual patient were compared based on their *CYP2D6* phenotype groups PM/IM (n = 14) and EM (n = 16). The results are expressed as mean ± 95% CI. The AUC₀₋₂₄ ratios were higher in EM patients compared to PM/IM patients as calculated by unpaired Mann–Whitney test. (B) The oxymorphone and oxycodone AUC₀₋₂₄ ratios were plotted with respect to *CYP2D6* total activity score (TAS). A trend line was drawn connecting mean AUC₀₋₂₄ ratios of groups with TAS values 1 and 2. The trend line showed high TAS value associated with higher AUC₀₋₂₄ ratio. AUC: Area under the curve; EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

required to better understand the effect of low and ultra-rapid activity *CYP2D6* phenotypes on oxycodone pharmacokinetics. It is an ongoing study and we will have a bigger sample with more PMs and UMs at the end of the study to associate not only with oxycodone's pharmacokinetics but also with clinical outcomes. Another limitation is that we were not able to perform a direct prospective comparison of clinical effects of oxycodone with codeine. In our institution, we have stopped the use of codeine in children following tonsillectomy and other surgery after the FDA's black box warning on codeine's use in the same because of its unpredictability and number of postoperative deaths and anoxic brain injuries.

More studies are warranted to investigate whether the incidence of adverse events in children taking oxycodone is influenced by the genetic impact on oxycodone metabolism. This will help in determining the safety profile of this opioid medication in children following painful surgery. Additionally, it may allow us to better tailor pain management strategies for individual children by optimizing pain relief while avoiding adverse reactions.

Conclusion & future perspective

In conclusion, our pediatric pharmacokinetic and pharmacogenetic association pilot study shows that *CYP2D6* genotypes play a significant role in the pharmacokinetics of oxycodone and its metabolite, oxymorphone. Specifically, children identified as being EMs of oxycodone had greater exposure to oxymorphone, an active and potent metabolite of oxycodone compared with PMs.

Pharmacokinetic variations due to multiple phenotypes of *CYP2D6* need to be considered when personalizing oxycodone use in a specific child. Based on *CYP2D6* phenotype, a patient might need oxycodone dose adjustment or even a different therapeutic alternative not metabolized by *CYP2D6* such as oral morphine, hydromorphone and tapentadol. Large studies are warranted to further ascertain whether the influence of pharmacogenetic variability on oxycodone

pharmacokinetics is associated with clinically important outcomes in children. Personalized opioid selection and oxycodone dosing based on *CYP2D6* genotype for an individual child may improve pain control following surgery while limiting dangerous adverse side effects.

Author contributions

The authors directed and had access to all the analyses and the full clinical and genetic database, wrote all drafts of the report, decided to publish the results, and attest for the accuracy and completeness of the data. S Sadhasivam participated in design, funding conduct and supervision of the project. All authors contributed to subject recruitment, data analysis and made critical revisions to the report for important intellectual content.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

All authors declare that approval was obtained from Institutional Review Board (IRB) and principles outlined in Declaration of Helsinki were followed in performing this study. Informed consent was obtained from participants in study involving human subjects.

Executive summary

- Interindividual variation in oxycodone pharmacokinetics and generation of active metabolite oxymorphone in children is dependent upon hepatic *CYP2D6* phenotype.
- Significantly higher exposure of dose-normalized oxymorphone C_{max} ($p = 0.02$); AUC_{0-6} ($p = 0.016$) and AUC_{0-24} ($p = 0.026$) was observed in extensive metabolizer phenotype, compared with poor/intermediate metabolizer phenotype.
- Greater total activity score value is associated with greater oxymorphone exposure in plasma ($p = 0.009$).
- Similarly, higher oxymorphone/oxycodone ratio observed for extensive metabolizer for C_{max} ($p = 0.0007$); AUC_{0-6} ($p = 0.001$) and AUC_{0-24} ($p = 0.004$) ruling out the contribution of bioavailability in variation in findings.
- Further studies needed to ascertain impact of *CYP2D6* phenotype on oxycodone pharmacodynamics in children and to tailor opioid selection and dosing in clinical setting.

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