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ARTICLE

Pediatric CYP2D6 metabolizer status and post-tonsillectomy nausea and vomiting after ondansetron

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Abstract

The goal of this study was to determine whether CYP2D6 metabolizer status within the ondansetron-treated pediatric tonsillectomy population is associated with risk of postoperative nausea and vomiting (PONV) in the post-anesthesia care unit. We conducted a retrospective cohort study of pediatric patients (<18 years) who underwent tonsillectomy and received ondansetron on the day of the procedure. Data were obtained from BioVU, an institutional biobank that links DNA to de-identified electronic health record data. Subjects were tested for 10 *CYP2D6* allelic variants and copy number variation, and genotype data translated into CYP2D6 metabolizer status. The cohort included 652 individuals, 105 (16.1%) of whom had PONV. Rates of PONV were similar across groups: ultrarapid metabolizers (UMs), 1 of 9 (11.1%); normal metabolizers (NMs), 64 of 354 (18.1%); intermediate metabolizers (IMs), 33 of 234 (14.1%); poor metabolizers (PMs), 6 of 39 (15.4%); and ambiguous phenotypes, 1 of 16 (6.3%). In multivariable analysis adjusted for age, sex, and time under anesthesia, CYP2D6 metabolizer status was not associated with PONV, with an odds ratio of 1.37 (95% confidence interval 0.9, 2.1) when comparing PM/IM versus NM/UM. In this large pediatric population, no significant differences were detected for PONV based on CYP2D6 metabolizer status. Further investigation is needed to determine mechanisms for ondansetron inefficacy in children.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

In adults, the Clinical Pharmacogenetics Implementation Consortium guideline recommends consideration of alternative anti-emetic therapy for CYP2D6 ultrarapid metabolizers in place of ondansetron.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study sought to determine if *CYP2D6* genotype-predicted metabolizer status was associated with increased risk of post-tonsillectomy postoperative nausea and vomiting in children after receiving ondansetron prophylaxis.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

These data do not support the use of a *CYP2D6* genotype or phenotype clinical support tool to guide anti-emetic therapy after tonsillectomy in children (as recommended in adults).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These findings highlight the need for pediatric validation of pharmacogenomic studies.

INTRODUCTION

Ondansetron, a selective antagonist to the serotonin 5-HT_3 receptor, is a commonly used medication in both children and adults.[1–3] Ondansetron is US Food and Drug Administration (FDA) approved for use in patients 6 months of age or older to prevent postoperative nausea and vomiting (PONV) and to prevent chemotherapy induced nausea and vomiting (CINV).[4,5] Tonsillectomy is considered a highly emetogenic surgery and is performed frequently in children for recurrent tonsillitis and increasingly for obstructive sleep apnea.[6,7] PONV prophylaxis recommendations for all pediatric patients undergoing tonsillectomy include the administration of dexamethasone and a 5-HT_3 antagonist, which in the United States is typically ondansetron.[8]

Although ondansetron is metabolized by multiple cytochrome P450 (CYP) enzymes, only genotypic variation in the *CYP2D6* gene, which leads to a wide range of enzymatic activity across individuals, has been linked to drug response.[9] Prior studies in adults have demonstrated that individuals with increased CYP2D6 activity experienced more PONV after treatment with ondansetron than those with reduced activity.[10,11] These data led the Clinical Pharmacogenetics Implementation Consortium (CPIC) to recommend consideration of alternative anti-emetic therapy for CYP2D6 ultrarapid metabolizers (UMs) in place of ondansetron; this recommendation is rated as having "moderate" strength, indicating that "there is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects."[12] Data from pediatric populations are limited, although one study found that children who are CYP2D6 UMs were more likely to experience CINV on days without opioid exposure,[13] whereas another study found no difference in CINV by CYP2D6 status.[14] Given the routine use of ondansetron in children undergoing tonsillectomy and the paucity of pediatric-specific pharmacogenomic data related to ondansetron in this population, the objective of this study was to determine if *CYP2D6* genotype-predicted metabolizer status was associated with increased risk of post-tonsillectomy PONV after receiving ondansetron prophylaxis.

METHODS

Study design and cohort

A retrospective cohort study was performed using the Vanderbilt University Medical Center repository, BioVU, which links DNA and genomic data to de-identified electronic health record (EHR) data.[15,16] This study was reviewed by the Vanderbilt University Medical Center Institutional Review Board and determined to be non-human subject research. Individuals consented to be included in the BioVU repository. An initial search was performed to identify individuals in the biobank participants who (1) had no prior surgical manipulation of the upper gastrointestinal tract (partial/total gastrectomy, sleeve gastrectomy, prior esophageal surgery, fundoplication, gastrostomy, or concomitant bronchoscopy) identified by International Classification of Disease 9th and 10th revision (ICD-9/10) codes (Table S1); (2) had no diagnosis of cyclic vomiting syndrome as defined by ICD-9/10 codes (Table S1); (3) had tonsillectomy with or without adenoidectomy, as defined by Current Procedural Terminology (CPT) codes 42820, 42821, 42825, and 42825, at age less than 18 years; and (4) were administered ondansetron on the day of surgery. Additional inclusion criteria were availability of pre-operative and postoperative data, noncompromised DNA available in BioVU, and confirmation of ondansetron exposure in the pre-operative or operative phase. In the case of a patient undergoing multiple tonsillectomies (either later in life or due to an initial complication), only the first tonsillectomy was included. Individuals with indeterminant *CYP2D6* genotype or phenotype (as defined below) were excluded from analysis. Potential CYP2D6 inhibitor exposure was defined as documented strong inhibitor use (bupropion, fluoxetine, paroxetine, or quinidine) in the EHR data at the time of tonsillectomy. Given uncertainty regarding persistence, compliance, and timing of the last dose of these potential exposures extracted from EHR data, primary analyses did not incorporate inhibitor data (i.e., no phenoconversion).

Outcome

The primary outcome of this study was PONV, defined as receiving an anti-emetic medication in the post-anesthesia care unit (PACU). Given the prior report of increased CINV among children who are CYP2D6 UMs specifically on days without opioid exposures,[13] we reviewed all peri-operative and postoperative medications and performed subset analysis of those individuals without opioid exposure (i.e., excluding those with one or more opioid doses on the day of surgery). Secondary outcomes were investigated, including presence of PONV on follow-up telephone call 24 h post-procedure by our anesthesia team, visits to the emergency department (ED) in the 7 days after the procedure for nausea/vomiting, and amount of time spent in the PACU prior to discharge or hospital admission. Patients presenting to the ED for hematemesis thought to be a procedural complication by manual review were not counted as ED visits for nausea/vomiting.

CYP2D6 genotyping

DNA samples were analyzed to determine *CYP2D6* genotype using commercially available TaqMan assays (Thermo Fisher Scientific, Waltham, MA) and manufacturer provided protocols in the Vanderbilt Technologies for Advanced Genomics (VANTAGE) Core Laboratory. DNA was assayed for 11 different single nucleotide variants (rs16947, rs1080985, rs35742686, rs3892097, rs5030655, rs5030867, rs5030656, rs1065852, rs28371706, rs59421388, and rs28371725) and two assays for copy number variation (CNV) targeting intron 6 and exon 9; variants were selected to be inclusive of those used in clinical *CYP2D6* genotyping at this institution. Astrolabe[17,18] and manual review were used to call *CYP2D6* diplotypes from genotype data. Subsequently, diplotypes were translated into activity scores and phenotypes (poor metabolizer [PM], intermediate metabolizer [IM], normal metabolizer [NM], and UM) per CPIC recommendations.[19] For a subject to be confirmed as having a CNV (e.g., 3 or more gene copies), both copy number assays had to be in agreement. Identification of the specific duplicated allele was not available. In some instances, this would not affect phenotype prediction, whereas in others this led to an ambiguous activity score and phenotype. Subjects with ambiguous activity scores were assigned the highest activity score for analytic purposes. DNA was listed as unavailable and subjects were excluded if there was a history of hematologic malignancies, recent blood transfusions, or DNA available was of insufficient quality or quantity.

Statistical analysis

Group comparisons for the primary outcome (PONV in the PACU) and secondary outcomes (PONV 24 h post-procedure, ED visits for nausea/vomiting, and time in PACU) by clinical covariates and metabolizer status based on genotype were done using chi-square or Fisher's exact tests, as appropriate, for categorical variables, and Kruskal-Wallis test for continuous variables. Genetically predicted metabolizer status was also analyzed as a binary variable (NM/UM vs. PM/IM), as previously described.[10] Individuals who could not be definitively assigned to these dichotomous groups (i.e., with ambiguity leading to either IM or NM status), were excluded in the binary analysis. Multivariate analysis was performed looking at PONV in the PACU across genetically predicted metabolizer status, adjusting for age, sex, and time under anesthesia. Univariate and multivariate analyses for the primary outcome were performed in the entire cohort and in the subset that did not receive any opioids peri- or postoperatively. Sensitivity analyses were performed to assess the impact of instances of CYP2D6 activity score ambiguity on the results, as well as the effect of phenoconversion due to potential exposure to CYP2D6 strong inhibitors. Post hoc analyses of UM versus NM/IM/PM and UM versus IM/PM, adjusting for age, sex, and anesthesia duration, were also performed. Statistical analyses were performed using STATA IC 16.0 (StataCorp LLC). The level of statistical significance was set at 0.05, and all p values were two-sided.

RESULTS

A total of 652 subjects met inclusion/exclusion criteria (Figure 1). Tonsillectomy dates spanned 2004–2017; of note, in the de-identified database, all dates within a record are uniformly shifted up to 365 days to provide anonymity while maintaining chronology of events. The cohort had a median age of 6.6 years (interquartile range 4.2–9.7) and 307 (47.1%) were female subjects (Table 1). The most frequent EHR-reported race and ethnicity were White or Caucasian (69.3%) and non-Hispanic (90.3%). In all, 636 (97.5%) had a definitive CYP2D6 metabolizer status assigned based on genotype. There were 39 PMs (6.0%), 234 IMs (35.9%), 354 NMs (54.3%), and nine UMs (1.4%). Ambiguous phenotypes were assigned to 16 subjects (2.5%) with 11 having either an IM or NM phenotype and five with NM or UM phenotype. Five individuals (2 IMs and 3 NMs) had potential CYP2D6 inhibitor exposures ($n = 1$ to bupropion, $n = 4$ to fluoxetine, none to paroxetine or quinidine). Ondansetron dose (mg/kg) administered was similar across metabolizer status groups

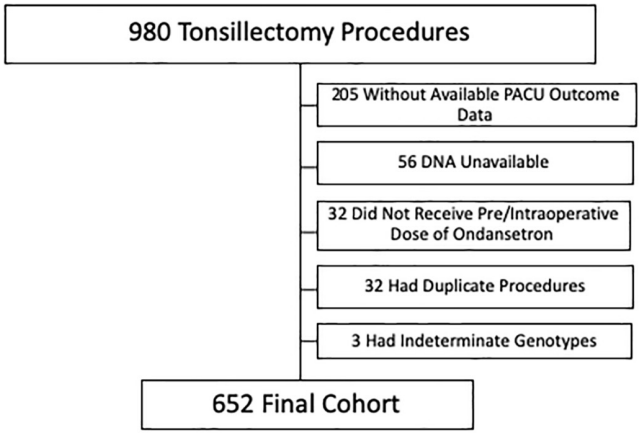

FIGURE 1 Cohort identification. PACU, post-anesthesia care unit.

($p = 0.9$). There was no difference in frequency of opioid exposure across metabolizer groups.

PONV in the PACU was documented for 105 individuals (16.1%), including six PMs (15.4%), 33 IMs (14.1%), one IM/NM (9.1%), 64 NMs (18.1%), zero NM/UM (0.0%), and one UM (11.1%; Figure 2a**)**. Only 18 (2.8%) individuals required a second dose of anti-emetic while in the PACU. Frequencies of PONV by activity score are shown in Figure 2b. In univariate analysis, older age and female sex were associated with increased risk of PONV (odds ratio [OR] 1.1, 95% confidence interval [CI] 1.02–1.13; OR 1.7, 95% CI 1.1–2.6, respectively). As shown in Figure 3a, in multivariate analysis, adjusted for age, sex, and duration of anesthesia, there was no increased risk of PONV in NM/UM versus PM/IM (OR 1.37, 95% CI 0.88–2.13). Multivariate analysis adjusting for the same covariates also showed no association between PONV and CYP2D6 activity score (OR 1.29, 95% CI 0.91–1.82; Figure 3b**)**. Dexamethasone exposure and propofol exposure were not associated with PONV in univariate analysis ($p > 0.05$). Results of the multivariable analyses were not substantially affected by inclusion of these variables as covariates.

Opioid administration data were available for 645 (98.9%) individuals. Opioids were administered to 184 individuals and included oxycodone, hydrocodone/acetaminophen, morphine, fentanyl, and hydromorphone. No codeine was administered to individuals in this cohort in the peri- or postoperative time frame. In subgroup analysis, excluding these 184 individuals and the seven lacking opioid administration data, adjusted for age, female sex, and duration of anesthesia, PONV was not associated with binary metabolizer status (OR 1.32, 95% CI 0.81–2.16) or CYP2D6 activity score (OR 1.29, 95% CI 0.88–1.90).

There were no differences across genetically predicted CYP2D6 metabolizer status (PM vs. IM vs. NM vs. UM) in the secondary outcomes of 24-h nausea on follow-up telephone call, 24-h vomiting or nausea on follow-up telephone call, or ED visits within 7 days for nausea or vomiting ($p = 0.716$, $p = 0.06$, and $p = 0.887$, respectively). The was no significant difference in time spent in the PACU by metabolizer status ($p = 0.172$).

In sensitivity analyses, there was no difference in results when individuals with ambiguous CYP2D6 activity scores were assigned the lowest, rather than highest possible score. Analysis with the five individuals (2 IMs and 3 NMs) potentially exposed to strong CYP2D6 inhibitors reassigned to PM status, none of whom had PONV, revealed no significant differences from the primary results: OR for PONV in NM/UM versus (phenoconverted or genetic) PM/IM: 1.41, 95% CI 0.90–2.10; OR for PONV by phenoconverted CYP2D6 activity score: 1.33, 95% CI 0.94, 1.88. There were no differences in PONV when comparing UM versus NM/IM/PM or UM versus IM/PM (Table S2).

DISCUSSION

Ondansetron is the most frequently prescribed medication with established pharmacogenetic interaction in children.[1] It is estimated that around 8% of children in the United States are prescribed ondansetron each year. Based on data for adults and children and the estimates of the UM actionable phenotype, ~4% of those patients prescribed ondansetron would have better outcomes with an alternate drug, if there is a clinically significant difference for CYP2D6 UM individuals.[2] The frequency of CYP2D6 UMs varies between less than 1% and 20% depending on ancestry, with those of European and African American/Afro-Caribbean ancestry having a frequency of 3.1% and 4.7%, respectively.[12] Prior studies have described up to five times higher risk of PONV among UM/NMs when compared with IM/PMs.[12,20] Our data did not show an association between CYP2D6 activity score or metabolizer status and PONV. The upper limit of the CI (2.1) indicates that if there is a relationship, the effect size is substantially smaller than described in adults.

Several studies have demonstrated the association of *CYP2D6* genotype or phenotype to ondansetron levels or effect, although results are inconsistent. In the postoperative setting, in a cohort of 146 adults with prophylactic ondansetron administered during elective abdominal surgery, Stamer et al.[21] found that 15.7–19.7% of adults had PONV depending on the dose of ondansetron they received. They also showed decreased area under the curve (AUC) for *S*-ondansetron in CYP2D6 UMs compared with PMs, and significant difference in AUC across metabolizer status. That study found no significant association between genotype and PONV, which may have been due to the small sample size. Another study of 250 women (among them 11 UMs) who underwent nonemergent

TABLE 1 Cohort identification

	CYP2D6 metabolizer status						
	PM ($n = 39$)	**IM ($n = 234$)**	**IM/NM ($n = 11$)**	**NM ($n = 354$)**	**NM/UM ($n = 5$)**	**UM ($n = 9$)**	**Overall ($n = 652$)**
Age, years	8.1 (5.4–10.4)	6.8 (4.2–10.3)	6.0 (5.2–8.0)	6.5 (4.0–9.5)	4.6 (4.3–4.8)	6.3(5.2–7.3)	6.6 (4.2–9.7)
Female	15 (38.5)	120 (51.3)	2 (18.2)	166 (46.9)	2 (40.0)	2 (22.2)	307 (47.1)
Race[a]							
Asian	0 (0.0)	2 (0.9)	0 (0.0)	14 (4.0)	0 (0.0)	0 (0.0)	16 (2.5)
African American or Black	2 (5.1)	38 (16.2)	4 (36.4)	71 (20.1)	2 (40.0)	1 (11.1)	118 (18.1)
Native American	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Caucasian or White	35 (89.7)	177 (75.6)	5 (45.5)	225 (63.6)	3 (60.0)	7 (77.8)	452 (69.3)
Other	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Unknown	2 (5.1)	17 (7.3)	2 (18.2)	44 (12.4)	0 (0.0)	1 (11.1)	66 (10.1)
Hispanic Latino Ethnicity[b]	2 (5.1)	17 (7.3)	2 (18.2)	41 (11.7)	0 (0.0)	1 (11.1)	63 (9.7)
American Society of Anesthesiologists class							
1	0 (0.0)	14 (6.0)	0 (0.0)	13 (3.7)	0 (0.0)	0 (0.0)	27 (4.1)
2	30 (77.0)	161 (68.8)	6 (54.5)	266 (75.1)	2 (40.0)	7 (77.8)	472 (72.4)
3	9 (23.1)	55 (23.5)	4 (36.4)	71 (20.1)	2 (40.0)	2 (22.2)	143 (21.9)
4	0 (0.0)	3 (1.3)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	4 (0.6)
Unknown	0 (0.0)	1 (0.4)	1 (9.1)	3 (0.8)	1 (20.0)	0 (0.0)	6 (0.9)
Time under anesthesia, min[c]	48 (41–59)	50 (40–63)	49.5 (35–61)	49 (40–61)	58 (39–68.5)	55 (45–69)	50 (40–62)
Strong CYP2D6 inhibitor as home medication	0 (0.0)	2 (0.9)[d]	0 (0.0)	3 (0.8)[d]	0 (0.0)	0 (0.0)	5 (0.8)
Ondansetron dose (mg/kg)[e]	0.10 (0.09–0.11)	0.10 (0.08–0.11)	0.10 (0.08–0.10)	0.10 (0.09–0.11)	0.10 (0.09–0.12)	0.09 (0.08–0.10)	0.10 (0.09–0.11)
Opioid exposure[f]	9 (23.1)	75 (32.1)	3 (27.3)	93 (26.3)	0 (0.0)	4 (44.4)	184 (28.2)
Dexamethasone exposed	38 (97.4)	230 (98.3)	9 (81.8)	343 (96.9)	5 (100)	9 (100)	634 (97.2)
Propofol exposed	30 (76.9)	155 (66.2)	7 (63.6)	249 (70.3)	4 (80.0)	4 (44.4)	449 (68.9)
Postoperative nausea/vomiting requiring a dose of anti-emetic in PACU	6 (15.4)	33 (14.1)	1 (9.1)	64 (18.1)	0 (0.0)	1 (11.1)	105 (16.1)
Continued nausea/vomiting requiring second dose of anti-emetic in PACU	2 (5.1)	5 (2.1)	0 (0.0)	11 (3.1)	0 (0.0)	0 (0.0)	18 (2.8)
Time spent in PACU, min	167 (116–191)	152 (105–217)	151 (77–201)	141 (102–195)	104 (80–194)	146 (91–188)	146 (103–201)

(Continues)

TABLE 1 (Continued)

	CYP2D6 metabolizer status					
	PM (n = 39)	IM (n = 234)	IM/NM (n = 11)	NM (n = 354)	NM/UM (n = 5)	UM (n = 9)	Overall (n = 652)
24-h nausea on follow-up telephone call	2 (5.1)	14 (6.0)	1 (9.1)	19 (5.4)	0 (0.0)	0 (0.0)	36 (5.5)
24-h vomiting on follow-up telephone call	4 (10.3)	11 (4.7)	1 (9.1)	12 (3.4)	0 (0.0)	0 (0.0)	28 (4.3)
ED visit with nausea/vomiting within 7 days of procedure	0 (0.0)	11 (4.7)	1 (9.1)	13 (3.7)	0 (0.0)	0 (0.0)	25 (3.8)

Note: Categorical variables reported as # (%); continuous variables reported as median (IQR).

Abbreviations: ED, emergency department; IM, intermediate metabolizer; NM, normal metabolizer; PACU, post-anesthesia care unit; PM, poor metabolizer; UM, ultrarapid metabolizer.

[a]May not add up to 100 as some individuals identified with multiple races.

[b]There were three unknown responses.

[c]There were six subjects with missing anesthesia duration.

[d]Individuals on strong inhibitors were reassigned PM status due to phenoconversion for sensitivity analysis only.

[e]There were four subjects with missing weight.

[f]Either i.v. opioids or p.o. hydrocodone.

surgery showed a significantly higher rate of postoperative vomiting but no significant change in nausea among UM patients when compared with all other metabolizer groups.[11] In the setting of CINV, Kaiser et al.[20] reported an increased number of vomiting episodes in adults who received moderately to highly emetogenic chemotherapy in UMs (n = 4) versus non-UMs (n = 266). However, Perwitasari et al.[22] did not find an association between CINV and CYP2D6 metabolizer status in a cohort of 202 individuals receiving chemotherapy with cisplatin; notably there were no UM or PM individuals in this cohort, and CNV was not assessed.

Based on these and other published findings, CPIC guidelines released in 2016 posed a recommendation, rated as "moderate," to consider alternate anti-emetic therapy to ondansetron in CYP2D6 UMs.[12] Since that time, multiple studies have been published with mixed results. Ninety-three women undergoing thyroid surgery demonstrated increased PONV among UMs/NMs (n = 1/n = 59) compared with IMs/PMs (n = 29/n = 4).[10] In a cohort of 128 children who underwent bone marrow transplantation, the CYP2D6 UMs (n = 3) experienced increased emesis after chemotherapy on days without opioid exposure.[13] Another study looking at children with a new diagnosis of cancer and receiving chemotherapy (n = 103) found no association between CINV and CYP2D6 metabolizer status when comparing UMs (n = 5) and PMs (n = 4).[14]

There are some limitations regarding the interpretation of prior study results. Some studies analyzed nausea and vomiting as separate outcomes, and others combined these into a single outcome. The dosing, timing of administration, and route of ondansetron administration was also not consistent across studies, nor within studies. There is also heterogeneity with respect to the study populations. Only two of the prior studies included ondansetron efficacy and CYP2D6 metabolizer status in children, neither of which assessed PONV; these studies have conflicting results.[13,14] *CYP2D6* expression rapidly rises within 24 h after birth, achieves about 50% of adult levels of enzyme activity by 1 month of age, and is close to 100% of adult levels by 1 year of age.[23,24] Given this ontogeny of *CYP2D6*, both child and adult UMs are expected to have the same diminished ondansetron efficacy. Indeed, the CPIC guidelines for ondansetron and CYP2D6 suggest "there is no reason to suspect that *CYP2D6* genetic variation will affect this drug's metabolism differently in children [>1 month] compared with adults."[12] However, there may be important differences in children that impact the effect of *CYP2D6* variation on ondansetron response. In addition to CYP2D6, ondansetron is metabolized by CYP3A and CYP1A enzymes,[25] which may more substantially contribute to ondansetron metabolism in children

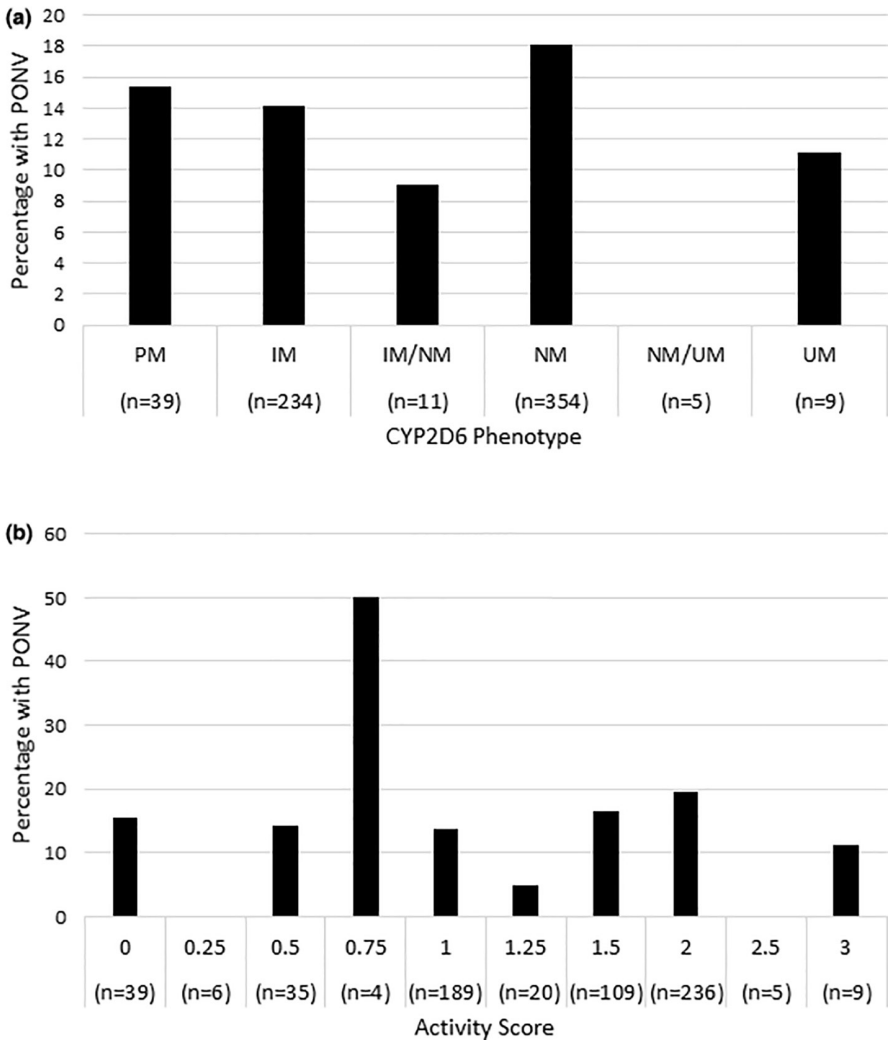

FIGURE 2 Percentage of patients with postoperative nausea/vomiting (PONV) by CYP2D6 metabolizer phenotype (a) and activity score (b). IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

than currently appreciated. Genetic variation in the 5-HT_3 transporter and receptor genes have also been described to affect the efficacy of ondansetron in preventing CINV in adults[22] and children.[14] Another important difference between children and adults is that pediatric dosing of medications, including ondansetron, is weight-based (e.g., 0.15 mg/kg), whereas for adults, fixed doses are used regardless of patient weight. Weight-based dosing may enable children who are CYP2D6 UMs to achieve a therapeutic level of ondansetron, despite their faster clearance of the drug. Reassuringly, in a prior study, there was no significant association demonstrated with CYP2D6 metabolizer status and QT prolongation, which is seen as a dose-dependent adverse event.[25,26]

Clinical risk factors for PONV in pediatrics include age, post-pubertal female sex, history/family history of PONV, and anesthetics.[8] Adenotonsillectomy is considered a unique risk factor for which ondansetron has been proven to be effective in preventing PONV.[27] These clinical risk factors for PONV may be of greater importance than CYP2D6 metabolizer status.

Pediatric pharmacogenomic studies are lacking in general, and specifically for the impact of CYP2D6 metabolizer status on ondansetron response.[12] As precision medicine approaches are implemented into clinical care, findings from adults must be validated for the pediatric population. A prior study investigating the impact of CYP2C19 metabolizer status on response to sertraline in children found results with an opposite direction of effect than what was anticipated based on data from adults and included in the CPIC guideline.[28,29] Our results present another instance of discordance of pediatric response from what is reported in adults. These findings highlight the need for pediatric validation as well as robust reporting of "negative results" to fully inform clinical practice.

Our study does have limitations. The retrospective nature of the study limited the data available and required PONV to be investigated as a binary outcome as emesis count was unavailable in our de-identified EHR data. We were unable to discern patients with nausea versus vomiting versus both. The defined follow-up time for the primary outcome ended at PACU discharge; however, later

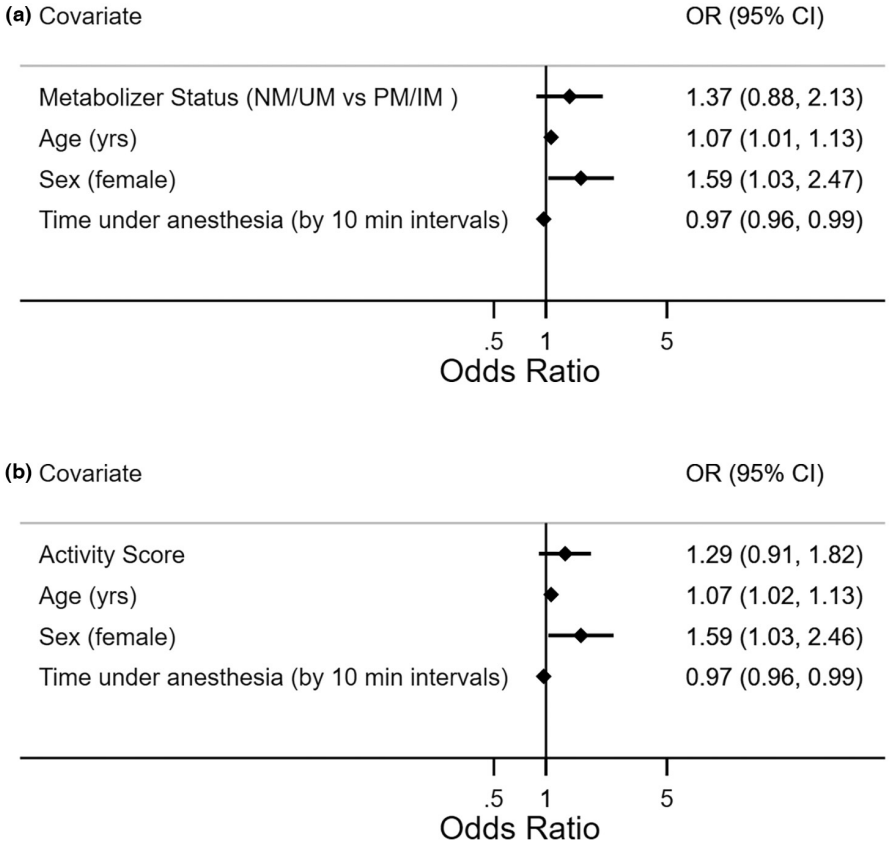

FIGURE 3 Forest plot depicting results of multivariate analysis risk for postoperative nausea/vomiting with metabolizer status (a) and activity score (b). CI, confidence interval; IM, intermediate metabolizer; NM, normal metabolizer; OR, odds ratio; PM, poor metabolizer; UM, ultrarapid metabolizer.

outcomes (at 24 h and 7 days) could be assessed as secondary outcomes. Another limitation is that only the most common *CYP2D6* allelic variants were tested for, and the nature of the duplicated allele could not be ascertained; in addition, some patients may carry hybrid alleles which could have contributed to ambiguous calls or were excluded due to inconsistent copy number calls between the two copy number assays. Furthermore, genetic variations in the 5-HT_3 receptor or transporter genes were not determined. Although our sample size is the largest reported, our UM frequency was only 1.4%, which may have limited our power to detect an association. There were some ambiguous phenotypes as well, although sensitivity analysis was done to account for these, as well as the small number of individuals exposed to CYP2D6 inhibitors. Due to uncertainty regarding veracity and timing of inhibitor exposure, phenoconversion was not incorporated into primary analyses. In prospective trials and clinical care, it is important to confirm CYP2D6 inhibitor exposures and combine this information with genetic test results to accurately predict metabolizer status.[30] More robust data are also needed to definitively classify inhibitors.[31]

In conclusion, in our cohort of post-tonsillectomy children, there was no association among CYP2D6 activity score, phenotype, and incidence of PONV after receiving ondansetron. These data do not support the clinical genotype testing of CYP2D6 to guide anti-emetic therapy after tonsillectomy in children. Larger studies with more UMs in the future may define a role for further *CYP2D6* and receptor gene testing in this population.

AUTHOR CONTRIBUTIONS

K.B., B.R.B., A.G., J.P.W., and S.L.V. wrote the manuscript. B.R.B., S.L.V, and K.B. designed the research. K.B., J.W., A.G., and S.L.V. performed the research. K.B. analyzed the data.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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