

ARTICLE

Influence of *CYP2D6* genetic variation on adverse events with propafenone in the pediatric and young adult population

Sudeep D. Sunthakar^{1,2}  | Prince J. Kannankeril^{1,2}  | Andrea Gaedigk³  |
Andrew E. Radbill¹ | Frank A. Fish¹ | Sara L. Van Driest^{2,4,5}

¹Thomas P. Graham Jr. Division of Pediatric Cardiology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

²Center for Pediatric Precision Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

³Division of Clinical Pharmacology, Toxicology, & Therapeutic Innovation, Children's Mercy Kansas City, Kansas City, Missouri, USA

⁴Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

⁵Division of General Pediatrics, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Correspondence

Sara L. Van Driest, Vanderbilt University Medical Center Department of Pediatrics, 8232 DOT, 2200 Children's Way, Nashville, TN 37232, USA.
Email: sara.van.driest@vumc.org

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Abstract

Propafenone is an antiarrhythmic drug metabolized primarily by cytochrome P450 2D6 (*CYP2D6*). In adults, propafenone adverse events (AEs) are associated with *CYP2D6* poor metabolizer status; however, pediatric data are lacking. Subjects were tested for 10 *CYP2D6* allelic variants and copy number status, and activity scores assigned to each genotype. Seventy-six individuals (median 0.3 [range 0–26] years old) were included. Propafenone AEs occurred in 29 (38%); 14 (18%) required drug discontinuation due to AE. The most common AEs were QRS ($n = 10$) and QTc ($n = 6$) prolongation. Those with AEs were older at the time of propafenone initiation (1.58 [0.13–9.92] vs. 0.20 [0.08–2.01] years old; $p = 0.042$). *CYP2D6* activity scores were not associated with presence of an AE (odds ratio [OR] 0.48 [0.22–1.03]; $p = 0.055$) but with the total number of AE ($\beta_1 = -0.31$ [-0.60, -0.03]; $p = 0.029$), systemic AEs (OR 0.33 [0.13–0.88]; $p = 0.022$), and drug discontinuation for systemic AEs (OR 0.28 [0.09–0.83]; $p = 0.017$). Awareness of *CYP2D6* activity score and patient age may aid in determining an individual's risk for an AE with propafenone administration.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Use of propafenone, an antiarrhythmic medication, may result in cardiac and/or systemic adverse events (AEs). Previous studies in adults demonstrated metabolizer status is associated with AEs; however, this has not been studied in the pediatric population.

WHAT QUESTION DID THIS STUDY ADDRESS?

The primary objective of this study was to assess the relationship between *CYP2D6* activity score and propafenone AEs in pediatric and young adult patients. The secondary objective was to test for associations of clinical characteristics to propafenone AEs.

for the analyses described were obtained from Vanderbilt University Medical Center's BioVU which is supported by numerous sources: institutional funding, private agencies, and federal grants. These include the NIH funded Shared Instrumentation Grant S10RR025141; and Clinical and Translational Science Award grants UL1TR002243, UL1TR000445, and UL1RR024975. Genomic data are also supported by investigator-led projects that include U01HG004798, R01NS032830, RC2GM092618, P50GM115305, U01HG006378, U19HL065962, R01HD074711; and additional funding sources listed at <https://vict.vumc.org/biovu-funding/>. This project utilized REDCap, funded by UL1 TR000445 from NCATS/NIH.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study demonstrates an association of CYP2D6 activity score with (1) systemic AEs, (2) drug discontinuation due to systemic AEs, and (3) total number of AEs. In addition, older patients were more likely to have an AE while on propafenone.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These data provide the first evidence of a relationship between CYP2D6 activity score and propafenone AEs in children and young adults. Thus, awareness of CYP2D6 activity score and patient age may aid in determining an individual's risk for an AE with propafenone administration.

INTRODUCTION

Supraventricular tachycardia occurs in up to 1 in 250 healthy children and 1 in 6 children with congenital heart disease.^{1,2} At our institution, propafenone is an option as a first-line enteral antiarrhythmic medication in pediatric patients with or without congenital heart disease diagnosed with supraventricular tachycardia. Propafenone is a Vaughn-Williams class 1C antiarrhythmic drug that primarily blocks the cardiac sodium channel, and has a weak beta blocking effect.³ The primary metabolism of propafenone is to 5-hydroxypropafenone and *N*-desalkyl-propafenone by the cytochrome P450 2D6 (CYP2D6) enzyme; CYP3A4 and CYP1A2 enzymes have also been reported to contribute to drug metabolism.^{3,4} 5-Hydroxypropafenone is an active metabolite with equipotent sodium channel blocking capabilities to propafenone.

The *CYP2D6* gene is highly polymorphic with common genetic variants including single nucleotide variants and copy number variants (including gene deletions and duplications, *CYP2D6-2D7* and *CYP2D7-2D6* hybrid genes, and complex combinations of the aforementioned) leading to a wide spectrum of enzyme activity.^{5,6} Based on genetic testing, predicted CYP2D6 activity scores can be calculated and individuals categorized as poor, intermediate, normal, or ultrarapid metabolizers.⁷ As expected, slower CYP2D6 metabolism leads to higher drug levels of propafenone in vitro and in vivo, but the clinical impact of these differences in drug concentration are not well established.⁸⁻¹⁰

Adverse events (AEs) commonly associated with propafenone are electrocardiogram (ECG) changes (atrioventricular nodal block, QRS or QTc prolongation,

and bradycardia) and systemic symptoms (dysgeusia, increased secretions, gagging, dizziness, hypotension, fatigue, and headache). Previous reports have described propafenone AE frequency to range between 4% and 27%.¹¹⁻¹⁵ CYP2D6 activity scores have been associated with propafenone pharmacokinetics, but there are limited data on the association between CYP2D6 activity scores and AEs, particularly in the pediatric population.^{4,9,10,16,17} The primary aim of our study was to test the hypothesis that CYP2D6 activity scores are associated with AEs in the pediatric and young adult population. Secondary aims included reporting the incidence and clinical risk factors of propafenone AEs for these patients.

METHODS

Study design

This was a single-center, retrospective, observational study using BioVU, an institutional biobank linking DNA to de-identified electronic health records (EHR) data at Vanderbilt University Medical Center (VUMC).¹⁸⁻²¹ The VUMC IRB determined that this study was non-human subjects research based on US Health & Human Services (HHS) regulation 45 CFR 46.102(f). Individuals for inclusion were initially identified through an automated search, followed by manual review of the record. Search criteria included those less than 30 years of age with propafenone mentioned in the EHR. Additional inclusion criteria confirmed through manual review were: (1) at least one documented administration of propafenone and (2) at least one clinical note from a VUMC provider managing propafenone. Exclusion criteria were: (1) no

evidence of propafenone administration; (2) propafenone used as pill-in-pocket as-needed abortive therapy; or (3) insufficient documentation of a patient's clinical course while on propafenone in order to determine presence or absence of AEs.

Clinical and outcome data

Demographic, clinical, and outcome data were collected manually for each patient by a single reviewer (S.D.S.). Demographic, clinical, and outcome data were stored in REDCap, an electronic data management tool housed by VUMC.^{22,23} Demographic data included age, race, and ethnicity as recorded in the EHR. Clinical data included presence of congenital heart disease, single ventricle anatomy, need for surgical intervention, arrhythmia diagnosis, and duration and dose of propafenone use including the starting and maximum dose indexed to body surface area. Use of concomitant antiarrhythmics, CYP2D6 inducers, and inhibitors were recorded.²⁴ Collection of outcome data was performed blinded to *CYP2D6* genotype and activity score. Reason for propafenone discontinuation was categorized as refractory arrhythmia, intolerance of propafenone AE, completion of therapy following ablation or spontaneous resolution of arrhythmia, and patient non-adherence.

The case status for AEs during propafenone use was determined by discussion of each potential case with electrophysiologists (P.J.K., A.E.R., F.A.F.) at our institution. Potential AEs were identified via chart review and included if they occurred within the first 3 years of drug therapy. ECG changes defined as AEs included atrioventricular nodal block, prolongation of QRS or QTc intervals, and bradycardia. Designation of prolonged QRS or QTc interval was determined by clinical documentation of the attending physician as there are no clear definitions in the literature for prolonged QRS or QTc while on propafenone. Baseline PR, QRS, and QTc intervals while on propafenone were recorded from the most recent ECG obtained prior to propafenone administration. Intervals while on propafenone were measured by recording the average interval from ECGs during therapy. In patients who underwent heart surgery and required propafenone in the postoperative period, ECG changes that occurred intraoperatively or within 24 h postoperatively were not attributed to propafenone AE.

Gastrointestinal (GI) AEs were defined as dysgeusia and GI intolerance, which encompassed increased secretions, gagging, decreased appetite, or poor feeding. In neonates and infants, it can be difficult to discern if increased secretions and gagging are due to drug AE or normal newborn behavior; therefore, these were included as AEs only

if it was a clear change from baseline, led to poor weight gain, or was documented as the reason for medication discontinuation, with resolution after drug discontinuation. Neurologic side effects were defined as dizziness, headaches, flushing, fatigue, and irritability. Systemic AEs encompassed hypotension, neurologic AEs, and GI AEs. If an AE was present, the number of days from propafenone initiation to first AE and dose at the time of AE were recorded, as well as the total number of different AEs observed.

Genetic data

CYP2D6 genotyping was performed for each individual if a DNA sample was available. Testing was carried out by Vanderbilt Technologies for Advanced Genomics (VANTAGE) laboratory using reagents and protocols as recommended by the manufacturer. Genotyping and copy number assays were performed using commercially available TaqMan assays (Thermo Fisher Scientific, Waltham, MA). Eleven *CYP2D6* single nucleotide variants (rs28371706, rs16947, rs59421388, rs1080985, rs35742686, rs3892097, rs1065852, rs28371725, rs5030655, rs5030867, and rs5030656) were tested which allowed assignment of 10 variant alleles: *CYP2D6**2, *3, *4, *6, *7, *9, *10, *17, *29, and *41. Copy number was detected by using assays targeting intron 6 and exon 9. A normal function allele (*CYP2D6**1) was assigned if no variants were identified. *CYP2D6* activity score and metabolizer status were assigned as recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and used in their guidelines (Tables S1 and S2).^{5,25,26} *CYP2D6* allele calls and activity score assignments were determined and agreed upon by two of the authors (A.G., S.L.V.).

Statistical analysis

Statistical analyses were performed using Stata version 16 (Stata Corp., College Station, TX). Univariate analysis using logistic regression was performed to test for an association between presence of an AE and *CYP2D6* activity score. An analysis was performed for those greater than and less than 1 year of age as this represented an age threshold at which therapy for supraventricular tachycardia can often be discontinued. With respect to demographic and clinical features, categorical variables were compared with Pearson's Chi square and continuous variables with Wilcoxon rank sum. Log rank statistical test was performed to assess difference in freedom from AE analysis. Logistic regression was performed to calculate odds ratio of activity score for AE analysis and AE subset

analyses. Linear regression was performed to test for association between activity score and total number of AEs observed. All statistical tests were two-sided and *p* values <0.05 were considered statistically significant.

RESULTS

Cohort demographics and clinical data

A total of 76 individuals met the criteria and were included in the analyses (Table 1). The median age at time of propafenone initiation was 0.3 (range 0–26) years. The median initial dose of propafenone was 235 (interquartile range [IQR] 230–350) mg/m²/day. Of the 76 subjects, 45 (59%) had congenital heart disease and 42 (55%) underwent surgery for congenital heart disease. Amongst those with congenital heart disease, 21 (47%) had single ventricle physiology. The most common arrhythmias were atrial tachycardia and atrioventricular reciprocating tachycardia. Beta blockers (33%) were the most common concomitant antiarrhythmic used (Table S3).

AE outcomes

AEs were seen in 29 (38%) individuals in this cohort. The most common AEs (Figure 1) were prolonged QRS (median increase of 18 [16–27] ms; *n* = 10) and QTc intervals (median increase 20 [17–40] ms; *n* = 6). Those without QRS prolongation had median increase in QRS of 10 (–1, 16) ms. Those without QTc prolongation had average increase in QTc of 5 (–8, 40) ms. Baseline median intervals for QRS and QTc amongst all patients were 78 (68–96) ms and 442 (417–466) ms, respectively. First degree (median increase 31 [20–42] ms; *n* = 4) and second-degree (*n* = 4) atrioventricular nodal block were also seen with propafenone use. Baseline median PR interval for the cohort was 114 (98–130) ms. No pro-arrhythmic events were observed. The most common systemic AEs included dizziness (*n* = 3), dysgeusia (*n* = 3), fatigue (*n* = 3), and GI intolerance (*n* = 3). Side effect profile was the reason for drug discontinuation in 14 patients. Of these, common AEs leading to drug discontinuation included prolonged QRS (*n* = 4), dysgeusia (*n* = 3), and fatigue (*n* = 3). Propafenone was discontinued in 11 patients due to inefficacy (refractory arrhythmia).

Characteristic	No adverse event (<i>n</i> = 47)	Adverse event (<i>n</i> = 29)	Total (<i>n</i> = 76)
Age (years) [†]	0.2 (0.1–2.0)	1.6 (0.1–9.9)	0.3 (0.1–5.9)
Female	19 (40%)	14 (48%)	33 (43%)
EHR-recorded race			
Caucasian	36 (77%)	21 (72%)	57 (75%)
African American	6 (13%)	4 (14%)	10 (13%)
Hispanic	5 (11%)	2 (7%)	7 (9%)
Asian	0 (0%)	1 (3%)	1 (1%)
Other	0 (0%)	1 (3%)	1 (1%)
Deceased	6 (13%)	1 (3%)	7 (9%)
Propafenone duration (days)	191 (49–492)	144 (54–659)	186 (51–603)
Initial dose of propafenone (mg/m ² /day)	240 (200–300)	228 (200–250)	235 (230–350)
Maximum dose of propafenone (mg/m ² /day)	283 (240–354)	250 (225–300)	250 (230–350)
Congenital heart disease	27 (57%)	18 (62%)	45 (59%)
Congenital heart surgery [‡]	26 (96%)	16 (89%)	42 (93%)
Single ventricle anatomy [‡]	11 (41%)	10 (56%)	21 (47%)
Concomitant use of CYP2D6 inhibitor	16 (34%)	7 (24%)	23 (30%)
Concomitant use of CYP2D6 inducer	1 (2%)	1 (3%)	2 (3%)

TABLE 1 Demographic and clinical characteristics

Note: Data are presented as median (IQR) for continuous measures and *n* (%) for categorical measures. Categorical variables were compared with Pearson's Chi square and continuous variables with Wilcoxon rank sum. EHR, electronic health record.

[†]Statistically significant between adverse event and non-adverse event groups (*p* < 0.05).

[‡]Percentages based on those with congenital heart disease.

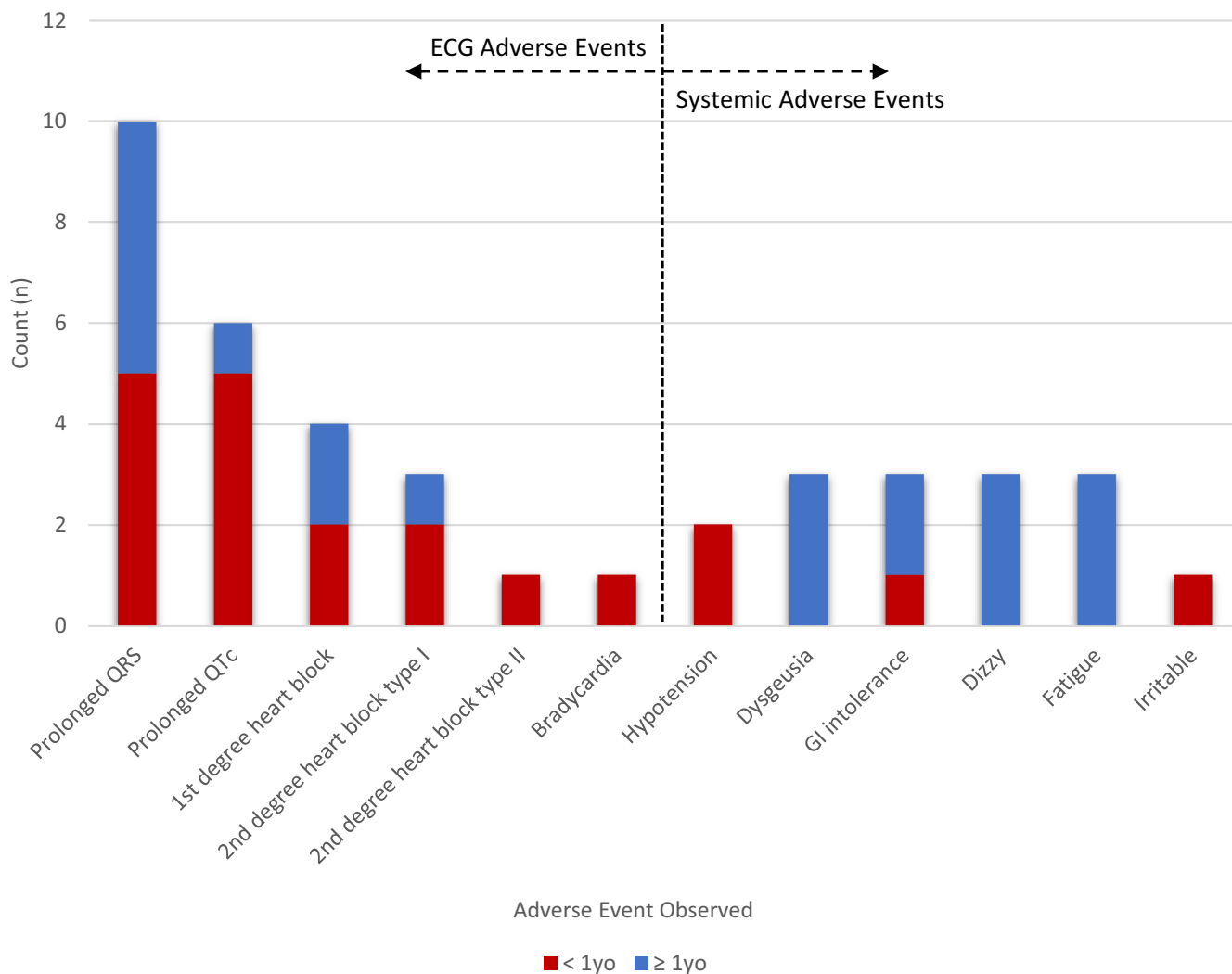


FIGURE 1 Propafenone adverse events. Histogram displaying adverse events (AEs) in those above (blue) and below (red) 1 year of age. AEs listed to the left of the dashed line represent electrocardiogram-associated AEs, while systemic AEs are shown to the right of the dashed line. ECG, electrocardiogram; GI, gastrointestinal.

Those with AEs were older at the time of propafenone initiation (1.58 [0.13–9.92] vs. 0.20 [0.08–2.01] years; $p = 0.042$). There was no difference in age between those with and without ECG-related AEs; however, those with a systemic AE (9.08 [2.54–18.25] years) were older than those without a systemic AE (0.21 [0.08–2.19] years). When dichotomized by age, those above 1 year of age were more likely to have AEs (17/29, 59% vs. 12/47, 25%; $p = 0.004$) and require propafenone discontinuation due to AE profile (10/29, 35% vs. 4/47, 9%; $p = 0.005$). Time to event analysis (Figure 2) demonstrated a difference in freedom from AE between those above and below 1 year of age ($p = 0.004$). Of the 29 patients with an AE, 69% (20/29) had an AE within 90 days of propafenone initiation. Excluding age, there were no differences for any other demographic or clinical variables between the AE and non-AE groups (Tables 1, S3).

Associations of AEs with CYP2D6 activity score or phenotype

DNA samples were available for 69 of the 76 individuals (Table 2). The most common metabolizer status in this cohort was normal metabolizer ($n = 43$) followed by intermediate metabolizer ($n = 20$); the distribution of genotype data and activity scores is shown in Table S2 and Figure S1. Univariate analysis demonstrated no association between activity score and presence of any AE (odds ratio [OR] 0.48, 95% confidence interval [0.22–1.03]; $p = 0.055$). Results were not significantly different in multivariable analysis correcting for age, maximum propafenone dose indexed for body surface area, and use of CYP2D6 inhibitors or inducers. There was no use of strong CYP3A4 or CYP1A2 inhibitors in this cohort.²⁴ When analyzing total number of AEs (Figure 3), linear regression demonstrated an inverse

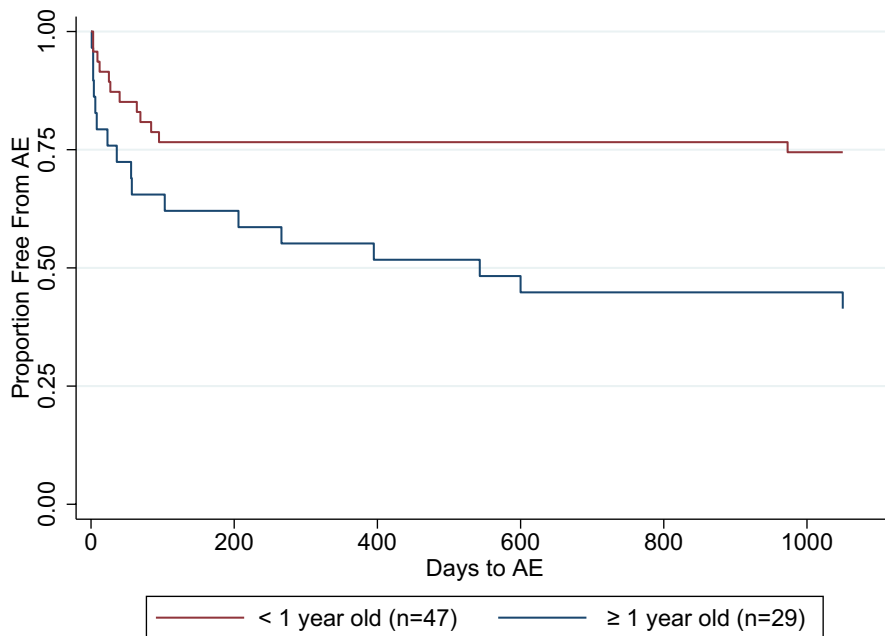


FIGURE 2 Effect of age on freedom from adverse event (AE). Kaplan–Meier curve demonstrating time to AE in those above (blue) and below (red) 1 year of age at time of propafenone initiation. Log-rank statistical test was performed to assess for difference (p value = 0.004). Of the 29 patients with an AE, 69% (20/29) had an AE within 90 days of propafenone initiation.

TABLE 2 Metabolizer status compared to clinical outcomes

Clinical outcome	Poor ($n = 4$)	Intermediate ($n = 20$)	Normal ($n = 43$)	Ultrarapid ($n = 2$)	Unknown ($n = 7$)
Any adverse event (%)	2 (50%)	10 (50%)	14 (33%)	0 (0%)	3 (43%)
ECG adverse event (%)	1 (25%)	6 (30%)	11 (26%)	0 (0%)	2 (29%)
Systemic adverse event (%)	1 (25%)	6 (30%)	5 (12%)	0 (0%)	1 (14%)
Discontinuation due to adverse event (%)	1 (25%)	5 (25%)	8 (19%)	0 (0%)	0 (0%)

Note: Outcome data relative to metabolizer classification. Genetic data were unavailable for seven patients. Additional supporting information may be found in the online version of the article on the publisher's website.

Abbreviation: ECG, electrocardiogram.

relationship between activity score and total number of AEs ($\beta_1 = -0.31 [-0.60, -0.03]$; $p = 0.029$).

Activity score had an OR of 0.47 [0.20–1.14] ($p = 0.094$) for propafenone discontinuation due to an AE ($n = 14$). Subset AE analysis was performed classifying AEs into ECG and systemic AEs. Higher CYP2D6 activity score was not associated with ECG AEs (OR 0.91 [0.41–2.06]) but was associated with fewer systemic AEs (OR 0.33 [0.13–0.88]; $p = 0.022$) and less drug discontinuation due to systemic AE ($n = 9$, OR 0.28 [0.09–0.83]; $p = 0.017$). Activity score was not associated with discontinuation due to drug inefficacy ($n = 11$, OR 0.71 [0.27–1.85]). Linear regression revealed CYP2D6 activity score was not associated with average PR, QRS, or QTc intervals.

DISCUSSION

To the best of our knowledge, this is the first study assessing the association between CYP2D6 genetic variability (i.e., activity scores) and propafenone AEs in the pediatric

population. In this single-center, retrospective pediatric study, we found that lower CYP2D6 activity scores trended towards increased risk of AEs and drug discontinuation due to AE; this was, however, only statistically significant for systemic AEs. We also found that individuals ≥ 1 year of age were more likely to have AEs. These data suggest that CYP2D6 activity score and age may be important considerations when prescribing propafenone and monitoring for AEs.

Studies focused on specific CYP2D6 alleles and propafenone drug concentrations have demonstrated that CYP2D6 poor metabolizers had higher drug concentrations.^{9,27–30} An adult study utilizing debrisoquine as phenotype probe and urinary metabolic ratios, which serves as a surrogate measure of CYP2D6 activity, reported an increased risk of neurologic AEs with propafenone in poor metabolizers compared to ultrarapid metabolizers.¹⁶ Similarly, in our study a significant association between activity score and systemic AEs was observed. Furthermore, we detected an association between activity score and drug discontinuation due to

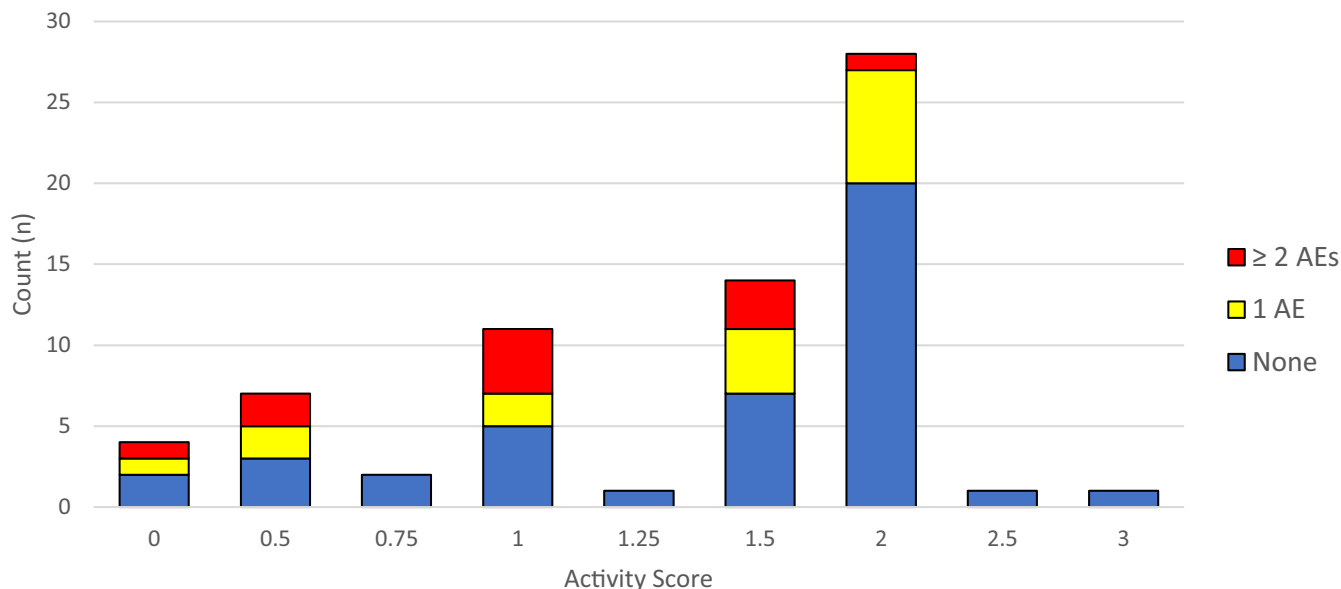


FIGURE 3 Total adverse events (AEs) by activity score. Stacked histogram demonstrating the frequency of total AEs for each activity score. Legend corresponds to the total number of AEs for a given patient. Amongst those with a *CYP2D6* genotype and activity score, 42/69 had no AE (blue), 16/69 had one AE (yellow), 10/69 had two AEs (red), and one had three AEs (red). Linear regression demonstrated an inverse relationship between activity score and total number of AEs ($\beta_1 = -0.31 [-0.60, -0.03]$; $p = 0.029$).

systemic AEs. For those with multiple AEs, lower activity scores were associated with an increasing number of AEs as demonstrated by linear regression analysis. These data provide the first insights and evidence supporting such relationships.

Our study comports with previous adult studies that demonstrated no significant difference in QRS or QTc prolongation based on metabolizer status.^{16,28} It is challenging to understand why activity score is associated with systemic AEs, but not ECG-associated AEs. One possible explanation is the presence of propafenone metabolites. 5-Hydroxypropafenone is known to have electrophysiologic properties; however, its effect on systemic AEs is not well understood. Future studies quantifying metabolite concentrations in subjects with known metabolizer status and presence of cardiac and systemic AEs could test these theories. Differential beta blocker effect has been observed in poor versus normal metabolizers with low dose, but not high dose propafenone,³¹ raising the possibility that at therapeutic doses of propafenone, *CYP2D6* metabolizer status may not be associated with ECG outcomes. In addition, propafenone is often titrated for its cardiac effects, which are monitored via ECG. It is plausible that early and significant changes in QRS or QTc duration may prompt dose adjustment prior to the detection and recording of an AE in the EHR.

An association between age and propafenone AEs has not been previously described in the literature. At our institution, newborns and infants with supraventricular tachycardia are maintained on antiarrhythmic therapy until 1 year, at which time a transesophageal electrophysiology

study is performed. If no arrhythmia is inducible, medication is discontinued; therefore, we had a special interest in this population, prompting the dichotomization time point of 1 year of age for our analysis. The increased incidence of AEs in those ≥ 1 year of age could be secondary to systemic AEs being subjective complaints, which cannot be elicited in those < 1 year of age. Alternatively, there may be differences in the pharmacokinetics or pharmacodynamics of the drug in infants. Metabolic pathways may vary in younger and older infants, predisposing older children to systemic AEs. Previous studies have shown an increase in *CYP2D6* activity in adults compared to neonates that are postulated to occur rapidly after birth; therefore, it is unclear if there are significant differences in *CYP2D6* activity amongst children of different ages.^{32,33} There also appears to be a decline in *CYP2D6* activity beyond the second decade of life.³⁴ This association between age and incidence of AEs is likely multifactorial in etiology. While our study demonstrated a statistically significant result, this should not preclude those ≥ 1 year of age from receiving propafenone when clinically indicated.

Guidelines from the Dutch Pharmacogenetics Working Group recommend an empiric decrease by 70% of standard starting propafenone dose for poor metabolizers.^{4,35} In our cohort, two of four poor metabolizers had an AE. Additionally, individuals classified as intermediate metabolizers had identical frequencies for AEs and discontinuation due to AE compared to those classified as poor metabolizers. Lower rates of AE and drug discontinuation due to AE were detected in normal metabolizers. However,

adverse events did occur in this subgroup, indicating these individuals are not invulnerable to AE or requiring drug discontinuation due to AE. Lower activity scores were associated with increasing number of AEs and presence of systemic AEs. This relationship should be further investigated and validated in a larger and more heterogeneous cohort with increased sample size of poor metabolizers and ultrarapid metabolizers. In the clinical setting, we propose providers utilize drug efficacy and presence of AEs to drive dosing changes, while being aware of patient age and activity score as these may predispose to development of an AE. Also, the presence of an AE did not always translate to immediate drug discontinuation as many of the AEs were not life threatening. Awareness of patient age and activity score can be beneficial to recognize those who may be at risk for an AE, but do not necessarily require a preemptive change to starting dose. Larger cohort studies are warranted to provide further insights into the predictive ability of *CYP2D6* genetic variation on AEs.

Limitations

The findings of this single-center, retrospective study may not be generalizable to other sites or patient populations. We also acknowledge that *CYP2D6* genotype analysis only included the more commonly observed variants and thus rare alleles and some gene copy number variants may have eluded detection. There was limited heterogeneity in metabolizer status, with few individuals categorized as poor or ultrarapid metabolizers; therefore, it is difficult to draw definitive conclusions for these individuals from these data. The use of *CYP2D6* inducers and inhibitors was not associated with propafenone AE; however, propafenone has several metabolic pathways. It is possible that other drug–drug interactions, through these alternative pathways, could play a role in propafenone adverse events.

Cardiac AEs are predominantly captured via electrocardiogram or ambulatory heart rate monitor. There is subjectivity in classifying QRS or QTc prolongation as an AE as, to some degree, this is an expected effect of propafenone. There is no universally accepted threshold for classification of interval prolongation on propafenone. We attempted to mitigate the subjectivity of this classification by attributing the designation of an AE based on the documentation by the attending electrophysiologist rather than by personnel involved in data collection.

Our study demonstrates that age at propafenone initiation and *CYP2D6* genetic variation or activity score affect the frequency of propafenone AEs. Future directions should include larger cohorts in order to capture a more heterogeneous population with respect to *CYP2D6* activity score, age, and ethnic diversity. Increased sample size of

poor and ultrarapid metabolizers is warranted to further our understanding of the association between *CYP2D6* genetic variation and metabolic capacity and drug discontinuation due to AE and inefficacy, respectively.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

S.D.S., P.J.K., A.G., A.E.R., F.A.F., and S.L.V. wrote the manuscript. S.D.S., P.J.K., A.E.R., F.A.F., and S.L.V. designed the research. S.D.S., P.J.K., and S.L.V. performed the research. S.D.S., P.J.K., A.G., A.E.R., and S.L.V. analyzed the data. A.G. and S.L.V. contributed new analytical tools.

ORCID

Sudeep D. Sunthakar  <https://orcid.org/0000-0002-2687-8204>

Prince J. Kannankeril  <https://orcid.org/0000-0002-1529-9872>

Andrea Gaedigk  <https://orcid.org/0000-0001-6968-1893>

<https://orcid.org/0000-0001-6968-1893>

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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