Cardiology in the Young

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Electrophysiological effects and clinical utility of propafenone in children

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Abstract

Aim: This retrospective case series study sought to describe the safety and clinical effectiveness of propafenone for the control of arrhythmias in children with and without CHD or cardiomyopathy. *Methods:* We reviewed baseline characteristics and subsequent outcomes in a group of 63 children treated with propafenone at 2 sites over a 15-year period Therapy was considered effective if no clinically apparent breakthrough episodes of arrhythmias were noted on the medication. *Results:* Sixty-three patients (29 males) were initiated on propafenone at a median age of 2.3 years. CHD or cardiomyopathy was noted in 21/63 (33%). There were no significant differences between demographics, clinical backgrounds, antiarrhythmic details, side effect profiles, and outcomes between children with normal hearts and children with CHD or cardiomyopathy. Cardiac depression at the initiation of propafenone was more common amongst children with CHD or cardiomyopathy compared to children with normal hearts. Systemic ventricular function was diminished in 15/63 patients (24%) prior to starting propafenone and improved in 8/15 (53%) of patients once better rhythm control was achieved. Other than one child in whom medication was stopped due to gastroesophageal reflux, no other child experienced significant systemic or cardiac side effects during treatment with propafenone. Propafenone achieved nearly equal success in controlling arrhythmias in both children with normal hearts and children with congenital heart disease or cardiomyopathy (90% versus 86%, $p = 0.88$). *Conclusion:* Propafenone is a safe and effective antiarrhythmic medication in children.

Propafenone, a class Ic antiarrhythmic drug, has been used to treat cardiac arrhythmias for nearly four decades.[1] Although propafenone was once the most commonly used antiarrhythmic agent in children in Europe in the 1990s, its use has since decreased due to concerns about new arrhythmias and sudden death raised by isolated reports.[2–4]

Unlike other class Ic agents, propafenone combines sodium channel blocking effects with beta- blocking capacity and weak Ca channel antagonism.[5,6] Its use in adults is limited to the treatment of arrhythmias in patients with structurally normal hearts[7,8] due to the results of the Cardiac Arrhythmia Suppression Trial that showed an increased rate of death in patients with a prior myocardial infarction treated with other Ic agents such as encainide or flecainide.[9] Though the applicability of the Cardiac Arrhythmia Suppression Trial results to other populations or other Ic agents is unstudied, the prevailing practice in adult patients is to avoid any Ic agents (including propafenone) in patients with structural heart disease or cardiac dysfunction. There appears to be sporadic but wider acceptance of the use of propafenone in children with structural heart disease.[10] The difference in use compared to adult patients may be attributable to the absence of life-threatening effects reported in this population either due to the inability of the small number of children reported in paediatric studies to identify side effects or the true absence of side effects possibly as a result of the drug's mild beta-blocking properties. The present study is the only recent study to review the efficacy and side effects of oral propafenone in children with tachyarrhythmias.

Method

We conducted a retrospective case series study after obtaining Institutional Review Board approval. We included all children 21 years and under with supraventricular or ventricular arrhythmias who received treatment with propafenone over a 15-year period at the University of North Carolina at Chapel Hill and the University of Florida at Jacksonville. We collected baseline data at the time of propafenone initiation and outcome data at regular

follow-up intervals. We abstracted demographic characteristics, clinical data including cardiac anatomy, type(s) of arrhythmia, doses, and duration of antiarrhythmic treatment, electrocardiograms, echocardiograms, liver and renal function tests, side effect profiles, and patient outcomes. The mechanism of arrhythmia was determined predominantly by surface electrocardiogram and telemetry recordings. Electrogram tracing was used if a patient had temporary pacing wires in place post-operatively or a permanent pacemaker. Atrioventricular node-dependent tachycardias like atrioventricular nodal re-entry tachycardia and atrioventricular re-entry tachycardia were grouped together because surface ECG often does not unambiguously differentiate these two mechanisms. Electrophysiology studies were typically not performed to establish an initial diagnosis, but later EP studies better elucidated the mechanism of arrhythmia for some patients.

Patients were classified into those with normal cardiac anatomy, those with structural CHD, and those with cardiomyopathy. Systemic ventricular ejection fraction was used to quantitate cardiac function at baseline and at follow-up evaluations.

Cardiac status was categorised as normal function (EF > 60%), mild depression (EF 50–59%), moderate depression (EF 30–49%), or severe depression (EF < 29%) or subjectively as mild, moderate, or severe depression if the LVEF was not determined. A greater than 25% change in PR, QRS, or QTc intervals, or an absolute QTc interval exceeding 470 ms, was considered significant. The QTc interval was calculated according to Bazett's formula. Severe bradycardia was defined as an average resting heart rate of <40 bpm or pauses >3 seconds while awake. Therapy was considered effective if no clinically apparent breakthrough episodes of SVT/VT were noted on the medication. Reasons for discontinuation were noted and grouped as (a) treatment not effective; (b) side effects due to medications; and (c) arrhythmia control achieved by alternative methods such as ablation therapy. Follow-up data was collected at scheduled clinic visits after discharge and these included ECGs, Holters, event recorder tracings, echocardiograms, and laboratory data when available.

Descriptive statistics are reported as median and range through the study. For comparisons of continuous variables, Student's t-test was used for normally distributed data while the Mann–Whitney U-test was used for non-normally distributed data. The Fisher's exact test and the Kruskal–Wallis test were used to assess between-group differences for categorical data. Statistical analyses were performed using SPSS (Version 24.0. Armonk, NY: IBM Corp.) A p-value of <0.05 was considered significant.

Results

During the 15-year study interval, we identified 63 patients (29 males) who were initiated on propafenone at a median age of 2.3 years (23 infants, 12 neonates) for the treatment of atrial and ventricular arrhythmias (Table 1). Study variables (demographics, clinical backgrounds, antiarrhythmic details, side effect profiles, and follow-up outcomes) of patients with and without CHD or CMP are detailed in Table 2. The type of arrhythmia diagnosis and CHD are outlined in Table 1 and Figure 1, respectively. Four children had CMP patients due to idiopathic dilated cardiomyopathy (2), restrictive cardiomyopathy (1), and dilated cardiomyopathy secondary to myocarditis (1). Tachycardia was noted in nine patients with CHD in the immediate post-operative setting. Severe cardiac dysfunction was present in one patient. Cardiac depression was more prevalent in the CHD patients at baseline compared to patients with normal hearts; however, this difference did not achieve statistical significance (38% versus 16%, p = 0.1).

Table 1. Indications for propafenone therapy

Arrhythmia	Total n = 63
AV nodal-dependent SVT	22 (35%)
Focal atrial tachycardia	11 (17%)
Macro re-entrant atrial flutter	6 (9.5%)
PJRT	5 (8%)
Junctional ectopic tachycardia	6 (9.5%)
Premature ventricular contractions	8 (13%)
Ventricular tachycardia	5 (8%)

Data are n (%).
PJRT = persistent junctional reciprocating tachycardia; SVT = supraventricular tachycardia.

Ventricular function was diminished in 15/63 patients (22.2%) prior to starting propafenone. Thirty patients were not adequately controlled on propranolol, metoprolol, digoxin, and/or sotalol prior to initiation of propafenone. Four patients transitioned from amiodarone to propafenone due to concerns about toxicity associated with long-term use of amiodarone. Propafenone was the only medication used in 38/63 (60%) of patients; in the other 25/63 (40%) patients, propafenone was used in combinations with other antiarrhythmic medications (Fig 2).

Subjective side effects included gastrointestinal disturbances (2), headache (1), and irritability (1). Reflux symptoms worsened in one infant with CHD necessitated cessation of propafenone and prescription of an alternate antiarrhythmic choice. No significant renal or liver function test abnormalities were found in any patient on propafenone.

Cardiac function could not be verified in one patient after the initiation of propafenone. This patient had a structurally normal heart and normal function prior to propafenone initiation. Two of the 62 remaining patients demonstrated a decline in function that was judged unrelated to propafenone. One patient was listed for a heart transplant due to a failing single ventricle despite good arrhythmia control. The cardiac function of the second patient declined due to poor arrhythmia control and improved with the addition of a third antiarrhythmic.

Initiation of propafenone did not result in any significant proarrhythmias. Follow-up ECG data showed a prolongation of PR interval by 40% in one patient. Significant QTc widening (>25% from baseline) was noted more in patients with CHD than in those with normal hearts (3 versus 1); QRS widening was noted in one patient in the CHD group which was attributed to the development of a bundle branch block. None of these changes prompted the discontinuation of propafenone. No patient developed significant hemodynamic instability or suffered cardiac arrest after initiation of propafenone. One patient with CHD died in the post-operative period due to fulminant sepsis despite good arrhythmia control. Twelve patients later had a therapeutic ablation. The duration of therapy was incomplete in seven patients that were lost to follow-up.

Propafenone achieved equal success in controlling arrhythmias in children with normal hearts and in children with CHD or CMP (90% versus 86%, p = 0.88). Treatment was discontinued in eight patients within 4 weeks due to failure of the drug to achieve adequate arrhythmia control in seven and due to side effects in one patient. Patients in whom propafenone was discontinued during this period were not included in the follow-up duration.

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Table 2. Comparison between study characteristics in patients with a normal heart versus CHD/CMP

Variable	Normal heart patients n = 42 (67%)	CHD/CMP patients n = 21 (33%)	p-value
Age at treatment (years)	2.3 (0–19.6)	2.5 (0–20.8)	0.67
Male	19 (45%)	10 (48%)	0.81
Type of arrhythmia			
Supraventricular	34 (81%)	16 (76%)	0.9
Ventricular	8 (19%)	5 (24%)	
Cardiac dysfunction			
None	35 (83%)	13 (62%)	0.1
Mild	5 (12%)	6 (28%)	
Moderate	1 (2%)	1 (5%)	
Severe	1 (2%)	1 (5%)	
Prior antiarrhythmic use	16 (38%)	14 (67%)	0.06
Hospital length of stay (days)	9 (4–21)	18 (7–141)	0.04
Initiation dose of medication (mg/m^2/day)	180 (167–205)	165 (150–220)	0.71
Average dose of medication (mg/m^2/day)	220 (180–340)	206 (176–350)	0.63
Adequate arrhythmia control	38 (90.4%)	18 (85.7%)	0.88
Medication stopped in <4 weeks	4 (9.5%)	4 (19%)	0.39
Treatment duration (weeks)	63 (32–165)	60 (29–112)	0.61
Side effects			
Non-cardiac	2 (5%)	2 (9%)	0.39
Lab abnormalities	0	0	
Cardiac	3 (7%)	3 (14%)	
Prolongation of intervals (PR, QRS, QTc)	0	0	
Proarrhythmia	0	0	
Myocardial depression	0	0	
Cardiac arrest	0	0	
Death	0	0	

Data are median (range) or n (%).
CHD = Congenital heart disease; CMP = Cardiomyopathy.

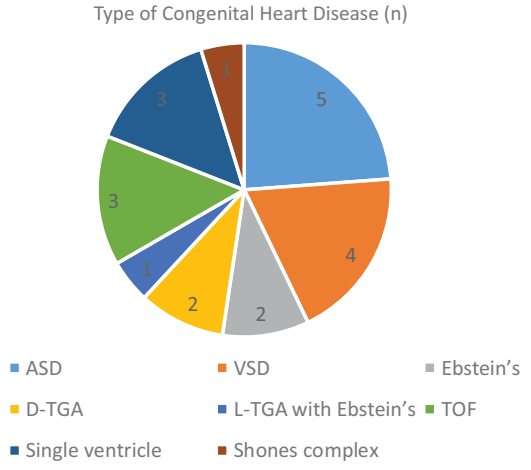

Figure 1. Distribution of types of CHD in the study cohort. ASD = atrial septal defect; TGA = transposition of great arteries; TOF = tetralogy of fallot; VSD = ventricular septal defect; n = number of patients.

Discussion

Propafenone is a Class Ic antiarrhythmic with weak beta-blocker and calcium antagonism effects that have been employed for the treatment of paediatric arrhythmias since the 1980s.[1,5,6] It previously was the most frequently used antiarrhythmic medication in children.[10] Despite its extensive use worldwide, there is a relative paucity of recent literature on its use in the last two decades.

After the findings of the 1991 Cardiac Arrhythmia Suppression Trial study demonstrated an increased mortality attributed to class I antiarrhythmics in adults with a prior myocardial infarction, clinicians generally avoided using any Ic agent in adult and children with underlying heart disease.[4,9,11] The largest study on propafenone in paediatrics is a questionnaire-based multicentre report from Europe conducted in the early 1990s that described a safety profile equivalent to other Ic agents in children with and without structural heart disease.[10] The rate of proarrhythmic events with propafenone compared to other Ic agents was significantly lower in this study.[10] In the mid-1990s, Fish et al. documented the efficacy of propafenone in seven children most of whom were infants

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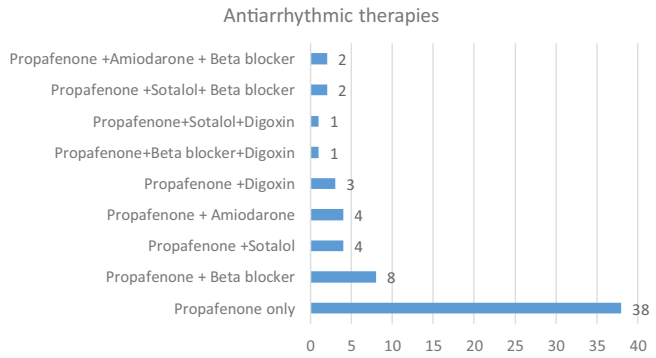

Figure 2. Antiarrhythmic therapy combinations in the study cohort.

and some of whom had congestive cardiac failure.[12] This information contrasted to a prior study that described a negative inotropic effect of propafenone and cautioned against its use in patients with structural heart disease or ventricular dysfunction.[13,14] Reimer et al. described sudden cardiac death in a patient with Tetralogy of Fallot and proarrhythmic effects in other patients with structural heart disease and Guccioni et al. described a lower efficacy in patients with structural heart disease.[4,11]

This cohort included 21/63 (33%) patients with CHD or CMP, similar to the 22–32% proportion reported in two other studies.[4,10] We found no difference in the antiarrhythmic efficacy in patients with structurally normal hearts versus patients with CHD or CMP (90 versus. 86%). Although no studies have compared efficacy in children with and without structural heart disease, studies on other Ic agents such as flecainide report a similar efficacy profile in patients with and without CHD (90% versus 77%).[15]

The authors noted side effects of propafenone in only 1 in 63 patients that required drug discontinuation and identified no significant electrophysiological side effects or associated cardiac morbidity/mortality. A prior questionnaire-based study on 772 patients did report that propafenone was associated with a 1.2% incidence of proarrhythmias and a 0.6% incidence of sudden death, but the authors could not conclude whether the deaths were a natural consequence of disease or drug-related.[10] These authors reported m electrophysiological effects including widening of the QRS and QTc interval in six patients, but no significant prolongation of other cardiac intervals or abnormalities in hepatic or renal function tests. Hence, these findings in contrast with the results of other studies report a 0.8% incidence of significant electrophysiological side effects and abnormal hepatic function tests. However, the highest dose of propafenone in our population cohort (350 mg/m^2) was at the low end of the maximum dose used in other reports (300–600 mg/m^2 BSA).[4,10] During the study period, we did not measure blood levels of propafenone because levels are not considered useful in guiding clinical therapy. Eto et al. have noted a poor correlation between serum concentrations of propafenone and therapeutic effects in children receiving the drug orally.[16]

AV nodal-dependent SVTs were the most common SVT treated with propafenone in this study. This is similar to reports of other Ic agents in which patients with AV nodal-dependent SVTs accounted for 83% of the patients receiving therapy.[15] As reported in other studies, a small proportion (5/63) of our study population received prior antiarrhythmic medications that included digoxin, metoprolol, propranolol, and/or sotalol yet failed to achieve adequate antiarrhythmic control.[10,12,17] Although 24% of patients had diminished ventricular function at the time of initiation of propafenone, we observed no subsequent progression of cardiac dysfunction. On the contrary, ventricular function improved in 8/15 (53%) of patients once propafenone had achieved better rhythm control.

The current study is limited by its retrospective design and its inability to capture complete outcome data on some patients. Importantly, in this population, patients with CHD and CMP had adequate longer term electrophysiological and echocardiographic data.

In summary, our longitudinal experience with propafenone in children with normal hearts or with CHD or CMP, at doses of 176–350 mg/m^2, provides additional information that supports efficacy and safety. Future studies or a registry that can evaluate the clinical utility and safety of propafenone in a broader population of children would be warranted.

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Conflicts of interest. None.

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