Ivabradine for treatment of tachyarrhythmias in children and young adults

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Introduction
Ivabradine, a novel heart rate–reducing agent, acts via selective inhibition of the funny current responsible for spontaneous depolarization of cardiac pacemaker cells. Ivabradine is currently FDA approved to reduce hospitalizations in adults with stable heart failure, and is also commonly used for the treatment of inappropriate sinus tachycardia.1 Isolated case reports and a few case series suggest a promising role for ivabradine in the treatment of pediatric tachyarrhythmias.2–5 Increased automaticity is the underlying mechanism of several pediatric tachyarrhythmias, including junctional ectopic tachycardia (JET) and ectopic atrial tachycardia (EAT). By inhibition of the funny current and reduction of automaticity, ivabradine represents a plausible potential therapy for these conditions. Ivabradine’s relatively hemodynamically neutral profile makes it an attractive antiarrhythmic agent.

In this case series, we report on the use of ivabradine in the treatment of automatic tachyarrhythmias in 4 children and young adults with diverse arrhythmia substrates, but with a common mechanism of increased automaticity. We have found ivabradine to be safe in all patients, with efficacy in 3 out of 4 patients treated.

Case report
Case 1
An 11-year-old female patient presented with palpitations and dizziness, and electrocardiogram (ECG) demonstrated EAT with variable atrioventricular (AV) conduction (Figure 1A). Surface P-wave morphology was suggestive of a left lower pulmonary vein origin. P-P interval was as short as 220 ms, though

ventricular rate was only 120 beats/min on average. Echocardiogram demonstrated normal anatomy and function. A trial of intravenous (IV) esmolol (as high as 150 mcg/kg/min) had no effect on the atrial tachycardia. Esmolol was discontinued, and ivabradine was started at a dose of 1.25 mg orally (PO) twice daily (BID) (0.05 mg/kg/day). Approximately 90 minutes after the first dose, the tachycardia terminated to sinus rhythm (Figure 1B and C). The patient remains symptom-free on this dose at 6 months of follow-up, with no medication adverse effects and with negative Holters.

Case 2
A 26-year-old male patient presented with episodic palpitations. A Holter monitor captured episodes of paroxysmal narrow QRS tachycardia at a rate of 160 beats/min, with preceding P waves, suspicious for EAT. He subsequently underwent electrophysiology study under conscious sedation at a nearby center. At electrophysiology study, there was no evidence for dual AV nodal physiology, and ventriculoatrial conduction was midline and decremental. No EAT was induced. A narrow QRS “V on A” tachycardia with cycle length 540 ms was induced with atrial pacing on isoproterenol. PACs introduced during tachycardia advanced the

KEY TEACHING POINTS

• Ivabradine is a novel heart rate–reducing agent that acts via selective inhibition of the pacemaker current.

• Ivabradine demonstrates use dependence, resulting in a greater effect at higher heart rates.

• Ivabradine has a hemodynamically neutral profile, in contrast to many alternative antiarrhythmic agents.

• Ivabradine shows promise as an effective treatment for automatic tachyarrhythmias in pediatric and congenital heart disease patients.
Figure 1  
A: A 12-lead electrocardiogram (ECG) demonstrating ectopic atrial tachycardia with variable atrioventricular conduction. B: Telemetry strips (lead II) demonstrating response to oral (PO) administration of ivabradine. At 1 hour, there is no change. At 1 hour, 25 minutes, there are increasing periods of sinus rhythm. At 1 hour, 28 minutes, there is sustained sinus rhythm. C: A 12-lead ECG demonstrating sinus rhythm, following first dose of ivabradine.
immediate His with a short AH interval, followed by continuation of tachycardia, consistent with a mechanism of junctional tachycardia. This mild junctional acceleration did not match the clinical arrhythmia. Given the low likelihood that this was the clinical arrhythmia and the not insignificant risk of heart block, ablation was deferred. He was started on propranolol and continued to have palpitations. At our center, therapy was switched to ivabradine 2.5 mg PO BID, and he has remained symptom free at 4 months of follow-up. He has not experienced any medication side effects.

Case 3
A 23-year-old female patient was diagnosed fetally with heart block in the setting of an intracardiac mass in the region of the AV junction. She underwent epicardial pacemaker placement in the newborn period, which was later upgraded to a dual-chamber trans venous pacemaker. Over time the mass regressed, though there is residual echogenicity noted in the interventricular septum, in association with dyssynchrony and diastolic dysfunction. At baseline, she exhibits 1:1 AV conduction with a right bundle branch block, with intermittent Mobitz II AV block during exercise. She developed frequent premature junctional contractions, often in bigeminy (Figure 2A and B). She then experienced frequent palpitations, with correlation of symptoms to episodes of an irregular usual QRS tachycardia with ventriculoatrial dissociation by ECG and device interrogation, consistent with a diagnosis of junctional tachycardia (Figure 2C and D).

Owing to bilateral femoral vein occlusion, catheter ablation was deferred for medical management. She continued to have frequent tachycardia despite beta blocker therapy (maximal daily nadolol dose of 60 mg). Symptoms were significantly disrupting her daily life. She was admitted for initiation of ivabradine. She was given a test dose of 2.5 mg PO, followed by dosing of 5 mg PO BID (with nadolol continued at a dose of 20 mg PO BID). Following the second dose of 5 mg (third total dose), there was significant reduction in junctional ectopy (Figure 2E). She has remained symptom free on this dose, though she continues to have asymptomatic premature junctional contractions and rare nonsustained runs by device interrogation. She has not experienced any medication side effects at 1 year from initiation, and reports a complete normalization of her quality of life.

Case 4
A 14-year-old female patient with a congenital myopathy, associated with noncompaction cardiomyopathy and chronic respiratory insufficiency, underwent orthotopic heart transplant 9 years ago. Her posttransplant course has been complicated by development of atrial tachyarrhythmias. She had recurrence of EAT following acutely successful radiofrequency catheter ablation and was treated with nadolol and flecainide. Owing to breakthrough symptomatic episodes on this regimen, nadolol and flecainide were discontinued, and ivabradine was started at a dose of 1.25 mg PO BID. Because of her complex history and comorbidities, she was...
admitted for monitoring during ivabradine initiation, and the
dose was titrated up to 2.5 mg PO BID (0.17 mg/kg/day). As
an outpatient, ivabradine was increased further to 5 mg in the
AM and 2.5 mg in the PM (0.25 mg/kg/day). Owing to recur-
rent episodes, nadolol was added. Ultimately, she was read-
mitted to the hospital with a prolonged episode of atrial
tachycardia, at which point ivabradine was discontinued,
and she was restarted on nadolol and flecainide. She experi-
enced no ivabradine-related adverse effects during 2 months
of therapy.

Discussion
In this case series, we describe short-term outcomes of ivab-
radine therapy in 4 children and young adults with automatic
tachyarrhythmias. These cases represent diverse arrhythmia
substrates—2 cases of focal EAT in a structurally normal
heart; 1 case of junctional tachycardia in a patient with his-
tory of a neonatal mass involving the AV junction, associated
with residual AV conduction disease; and 1 case of atrial
tachycardia in a teenager following heart transplant. Ivabra-
dine was safe in all patients, with no adverse events or side
effects. Ivabradine was effective as monotherapy in 2 pa-
tients, with immediate rhythm control observed in the
11-year-old girl with EAT. Ivabradine was effective in
conjunction with beta-blocker in case 3. Ivabradine was not
observed to be effective for arrhythmia control in the patient
with posttransplant atrial tachycardia. Failure of ivabradine in
this case likely relates to an underlying mechanism of micro-
reentry rather than enhanced automaticity; in a recent series,
78% of focal atrial tachycardias in pediatric heart transplant
recipients were nonautomatic.6 Together, the presented cases
provide further evidence that ivabradine is a safe and poten-
tially effective therapy for arrhythmias with a mechanism of
enhanced automaticity, and add to the emerging literature on
the role of ivabradine as an antiarrhythmic agent. It appears to
be a safe alternative option for patients who are not interested
in or are not good candidates for catheter ablation.

There are little published data on use of ivabradine for
 treatment of EAT in pediatric patients. At present, there is
a single case report of a child with EAT and tachycardia-
induced cardiomyopathy (TIC) effectively treated with ivabra-
dine. Rate control was achieved after 2 days of ivabradine
therapy, and ventricular function recovered after 1 month.
There is also a case report of TIC due to inappropriate sinus
tachycardia, with successful treatment using ivabradine.3
This case may in fact have represented EAT, as the ECG of
tachycardia shows a prolonged PR interval.

There is a growing literature on utility of ivabradine for
congenital JET. Dieks and colleagues reported a series of
5 infants and children with congenital JET refractory to stan-
dard antiarrhythmics, including amiodarone, who were then
started on oral ivabradine as adjunctive therapy. The addition
of ivabradine resulted in rhythm control in 4 subjects and rate
control in the fifth patient. In a separate report, Al-Ghamdi
and colleagues described successful treatment of congenital
JET in a 3-year-old girl, allowing catheter ablation to be
deferred. This child converted to sinus rhythm following a
second oral dose of ivabradine. Finally, Ergul and col-
leagues reported 3 infants with medically refractory congen-
tial JET and TIC who responded to adjunctive oral
ivabradine, with significant rhythm control noted at 6–8
hours following the initial ivabradine dose. There were no
observed drug-related side effects in any of these reports.
Our case represents the first described case of ivabradine
treatment for a form of Junctional tachycardia distinct from
congenital JET.

Together, these cases demonstrate that ivabradine effect-
ively targets the abnormal automaticity of the AV junction
that underlies congenital and noncongenital forms of junc-
tional tachycardia. A critical question remains whether there
is a role for ivabradine in treatment of postoperative JET.
There are very limited data in this arena, but Kumar and col-
leagues recently reported on 2 infants with postoperative
JET successfully treated with oral ivabradine. Both infants
had JET refractory to standard therapies, including sedation,
reduction in inotropes, cooling, and amiodarone. Oral ivabra-
dine resulted in rate control within 2–3 hours of administra-
tion. A major limitation of ivabradine in treatment of
postoperative JET is the absence of an IV formulation and
the unknown effect of a postoperative low cardiac output
state on drug absorption; however, the observed rapidity of
ivabradine effect in these cases is quite promising and calls
for further research.

Ivabradine is an attractive therapeutic option, in part
owing to its relatively hemodynamically neutral profile. In
contrast to many currently available antiarrhythmic agents,
ivabradine has no effect on cardiac contractility, and it has
not been associated with hypotension. This profile makes it
especially attractive for patients with ventricular dysfunction,
as in TIC, or in the immediate postoperative setting. Ivabra-
dine has little effect on repolarization and has not been asso-
ciated with increased risk of ventricular arrhythmias. The
safety of oral ivabradine therapy in infants and children has
been established in a cohort of children with dilated cardio-
myopathy and stable heart failure.9 In a randomized,
double-blind, placebo-controlled trial, 116 children with
dilated cardiomyopathy received either ivabradine (n = 74)
or placebo (n = 42); the majority of patients in both study
groups were on beta-blocker, and many were also on digoxin.
Adverse event rates were low overall and similar in both
arms. There were no instances of AV block, atrial fibrillation,
or other arrhythmia. Importantly, this trial also established
that oral ivabradine has a similar pharmacokinetic and phar-
macodynamic profile in children aged 6 months to 18 years to
that seen in adults.10,11 Finally, no ivabradine-related adverse
effects have been reported in any of the above published
cases.

Conclusion
In conclusion, ivabradine represents a promising adjunctive
antiarrhythmic agent for treatment of automatic tachyarrhyth-
miass in children and young adult patients. Its property of use
dependence, with a greater effect at higher heart rates, makes it particularly attractive to the pediatric population. Consistent with other published reports, we have found it to be safe, and the rapidity of response in some cases has been striking. One major limitation of the drug is absence of an IV formulation at present. Further prospective studies should evaluate the safety, efficacy, and dosing of oral ivabradine for treatment of automatic tachyarrhythmias in children and young adult patients.

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