Received: 21 June 2023 | Revised: 24 November 2023 | Accepted: 29 November 2023

DOI: 10.1002/emp2.13090

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
Open Access
WILEY

REVIEW ARTICLE

Pediatrics

Pediatric antiarrhythmics and toxicity: A clinical review

Alexandra T. Geanacopoulos MD[1,2] | **Benjamin Zielonka MD**[2,3] | **Miriam T. Fox MD**[2] | **Sarah Kerr MD**[2] | **Kristina D. Chambers MD**[2] | **Robert Przybylski MD**[2,3] | **Michele M. Burns MD, MPH**[1,2,4]

[1]Division of Emergency Medicine, Boston Children's Hospital, Boston, Massachusetts, USA

[2]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts, USA

[4]Harvard Medical Toxicology Program, Boston Children's Hospital, Boston, Massachusetts, USA

Correspondence
Benjamin J. Zielonka, MD, Department of Cardiology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115, USA.
Email: Benjamin.zielonka@cardio.chboston.org

Funding and support: By *JACEP Open* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Supervising Editor: Sing-Yi Feng, MD

Abstract

Antiarrhythmic medications are fundamental in the acute and chronic management of pediatric arrhythmias. Particularly in the pediatric patient population, associated antiarrhythmic toxicities represent important potential adverse effects. Emergency medicine clinicians must be skilled in the detection, workup, and management of antiarrhythmic toxicity. This is a clinical review of the indications, pharmacology, adverse effects, and toxicologic treatment of antiarrhythmics commonly used in the pediatric patient population.

KEYWORDS
antiarrhythmic ingestion, antiarrhythmics, pediatric electrophysiology, pediatrics, pharmacology, toxicology

1 | INTRODUCTION

Cardiac arrhythmias are observed in as many as 1 in 250 children.[1,2] These rhythm disturbances are frequently recurrent and occur in the presence or absence of structural heart disease, posing unique management challenges to clinicians. Antiarrhythmic medications are commonly used for the acute management and chronic therapy of pediatric arrhythmias. Intentional or exploratory ingestion of antiarrhythmics by children can be fatal at low doses and requires quick recognition and treatment to prevent mortality.[3] Knowledge of antiarrhythmic medications and associated toxicities is an important tool for health care practitioners in the emergency department.

The purpose of this review is to summarize the indications, pharmacology, and toxicologic considerations for antiarrhythmics in the pediatric patient population. We report on standard dosing, available preparations, drug–drug and food–drug interactions, and recommendations for therapeutic monitoring (Table 1). We also propose a generalized management approach to all antiarrhythmic toxicities (Table 2). In the following sections, we review commonly used antiarrhythmic agents according to Vaughan-Williams classification.

Alexandra T. Geanacopoulos and Benjamin Zielonka contributed equally as first authors.

2 | PROCAINAMIDE (CLASS IA)

2.1 | Pediatric indications

Procainamide is a Class IA antiarrhythmic that is administered as an intravenous bolus and/or continuous infusion. An oral formulation of procainamide previously used for chronic arrhythmia management is no longer available in the United States. Procainamide is used for the acute treatment of a wide variety of supraventricular tachycardias (SVT) and monomorphic ventricular tachycardia (VT). Small series have suggested that procainamide may be superior to amiodarone in the management of refractory SVT in pediatric patients.[4] Procainamide is also an effective agent for rate control of junctional ectopic tachycardia in the postoperative setting, particularly when used in combination with hypothermia.[5,6]

2.2 | Mechanism of action

Procainamide binds and inhibits the open-state fast inward sodium channel (Nav1.5) encoded by SCN5A resulting in reduced fast sodium current (I_{Na}). This slows depolarization and conduction velocity, corresponding to a blunted upstroke in phase 0 of the action potential in the atria, ventricular muscle fibers, and His-Purkinje system.[7] The main active metabolite of procainamide, N-acetylprocainamide (NAPA), is a Class III antiarrhythmic that delays repolarization and contributes to increases in action potential duration and effective refractory period in the cardiomyocytes (Figure 1). Of note, there is genetic variation in the rate of acetylation and accumulation of NAPA, with patients exhibiting either a fast or slow acetylator phenotype.

2.3 | Toxicity

The cardiotoxic effects of procainamide are closely related to serum procainamide and/or NAPA levels and primarily occur in the setting of hepatic or renal dysfunction. Electrocardiographic signs of toxicity include PR interval prolongation, QRS widening, and QTc prolongation that can predispose to torsades de pointes (TdP). Procainamide can cause bradycardia and hypotension, the latter of which is largely secondary to vasodilation. It may have weak negative inotropic effects but has a more neutral impact on cardiac contractility than other intravenous antiarrhythmic agents.[8] Oral procainamide can result in positive antinuclear antibody titers that can manifest as a drug-induced lupus syndrome.[9] Blood dyscrasias including pancytopenia or agranulocytosis are a rare complication of oral procainamide.[10]

2.4 | Toxicologic treatment

The generalized management approach for all antiarrhythmic toxicities in Table 2 is recommended for acute procainamide toxicity, including treatment of TdP. Sodium bicarbonate or lidocaine (Class IB) may reverse fast sodium channel blockade and result in QRS narrowing. There are case reports of hemodialysis in the treatment of procainamide toxicity.[11]

3 | LIDOCAINE (CLASS IB)

3.1 | Pediatric indications

Lidocaine is a Class IB antiarrhythmic administered as an intravenous bolus and/or continuous infusion in the acute treatment of ventricular arrhythmias. Current Pediatric Advanced Life Support guidelines recommend either amiodarone or lidocaine for the treatment of shock refractory ventricular fibrillation or pulseless VT.[12] Historically, lidocaine was also used for the treatment of arrhythmias resulting from digoxin toxicity.[13]

3.2 | Mechanism of action

Lidocaine primarily binds to inactivated state fast inward sodium channels, which decreases the duration of the action potential in the His-Purkinje system and ventricular muscle fibers via reduction of the late I_{Na}. Thus, lidocaine's major effect is to reduce the action potential duration and effective refractory period.[14] Lidocaine may also decrease the slope of phase 0 via reduction of I_{Na}, though to a much lesser extent than Class IA or Class IC antiarrhythmics, and decreases the slope of phase 4, the spontaneous depolarization (Figure 1).[15] Compared to Class IC antiarrhythmic, lidocaine dissociates comparatively quickly from sodium channels, particularly during diastole. As a result, lidocaine demonstrates use-dependence with a more pronounced sodium channel blockade at faster heart rates.[16] Due to its affinity for binding inactivated sodium channels in depolarized cells, lidocaine is particularly efficacious in treating ventricular arrhythmias arising from myocardial ischemia.[17,18]

3.3 | Toxicity

Severe lidocaine toxicity may result in respiratory depression, hypotension, myocardial depression, arrhythmias, or cardiorespiratory arrest.[15,19,20] Due to the risk of bradycardia, lidocaine should be used with caution in patients with abnormal atrioventricular or intraventricular conduction.[14,21] Central nervous system effects include tremors, confusion, twitching, vision changes, and loss of consciousness, with seizure activity and central nervous system depression resulting from more severe toxicity. The central nervous system effects typically manifest before cardiorespiratory effects, which occur at higher levels of toxicity.

3.4 | Toxicologic treatment

Management of lidocaine toxicity includes targeted supportive care and discontinuing lidocaine administration. Antiseizure medications

TABLE 1 Cardiac antiarrhythmic descriptive, pharmacologic, and treatment characteristics.[15,18,20,47,50,60,78,84,87–96]

Drug	Procainamide	Lidocaine	Flecainide	Propranolol	Esmolol	Amiodarone	Sotalol	Diltiazem	Adenosine
Vaughan Williams class	Class IA	Class IB	Class IC	Class II	Class II	Class III	Class III	Class IV	Class V
Alternative names	Procan, Procanbid, Pronestyl, Pronestyl SR	Lidocaine hydrochloride, Lignocaine	Flecainide acetate, Tambocor	Propranolol hydrochloride, Inderal	Brevibloc Esmolol hydrochloride	Amiodarone Hydrochloride, Pacerone, Cordarone, Nexterone	Betapace, Betapace AF, Sorine, Sotalol hydrochloride, Sotylize	Cardizem, Cartia XT Tiazac, Taztia XT, Tiadylt ER	Adenocard, Adenoscan
Dosing[a]	*IV loading*: 7–10 mg/kg in neonates and 10–15 mg/kg/day in children and adolescents (max 1000–1500 mg) given over 30 to 45 minutes. *IV continuous*: 20–80 mcg/kg/min (max 2 g/day)	*IV loading*: 1 mg/kg rapid bolus (may give second bolus if >15 min between initial bolus and start of infusion) *IV continuous*: 20–50 mcg/kg/min	*Oral initial*: 1–3 mg/kg/day or 50–100 mg/m2/day in 3 divided doses *Oral maintenance*: 3–6 mg/kg/day or 100–150 mg/m^2/day in 3 divided doses	*Oral*: 2–4 mg/kg/day in 3–4 divided doses	*IV bolus*: 100–500 mcg/kg over 1–2 min *IV continuous*: 100–500 mcg/kg/min	*Oral*: 10–15 mg/kg/day in 1–2 divided doses for 4–14 days followed by 5 mg/kg/day daily *IV loading*: 5 mg/kg over 60 min *IV continuous*: 5–15 mcg/kg/min	*Oral*: 30–60 mg/m^2/dose (max 320 mg/day) every 8 hours[b] *IV bolus*: 1 mg/kg over 1 hour (max 80 mg) *IV continuous*: 80–90% of calculated oral daily dose in 2–3 divided doses and administered over 3–5 hours	*Oral*: 1.5–2 mg/kg/day in 3–4 divided doses (max 360 mg/day) *IV bolus*: 0.25 mg/kg over 5 minutes *IV continuous*: 0.05–0.15 mg/kg/hour	*IV bolus*: 0.05–0.1 mg/kg rapid bolus; increase incrementally to max 0.3 mg/kg
Therapeutic level	Combined procainamide and NAPA level trended for toxicity	1.5–5.0 mcg/mL	0.2–1.0 mcg/mL	Not routinely measured	Not routinely measured	Not routinely measured but effective at 1.0–2.5 mg/L (adults, plasma)	Not routinely measured	Not routinely measured	Not routinely measured
Oral preparations	N/A	N/A	Tablet liquid (EC)	Tablet (IR) Capsule (ER) Liquid	N/A	Tablet liquid (EC)	Tablet liquid	Tablet (IR, ER) Capsule (ER) Liquid (EC)	N/A

(Continues)

TABLE 1 (Continued)

Drug	Procainamide	Lidocaine	Flecainide	Propranolol	Esmolol	Amiodarone	Sotalol	Diltiazem	Adenosine
Half-life	Procainamide: 1.5-2 hours NAPA: 6 hours	1.5–2 hours	Newborn: up to 29 hours Children: 8–12 hours	Immediate release: 4–6 hours Long-acting: 8–11 hours	2.7–4.8 minutes	15-142 days	7–9.2 hours	Oral: 3–4.5 hours IV: 3.4 hours	<10 seconds
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	Red blood cell	Hepatic	Renal	Hepatic	Intracellular
Elimination	Renal	Renal	Renal	Renal	Renal	Hepatobiliary	Renal	Renal	–
Drug and food interactions	N/A	Propranolol and amiodarone increase serum levels Phenobarbital reduces serum levels	Milk may interfere with drug absorption	Alcohol exerts variable effect on serum levels	Alcohol exerts variable effect on serum levels	Grapefruit juice increases serum levels May increase concentrations of lidocaine, digoxin, warfarin, and statins	N/A	Grapefruit juice increases serum levels	Inhibited by caffeine and theophylline
Acute monitoring	BP; combined procainamide and NAPA level 4 hours after initiation and daily thereafter; daily EKG	EKG and BP; consider monitoring of plasma level if prolonged use or concern for altered metabolism	Serum flecainide level within 48–72 hours of treatment initiation; serial EKGs	Titrate to heart rate and BP goals	Titrate to heart rate and BP goals	Assess liver transaminases, thyroid function; EKG and BP	EKG, heart rate, and BP	Titrate to heart rate and BP goals	Titrate to achieve sinus rhythm

Abbrevations: BP, blood pressure; EC, extemporaneously compounded; ER, extended-release; IR, immediate-release; NAPA, N-acetylprocainamide.

[a]Dosing should be confirmed with your local institution before administration as titrations may be required given individual patient needs.

[b]For patients ≤2 years of age, the starting sotalol dose should be reduced according to a drug-specific age factor nomogram.

TABLE 2 General management principles for antiarrhythmic toxicologic ingestions.[11]

Primary evaluation	Airway *Assess and maintain airway patency* Breathing *Assess breath sounds and ensure adequate tidal volumes with continuous pulse oximetry and end-tidal carbon dioxide monitoring* Circulation *Assess perfusion, blood pressure, and secure intravenous access* Disability *Assess level of consciousness in addition to pupillary size and reactivity*
Decontamination	Activated charcoal *Consider in patients with known ingestion within the first several hours of presentation. Patient must have a soft, nondistended abdomen with bowel sounds present.*
Diagnostics	Continuous cardiorespiratory monitoring Serial electrocardiograms for diagnostics and evaluation of acute management Laboratory studies including chemistries and serum drug concentrations
Therapeutics	Sodium bicarbonate Administer for QRS widening secondary to Class IA or IC toxicity High dose insulin and IV calcium Promote inotropy in Class II or Class IV toxicity Intravenous fat emulsion *Consider in seriously ill, deteriorating or refractory cases* Targeted management of arrhythmias *Magnesium for yorsades de pointes* Hemodialysis *Rarely used for due to large volumes of distribution, but discuss with a medical toxicologist if procainamide ingestion* Extracorporeal membrane oxygenation *Consider in severe cases refractory to medical intervention*

should be provided for prolonged seizure activity. Hemodynamic support should be initiated as clinically indicated. Toxic effects are generally short lived once the medication is discontinued, though effects may be prolonged in patients with hepatic insufficiency or low cardiac output due to impaired lidocaine clearance.[15,20] Sodium bicarbonate and intralipid are used early in resuscitation to prevent potentiation of cardiac toxicity, with extracorporeal membrane oxygenation reserved for severe or refractory cases.[22]

4 | FLECAINIDE (CLASS IC)

4.1 | Pediatric indications

Flecainide is an oral Class IC antiarrhythmic most commonly used for the maintenance of sinus rhythm in children and infants with a history of SVT. There is also a limited role for flecainide in the management of VT.[23] Flecainide can be used as monotherapy or in combination with other oral antiarrhythmics for refractory arrhythmias.[24] Although the findings of the Cardiac Arrhythmia Suppression Trial have historically limited the use of flecainide in the adult population to patients without structural heart disease, flecainide is used in pediatric patients with structurally normal hearts as well as those with congenital heart disease.[25,26]

4.2 | Mechanism of action

Flecainide selectively binds and inhibits the open-state fast inward sodium channel, which causes blunting of the depolarization upstroke corresponding to phase 0 of the cardiac action potential (Figure 1) in the ventricular muscle fibers and His-Purkinje system.[27] In addition, flecainide inhibits the delayed rectifier potassium current (I_{Kr}) encoded by the *KCNH2* gene and prolongs repolarization in atrial and ventricular myocytes.[28] This results in increased action potential duration and effective refractory period in atrial and ventricular myocytes and increased refractoriness in the His-Purkinje system. Flecainide exhibits use-dependence, with increased sodium channel blockade with increasing heart rate.

4.3 | Toxicity

Children are particularly susceptible to flecainide toxicity given its narrow therapeutic window and the frequent need among younger patients for extemporaneous compounding of a liquid formulation, increasing the risk for medication dosing errors.[29] Flecainide has proarrhythmic properties that are characterized by a prolonged PR interval, widening of the QRS duration, bundle branch block, and a Brugada-like pattern on ECG with the potential to progress to sinus bradycardia, sinus arrest, or TdP.[30] Flecainide also exerts a negative

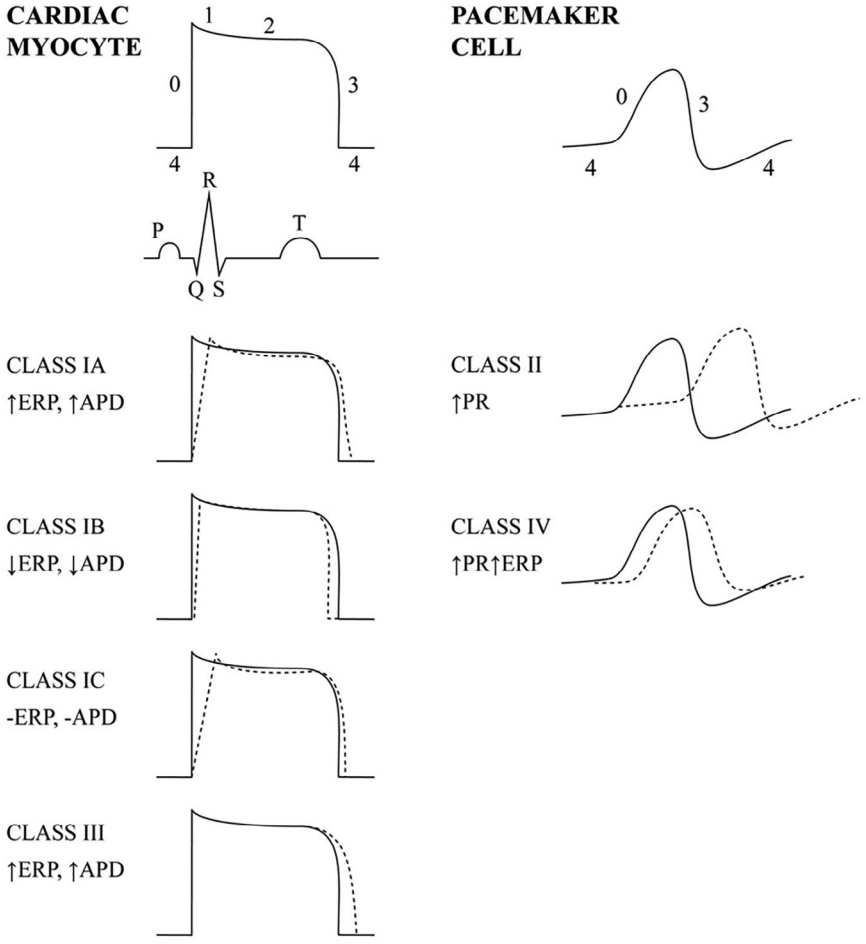

FIGURE 1 Cardiac action potentials and effects of antiarrhythmics by Vaughan-Williams classification. Left-hand panel: Cardiac myocyte action potential with corresponding electrocardiographic findings. Right-hand panel: Pacemaker cell action potential; Solid lines represent typical action potential and dotted lines represent expected changes with administration of each antiarrhythmic class. Abbreviations: APD, action potential duration; ERP, effective refractory period.

inotropic effect and may cause or worsen myocardial dysfunction. These effects may present clinically with palpitations, chest pain, dizziness, and syncope. Extracardiac effects may include dyspnea, abdominal pain, nausea, vomiting, constipation, visual changes, and seizures.

4.4 | Toxicologic treatment

The mainstay of therapy for flecainide toxicity in children is administration of intravenous sodium bicarbonate in 1 mEq/kg aliquots given over 1–2 minutes and repeated as needed until the QRS duration remains <100 milliseconds.[31,32] Case reports have demonstrated success in using intravenous lipid emulsion therapy.[33]

5 | PROPRANOLOL (CLASS II)

5.1 | Pediatric indications

Propranolol is an oral Class II antiarrhythmic commonly used for the treatment of SVT and the prevention of recurrence in infants and children.[34] It is also prescribed for symptom management in children with palpitations secondary to premature ventricular complexes.[35] Propranolol is associated with reduced risk of cardiac arrest among patients with cardiac channelopathies including long QT syndrome and catecholaminergic polymorphic VT.[35] Apart from its antiarrhythmic effects, propranolol is also used for the treatment of pediatric hypertension, infantile hemangioma, migraine prophylaxis, and thyrotoxicosis.

5.2 | Mechanism of action

Propranolol is a non-selective beta-adrenergic antagonist with equal affinity for ß1 and ß2 receptors. At the cardiomyocyte ß1 receptors, binding of propranolol results in reduced intracellular calcium influx through the cyclic AMP pathway. This results in reduced automaticity and slowing of conduction velocity in nodal tissue, thereby prolonging the PR interval. Additionally, propranolol has sodium-channel blocking effects, which may enhance its antiarrhythmic properties.[36]

5.3 | Toxicity

The majority of pediatric propranolol and other beta-blocker toxicities are associated with small-dose exploratory ingestions in young children after ingestion of a caregiver's prescription medication.[37]

Clinical symptoms and signs secondary to these exploratory ingestions are rare.[38] The most common cardiac side effects are bradycardia and hypotension, though significant ingestions can result in atrioventricular block (Figure 1) and heart failure. Extracardiac effects include lethargy, seizures, dizziness, bronchospasms, diarrhea, and hypoglycemia.[35] Propranolol is more lipophilic than other beta-blockers and can more easily penetrate the blood–brain barrier, leading to more significant neurologic toxicity.[37]

5.4 | Toxicologic treatment

Preliminary management of beta blocker toxicity involves stabilization and support of bradycardia and hypotension with intravenous isotonic fluids and atropine if bradycardia is symptomatic.[39] Despite limited evidence to support its efficacy, glucagon is commonly administered as an intravenous bolus and continuous infusion with the goal of increasing cardiac contractility through the cyclic AMP pathway.[40] Similarly, intravenous calcium, administered either as calcium gluconate or calcium chloride, may be used to augment inotropy.[41] More recently, high-dose insulin therapy is used with greater frequency for the treatment of beta blocker and calcium channel toxicity with the theory that insulin increases inotropy and vasodilation and minimizes insulin resistance.[42] Common protocols involve a bolus insulin dose of 0.5–1.0 U/kg followed by continuous infusion with concurrent dextrose containing fluids to maintain euglycemia.[43] Finally, lipid emulsion therapy may be considered in situations where more traditional therapies are unsuccessful though experience is limited primarily to adults.[44] Propranolol may be particularly susceptible to lipid emulsion therapy given its highly lipophilic properties. In asymptomatic cases of propranolol ingestion, children may be safely discharged from care 6 hours after ingestion. Ingestion of extended-release preparations may warrant up to 24 hours of observation.[38]

6 | ESMOLOL (CLASS II)

6.1 | Pediatric indications

Esmolol is a short-acting, rapid-onset Class II antiarrhythmic used as a continuous intravenous infusion in acute care and surgical settings for the treatment of tachycardia and hypertension in the setting of cardiac surgery.[45–48] Among infants with SVT, esmolol is commonly used, along with other adjunctive therapies, as an abortive medication in the acute care setting.[45] It has also been used as an adjunct to anesthesia during cardiac surgeries in children requiring cardiopulmonary bypass.[49]

6.2 | Mechanism of action

Esmolol is a cardioselective beta-adrenergic antagonist with binding only to ß1 receptors. At the ß1 receptors on cardiac myocytes, esmolol binds and works by the same mechanism of action as propranolol.[50]

6.3 | Toxicity

Similar to other beta blockers, esmolol can be associated with symptomatic bradycardia and hypotension. Extracardiac effects include dizziness, fatigue, headache, nausea, vomiting, and local infusion site reactions.

6.4 | Toxicologic treatment

Given its short half-life, the first step in the treatment of esmolol toxicity in the acute care setting should be discontinuation of the infusion. For ongoing symptomatic management, similar treatment strategies to those discussed for toxicologic treatment for propranolol toxicity may be employed.

7 | SOTALOL (CLASS III)

7.1 | Pediatric indications

Sotalol is a non-cardioselective beta blocker with Class III antiarrhythmic properties that can be administered orally or as an intravenous infusion. Sotalol is commonly used for the treatment of reentrant tachyarrhythmias, including atrial flutter and intra-atrial reentrant tachycardia, in the postoperative setting in patients with congenital heart disease.[51,52] More recently, intravenous sotalol has emerged as an option for termination of acute arrhythmias or for more rapidly achieving steady-state concentrations during sotalol initiation in pediatric patients.[53,54]

7.2 | Mechanism of action

Sotalol comprises a racemic mixture of *d*- and *l*-sotalol isomers, with *l*-sotalol having more pronounced beta-blockade activity. At lower doses, beta blocker activity predominates and results in inhibitory binding of ß1- and ß2-adrenergic receptors with a corresponding increase in the effective refractory period in the atrioventricular node (Figure 1). At higher doses, sotalol inhibits the rapid component of the delayed-rectifier potassium current potassium current (I_{Kr}) encoded by the *KCHN2* gene. This increases the action potential duration and effective refractory period in the atria, ventricles, and His-Purkinje system.[55] Sotalol exhibits reverse use dependence with more potent potassium channel blockade and prolongation of the action potential at lower heart rates.

7.3 | Toxicity

The cardiovascular toxicities of sotalol overlap with those of other Class II and Class III antiarrhythmics. Sotalol is associated with bradycardia and hypotension and exerts negative inotropic effects. In

addition, sotalol can be proarrhythmic and exhibits dose-dependent QTc prolongation that can progress to ventricular arrhythmias such as TdP. Extracardiac effects include dyspnea, fatigue, dizziness, and nausea/vomiting and sotalol may cause bronchospasm in patients with reactive airway disease or asthma. Toxicity related to sotalol in the adult population has been most often reported within the first 3 days of initiation; therefore, it is recommended that sotalol initiation or upward titration occur in the inpatient setting.[56]

7.4 | Toxicologic treatment

Management of sotalol toxicity including TdP is primarily supportive (Table 2) with an emphasis on electrolyte optimization in the setting of QTc prolongation. Sotalol is not protein bound and hemodialysis can be used to reduce plasma concentrations of sotalol.[57]

8 | AMIODARONE (CLASS III)

8.1 | Pediatric indications

Amiodarone is an intravenous Class III antiarrhythmic approved in pediatric patients to control SVT (including postoperative junctional ectopic tachycardia) and VT and for use during pediatric resuscitation in shock resistant ventricular fibrillation and pulseless VT.[58–60] Given its extensive side effect profile, amiodarone is typically used in refractory cases. As described previously (see Section 3.1 **Lidocaine**, *Pediatric Indications*), amiodarone and lidocaine are recommended in patients with shock-refractory ventricular fibrillation or pulseless VT.

8.2 | Mechanism of action

Similar to other Class III antiarrhythmics, amiodarone inhibits efflux through potassium rectifier channels to prolong phase 3 of the action potential.[61] This delays repolarization and prolongs the effective refractory period (Figure 1). Amiodarone also displays characteristics of other antiarrhythmics including those in Class I, II, and IV.[62,63]

8.3 | Toxicity

In the acute setting, intravenous amiodarone administration is associated with hypotension (secondary to the vasodilatory effects of the drug itself or its cosolvents), bradycardia, and heart block.[64] In young children, particularly those under 3 months of age and with ventricular dysfunction, intravenous amiodarone can be associated with cardiovascular collapse, necessitating slow infusion and close cardiorespiratory monitoring.[65] Acute respiratory distress syndrome after intravenous administration in children is rare but is associated with high mortality.[66,67] Organ dysfunction typically occurs after long-term oral therapy and can include pulmonary toxicity (the leading cause of death), transaminitis, hypo- and hyperthyroidism, optic neuropathy, corneal deposits, skin discoloration, bradycardia, and QT prolongation (although resultant TdP is rare).

8.4 | Toxicological treatment

Treatment of amiodarone toxicity includes dose reduction or drug cessation; however, symptoms may persist for months because of the drug's long half-life. In the acute setting, bradycardia is treated with beta-adrenergic agonists, transcutaneous pacing, or temporary transvenous pacing. Hypotension is treated with fluid resuscitation or vasopressors. Although animal studies of amiodarone-induced hypotension show efficacy with lipid emulsion therapy, there are no case reports indicating success in humans with amiodarone toxicity.[68] Chronic pulmonary toxicity, the most fatal complication, is treated with drug cessation, steroids for at least 4–12 months, and in severe cases, mechanical ventilation.

9 | DILTIAZEM (CLASS IV)

9.1 | Pediatric indications

Diltiazem is a Class IV intravenous antiarrhythmic effective for ventricular rate control in those with primary atrial tachyarrhythmias.[69] Intravenous diltiazem can be used in children with hemodynamically stable SVT unresponsive to initial vagal maneuvers or adenosine and in patients with bronchospasm for whom adenosine is contraindicated.[70] It may also be effective for patients with fascicular VT.[71] As an antihypertensive, oral diltiazem is not first line in pediatrics. In transplant patients, however, it can be doubly advantageous in providing blood pressure control and increasing immunosuppressive concentrations.[72,73]

9.2 | Mechanism of action

Diltiazem is a non-dihydropyridine calcium channel blocker that inhibits calcium influx in cardiac tissue and smooth muscle vasculature. In cardiac tissue, diltiazem exhibits dose-dependent prolongation of intranodal conduction time and delays the atrioventricular node refractory period (Figure 1).[74] In smooth muscle vasculature, diltiazem is a potent vasodilator with minimal inotropic effects but with dose-dependent decreases in blood pressure.[75]

9.3 | Toxicity

Diltiazem overdose causes cardiovascular compromise with bradycardia, atrioventricular block, hypotension, and in severe cases, cardiogenic shock and heart failure. Diltiazem causes insulin resistance with

resultant hyperglycemia.[76] Lactic acidosis is also noted secondary to cardiogenic shock and hyperglycemia.

9.4 | Toxicologic treatment

Supportive measures are used for the treatment of bradycardia, atrioventricular block, hypotension, and cardiac shock (Table 2).[77] Evidence for intravenous calcium and high-dose insulin in mitigating toxicity in pediatric patients is variable but should be considered (see Section 5.4 **Propranolol**, *Toxicologic Treatment*). Use of intravenous lipid emulsion therapy in pediatric patients with diltiazem overdose is limited to case reports with varied success and is often considered in treatment-resistant cases.[42]

10 | ADENOSINE (CLASS V)

10.1 | Pediatric indications

Adenosine is a Class V (miscellaneous) intravenous antiarrhythmic drug used in the diagnosis and treatment of paroxysmal SVT whose substrate is a reentrant circuit that involves the atrioventricular node. In addition to treating SVT, adenosine can also be a diagnostic tool for unmasking primary atrial tachycardias (atrial flutter, atrial fibrillation) by inducing atrioventricular block. It also has utility in myocardial perfusion stress imaging as it has vasodilatory effects. Although most VT is unresponsive to adenosine, adenosine may aid in terminating outflow tract VT caused by catecholamines or exercise by inhibiting the production of intracellular cyclic AMP.[78]

10.2 | Mechanism of action

Adenosine functions as a pharmacologic drug by binding the purinergic adenosine receptors (A1, A2a, A2b, A3) found throughout the body.[79] It exerts transient negative dromotropic effects on the atrioventricular node, as well as transient negative chronotropic effects on the sinoatrial node via A1 receptors.[80] Adenosine increases potassium conductance in myocardial tissue, which results in hyperpolarization of the cell membrane and an increase in the threshold for triggering an action potential; this leads to transient slowing or block of spontaneous cell activity.[81] Adenosine is quickly metabolized by endothelial cells and erythrocytes via adenosine deaminase, hence why a rapid bolus in a vein close to the heart is required.[82]

10.3 | Toxicity

Adverse effects of adenosine are typically transient (<60 seconds) due to the medication's short half life. Common side effects include facial flushing, hyperpnea, headache, lightheadedness, nervousness, and chest pain secondary to peripheral vasodilation. Less common but more severe side effects include bradycardia, prolonged sinus arrest, complete atrioventricular block, atrial fibrillation, acceleration of VT, and apnea.[83,84] There are case reports of bronchospasm after administration of adenosine, and it should be used with caution in patients with asthma.[85] It has also been previously demonstrated that transplanted hearts exhibit hypersensitivity to adenosine and thus use in these patients requires caution and consideration of dose-reduction.[86]

10.4 | Toxicologic treatment

Given the short half-life of adenosine, side effects are typically transient and usually do not require intervention. Treatment is primarily supportive, although theophylline, an adenosine antagonist, has been used to attenuate more severe or prolonged adverse reactions.

11 | CONCLUSIONS

Cardiac antiarrhythmics are commonly used in the treatment of pediatric arrhythmias. Antiarrhythmics have distinct pharmacokinetics, potential interactions, and dosing and formulation considerations in the pediatric population that represent important sources of medication error and toxicity. An understanding of the mechanisms of action and potential associated toxicities of these medications is essential to ensure the appropriate management and monitoring of patients with rhythm disturbances as well as those presenting with accidental or intentional antiarrhythmic ingestion. Prompt recognition of antiarrhythmic toxicity is required to prevent significant morbidity and mortality.

There are several important gaps in the literature regarding antiarrhythmics and toxicity in the pediatric population. Epidemiologic data regarding the incidence of ingestions are limited to the cardiovascular drug classification and information surrounding the rate of accidental and/or intentional ingestion of individual antiarrhythmics is lacking. There is limited evidence regarding antiarrhythmic toxicity management in the children, and management strategy continues to be guided by case series and expert consensus. The toxicologic profile and management strategy in pediatrics for newer medications, such as ivabradine, a voltage-regulated inward funny current (I_f) anatagonist used in the management of heart failure and automatic atrial arrhythmias, merits further study.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

ORCID

Benjamin Zielonka MD https://orcid.org/0000-0003-1052-9736

TWITTER

Benjamin Zielonka MD https://twitter.com/bzielonkamd

REFERENCES

1. Wu MH, Chen HC, Kao FY, Huang SK. Postnatal cumulative incidence of supraventricular tachycardia in a general pediatric population: a national birth cohort database study. *Heart Rhythm*. 2016;13(10):2070-2075. doi:10.1016/j.hrthm.2016.06.006
2. Salerno JC, Seslar SP. Supraventricular tachycardia. *Arch Pediatr Adolesc Med*. 2009;163(3):268-274. doi:10.1001/archpediatrics.2008.547
3. Bar-Oz B, Levichek Z, Koren G. Medications that can be fatal for a toddler with one tablet or teaspoonful: a 2004 update. *Paediatr Drugs*. 2004;6(2):123-126. doi:10.2165/00148581-200406020-00005
4. Chang PM, Silka MJ, Moromisato DY, Bar-Cohen Y. Amiodarone versus procainamide for the acute treatment of recurrent supraventricular tachycardia in pediatric patients. *Circ Arrhythm Electrophysiol*. 2010;3(2):134-140. doi:10.1161/CIRCEP.109.901629
5. Mandapati R, Byrum CJ, Kavey REW, et al. Procainamide for rate control of postsurgical junctional tachycardia. *Pediatr Cardiol*. 2000;21(2):123-128. doi:10.1007/s002469910018
6. Walsh EP, Saul JP, Sholler GF, et al. Evaluation of a staged treatment protocol for rapid automatic junctional tachycardia after operation for congenital heart disease. *J Am Coll Cardiol*. 1997;29(5):1046-1053. doi:10.1016/S0735-1097(97)00040-5
7. Zamponi GW, Sui X, Codding PW, French RJ. Dual actions of procainamide on batrachotoxin-activated sodium channels: open channel block and prevention of inactivation. *Biophys J*. 1993;65(6):2324-2334. doi:10.1016/S0006-3495(93)81291-8
8. Mackin C, DeWitt ES, Black KJ, et al. Intravenous amiodarone and sotalol impair contractility and cardiac output, but procainamide does not: a Langendorff study. *J Cardiovasc Pharmacol Ther*. 2019;24(3):288-297. doi:10.1177/1074248418810811
9. Hanlon TM, Binkiewicz A, Feingold M, Necheles TF. Procainamide HCl-induced Lupus Syndrome in a child with myotonia congenita. *Am J Dis Child*. 1967;113(4):491-493. doi:10.1001/archpedi.1967.02090190137019
10. Danielly J, DeJong R, Radke-Mitchell LC, Uprichard ACG. Procainamide-associated blood dyscrasias. *Am J Cardiol*. 1994;74(11):1179-1180. doi:10.1016/0002-9149(94)90478-2
11. Low CL, Phelps KR, Bailie GR. Relative efficacy of haemoperfusion, haemodialysis and CAPD in the removal of procainamide and NAPA in a patient with severe procainamide toxicity. *Nephrol Dial Transplant*. 1996;11(5):881-884. doi:10.1093/oxfordjournals.ndt.a027421
12. Duff JP, Topjian A, Berg MD, et al. 2018 American Heart Association focused update on pediatric advanced life support: an update to the American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2018;138:e731-e739. doi:10.1161/CIR.0000000000000612
13. Moses HW, Yu PN. Antiarrhythmic drugs. *J Clin Pharmacol*. 1980;20(10):598-618. doi:10.1002/j.1552-4604.1980.tb01676.x
14. Rosen MR, Hoffman BF, Wit AL. Electrophysiology and pharmacology of cardiac arrhythmias. V. Cardiac antiarrhythmic effects of lidocaine. *Am Heart J*. 1975;89(4):526-536. doi:10.1016/0002-8703(75)90162-3
15. Collinsworth KA, Kalman SM, Harrison DC. The clinical pharmacology of lidocaine as an antiarrhythmic drug. *Circulation*. 1974;50(6):1217-1230. doi:10.1161/01.CIR.50.6.1217
16. Mallampati SR, Liu PL, Knapp RM. Convulsions and ventricular tachycardia from bupivacaine with epinephrine: successful resuscitation. *Anesth Analg*. 1984;63(9):856-859.
17. Dowd FJ, Johnson BS, Mariotti AJ. *Pharmacology and Therapeutics for Dentistry*. 7th ed. Elsevier; 2016. doi:10.1038/sj.bdj.2011.191
18. Darbar D. Standard Antiarrhythmic Drugs. *Cardiac Electrophysiology: From Cell to Bedside*. 7th ed. Elsevier; 2018. doi:10.1016/B978-0-323-44733-1.00112-7
19. Mofenson HC, Caraccio TR, Schauben J. Poisoning by antidysrhythmic drugs. *Pediatr Clin North Am*. 1986;33(3):723-738. doi:10.1016/S0031-3955(16)36052-7
20. Mehra P, Caiazzo A, Maloney P. Lidocaine toxicity. *Anesth Prog*. 1998;45(1):38-41.
21. Kunkel F, Rowland M, Scheinman MM. The electrophysiologic effects of lidocaine in patients with intraventricular conduction defects. *Circulation*. 1974;49(5):894-899. doi:10.1161/01.CIR.49.5.894
22. Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR, eds. Goldfrank's Toxicologic Emergencies, 10e. McGraw Hill; 2015. Accessed November 07, 2022. https://accesspharmacy.mhmedical.com/content.aspx?bookid=1163&sectionid=64552562
23. Kannankeril PJ, Moore JP, Cerrone M, et al. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia a randomized clinical trial. *JAMA Cardiol*. 2017;2(7):759-766. doi:10.1001/jamacardio.2017.1320
24. Price JF, Kertesz NJ, Snyder CS, Friedman RA, Fenrich AL. Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol*. 2002;39(3):517-520. doi:10.1016/S0735-1097(01)01773-9
25. Moffett BS, Valdes SO, Lupo PJ, et al. Flecainide use in children with cardiomyopathy or structural heart disease. *Pediatr Cardiol*. 2015;36(1):146-150. doi:10.1007/s00246-014-0978-3
26. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the cardiac arrhythmia suppression trial. *N Engl J Med*. 1991;324(12):781-788. doi:10.1056/NEJM199103213241201
27. Holmes B, Heel RC. Flecainide: a preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. 1985;29(1):1-33. doi:10.2165/00003495-198529010-00001
28. Follmer CH, Colatsky TJ. Block of delayed rectifier potassium current, I(K), by flecainide and E-4031 in cat ventricular myocytes. *Circulation*. 1990;82(1):289-293. doi:10.1161/01.CIR.82.1.289
29. Tamargo J, Le Heuzey JY, Mabo P. Narrow therapeutic index drugs: a clinical pharmacological consideration to flecainide. *Eur J Clin Pharmacol*. 2015;71(5):549-567. doi:10.1007/s00228-015-1832-0
30. Brugada J, Boersma L, Kirchhof C, Allessie M. Proarrhythmic effects of flecainide. Experimental evidence for increased susceptibility to reentrant arrhythmias. *Circulation*. 1991;84(4):1808-1818. doi:10.1161/01.CIR.84.4.1808
31. D'Alessandro LCA, Rieder MJ, Gloor J, Freeman D, Buffo-Sequiera I. Life-threatening flecainide intoxication in a young child secondary to medication error. *Ann Pharmacother*. 2009;43(9):1522-1527. doi:10.1345/aph.1L549
32. Gardner Yelton SE, Leonard JB, De La Uz CM, Wadia RS, Barnes SS. Flecainide toxicity secondary to accidental overdose: a pediatric case report of two brothers. *Case Rep Crit*. 2021;2021:4-9. doi:10.1155/2021/6633859
33. Vu NM, Hill TE, Summers MR, Vranian MN, Faulx MD. Management of life-threatening flecainide overdose: a case report and review of the literature. *HeartRhythm Case Reports*. 2016;2(3):228-231. doi:10.1016/j.hrcr.2015.12.013
34. Sanatani S, Potts JE, Reed JH, et al. The study of antiarrhythmic medications in infancy (SAMIS): a multicenter, randomized controlled trial comparing the efficacy and safety of digoxin versus propranolol for prophylaxis of supraventricular tachycardia in infants. *Circ Arrhythm Electrophysiol*. 2012;5(5):984-991. doi:10.1161/CIRCEP.112.972620
35. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2018;15(10):e190-e252. doi:10.1016/j.jacc.2017.10.054
36. Matthews JC, Baker JK. Effects of propranolol and a number of its analogues on sodium channels. *Biochem Pharmacol*. 1982;31(9):1681-1685. doi:10.1016/0006-2952(82)90668-2

37. Love JN, Howell JM, Klein-Schwartz W, Litovitz TL. Lack of toxicity from pediatric beta-blocker exposures. *Hum Exp Toxicol*. 2006. doi:10.1191/0960327106ht632oa
38. Belson MG, Sullivan K, Geller RJ. Beta-adrenergic antagonist exposures in children. *Vet Hum Toxicol*. 2001;43(6):361-365.
39. Soni N, Baines D, Pearson IY. Cardiovascular collapse and propranolol overdose. *Med J Aust*. 1983;2(12):629-630. doi:10.5694/j.1326-5377.1983.tb122727.x
40. Bailey B. Glucagon in β-blocker and calcium channel blocker overdoses: a systematic review. *J Toxicol Clin Toxicol*. 2003;41(5):595-602. doi:10.1081/CLT-120023761
41. Pertoldi F, D'Orlando L, Mercante WP. Electromechanical dissociation 48 hours after atenolol overdose: usefulness of calcium chloride. *Ann Emerg Med*. 1998;31(6):777-781. doi:10.1016/S0196-0644(98)70241-0
42. Bartlett JW, Walker PL. Management of calcium channel blocker toxicity in the pediatric patient. *J Pediatr Pharmacol Ther*. 2019;24(5):378-389. doi:10.5863/1551-6776-24.5.378
43. Krenz JR, Kaakeh Y. An Overview of hyperinsulinemic-euglycemic therapy in calcium channel blocker and β-blocker overdose. *Pharmacotherapy*. 2018;38(11):1130-1142. doi:10.1002/phar.2177
44. Doepker B, Healy W, Cortez E, Adkins EJ. High-dose insulin and intravenous lipid emulsion therapy for cardiogenic shock induced by intentional calcium-channel blocker and beta-blocker overdose: a case series. *J Emerg Med*. 2014;46(4):486-490. doi:10.1016/j.jemermed.2013.08.135
45. Tunca Sahin G, Ozturk E, Kasar T, Guzeltas A, Ergul Y. Sustained tachyarrhythmia in children younger than 1 year of age: six year single-center experience. *Pediatr Int*. 2018;60(2):115-121. doi:10.1111/ped.13445
46. Roeleveld PP, Zwijsen EG. Treatment strategies for paradoxical hypertension following surgical correction of coarctation of the aorta in children. *World J Pediatr Congenit Heart Surg*. 2017;8(3):321-331. doi:10.1177/2150135117690104
47. Wiest DB, Haney JS. Clinical pharmacokinetics and therapeutic efficacy of esmolol. *Clin Pharmacokinet*. 2012;51(6):347-356. doi:10.2165/11631590-000000000-00000
48. Tabbutt S, Nicolson SC, Adamson PC, et al. The safety, efficacy, and pharmacokinetics of esmolol for blood pressure control immediately after repair of coarctation of the aorta in infants and children: a multicenter, double-blind, randomized trial. *J Thorac Cardiovasc Surg*. 2008;136(2):321-338. doi:10.1016/j.jtcvs.2007.09.086
49. Gui P, Wu Q, Wu J, Yao S. Protective effect of esmolol on myocardial ischemic injury during open heart surgery in children. *Paediatr Anaesth*. 2013;23(3):217-221. doi:10.1111/pan.12117
50. Cuneo BF, Zales VR, Blahunka PC, Benson DW. Pharmacodynamics and pharmacokinetics of esmolol, a short-acting β-blocking agent, in children. *Pediatr Cardiol*. 1994;15(6):296-301. doi:10.1007/BF00798123
51. Pfammatter JP, Paul T, Lehmann C, Kallfelz HC. Efficacy and proarrhythmia of oral sotalol in pediatric patients. *J Am Coll Cardiol*. 1995;26(4):1002-1007. doi:10.1016/0735-1097(95)00268-3
52. Beaufort-Krol GCM, Bink-Boelkens MTHE. Sotalol for atrial tachycardias after surgery for congenital heart disease. *Pacing Clin Electrophysiol*. 1997;20:2125-2129. doi:10.1111/j.1540-8159.1997.tb03642.x
53. Borquez AA, Aljohani OA, Williams MR, Perry JC. Intravenous sotalol in the young: safe and effective treatment with standardized protocols. *JACC Clin Electrophysiol*. 2020;6(4):425-432. doi:10.1016/j.jacep.2019.11.019
54. Malloy-Walton LE, Von Bergen NH, Balaji S, et al. IV sotalol use in pediatric and congenital heart patients: a multicenter registry study. *J Am Heart Assoc*. 2022;11(9):e024375. doi:10.1161/JAHA.121.024375
55. Zhang Y, Dempsey C, Hancox J. The basis for low-affinity herg potassium channel block by sotalol. *J Pharmacol Pharmacother*. 2017;8(3):130-131. doi:10.4103/jpp.JPP_69_17
56. Chung MK, Schweikert RA, Wilkoff BL, et al. Is hospital admission for initiation of antiarrhythmic therapy with sotalol for atrial arrhythmias required? Yield of in-hospital monitoring and prediction of risk for significant arrhythmia complications. *J Am Coll Cardiol*. 1998;32(1):169-176. doi:10.1016/S0735-1097(98)00189-2
57. Bouchard J, Shepherd G, Hoffman RS, et al. Extracorporeal treatment for poisoning to beta-adrenergic antagonists: systematic review and recommendations from the EXTRIP workgroup. *Crit Care*. 2021;25(1):201. doi:10.1186/s13054-021-03585-7
58. Hamilton D, Nandkeolyar S, Lan H, et al. Amiodarone: a comprehensive guide for clinicians. *Am J Cardiovasc Drugs*. 2020;20(6):549-558. doi:10.1007/s40256-020-00401-5
59. Saul JP, Scott WA, Brown S, et al. Intravenous amiodarone for incessant tachyarrhythmias in children: a randomized, double-blind, antiarrhythmic drug trial. *Circulation*. 2005;112(22):3470-3477. doi:10.1161/CIRCULATIONAHA.105.534149
60. Saul JP, Ross B, Schaffer MS, et al. Pharmacokinetics and pharmacodynamics of sotalol in a pediatric population with supraventricular and ventricular tachyarrhythmia. *Clin Pharmacol Ther*. 2001;69(3):145-157. doi:10.1067/mcp.2001.113795
61. Singh BN, Williams EMV. The effect of amiodarone, a new anti-anginal drug, on cardiac muscle. *Br J Pharmacol*. 1970;39(4):657-667. doi:10.1111/j.1476-5381.1970.tb09891.x
62. Charlier R. Cardiac actions in the dog of a new antagonist of adrenergic excitation which does not produce competitive blockade of adrenoceptors. *Br J Pharmacol*. 1970;39(4):668-674. doi:10.1111/j.1476-5381.1970.tb09892.x
63. Mason JW, Hondeghem LM, Katzung BG. Amiodarone blocks inactivated cardiac sodium channels. *Pflugers Arch*. 1983;396(1):79-81. doi:10.1007/BF00584702
64. Ramusovic S, Läer S, Meibohm B, Lagler FB, Paul T. Pharmacokinetics of intravenous amiodarone in children. *Arch Dis Child*. 2013;98:989-993. doi:10.1136/archdischild-2013-304483
65. Maghrabi K, Uzun O, Kirsh JA, Balaji S, Von Bergen NH, Sanatani S. Cardiovascular collapse with intravenous amiodarone in children: a multicenter retrospective cohort study. *Pediatr Cardiol*. 2019;40(5):925-933. doi:10.1007/s00246-019-02090-7
66. Daniels CJ, Schutte DA, Hammond S, Franklin WH. Acute pulmonary toxicity in an infant from intravenous amiodarone. *Am J Cardiol*. 1997;80(8):1113-1116. doi:10.1016/S0002-9149(97)00619-X
67. Kothari SS, Balijepally S, Taneja K. Amiodarone-induced pulmonary toxicity in an adolescent. *Cardiol Young*. 1999;9(2):194-196. doi:10.1017/s1047951100008441
68. Niiya T, Litonius E, Petj L, Neuvonen PJ, Rosenberg PH. Intravenous lipid emulsion sequesters amiodarone in plasma and eliminates its hypotensive action in pigs. *Ann Emerg Med*. 2010;56(4):402-408.e2. doi:10.1016/j.annemergmed.2010.06.001
69. Ferguson JD, DiMarco JP. Contemporary management of paroxysmal supraventricular tachycardia. *Circulation*. 2003;107(8):1096-1099. doi:10.1161/01.CIR.0000059743.36226.E8
70. Pass RH, Liberman L, Al-Fayaddh M, Flynn P, Hordof AJ. Continuous intravenous diltiazem infusion for short-term ventricular rate control in children. *Am J Cardiol*. 2000;86(5):559-562. doi:10.1016/S0002-9149(00)01016-X
71. Gill JS, Ward DE, Camm AJ. Comparison of verapamil and diltiazem in the suppression of idiopathic ventricular tachycardia. *Pacing Clin Electrophysiol*. 1992;15:2122-2126. doi:10.1111/j.1540-8159.1992.tb03033.x
72. Sahney S. A review of calcium channel antagonists in the treatment of pediatric hypertension. *Pediatric Drugs*. 2006;8(6):357-373. doi:10.2165/00148581-200608060-00004
73. al Edreesi M, Caillé G, Dupuis C, Théoret Y, Paradis K. Safety, tolerability, and pharmacokinetic actions of diltiazem in pediatric liver transplant recipients on cyclosporine. *Liver Transpl Surg*. 1995;1(6):383-388. doi:10.1002/lt.500010609

74. Epstein FH, Braunwald E. Mechanism of action of calcium-channel-blocking agents. *N Engl J Med*. 1982;307(26):1618-1627. doi:10.1056/nejm198212233072605
75. Nakaya H, Schwartz A, Millard RW. Reflex chronotropic and inotropic effects of calcium channel-blocking agents in conscious dogs: diltiazem, verapamil, and nifedipine compared. *Circ Res*. 1983;52(3):302-311. doi:10.1161/01.RES.52.3.302
76. Levine M, Boyer EW, Pozner CN, et al. Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Crit Care Med*. 2007;35(9):2071-2075. doi:10.1097/01.CCM.0000278916.04569.23
77. Boyd RA, Chin SK, Don-Pedro O, et al. The pharmacokinetics and pharmacodynamics of diltiazem and its metabolites in healthy adults after a single oral dose. *Clin Pharmacol Ther*. 1989;46(4):408-419. doi:10.1038/clpt.1989.159
78. Lerman BB, Belardinelli L. Cardiac electrophysiology of adenosine: basic and clinical concepts. *Circulation*. 1991;83(5):1499-1509. doi:10.1161/01.CIR.83.5.1499
79. Samsel M, Dzierzbicka K, Trzonkowski P. Adenosine, its analogues and conjugates. *Postepy Hig Med Dosw*. 2013;67:1189-1203. doi:10.5604/17322693.1078588
80. Belhassen B, Pelleg A. Electrophysiologic effects of adenosine triphosphate and adenosine on the mammalian heart: clinical and experimental aspects. *J Am Coll Cardiol*. 1984;4(2):414-424. doi:10.1016/S0735-1097(84)80233-8
81. Freilich A, Tepper D. Adenosine and its cardiovascular effects. *Am Heart J*. 1992;123(5):1324-1328. doi:10.1016/0002-8703(92)91040-8
82. Moser GH, Schrader J, Deussen A. Turnover of adenosine in plasma of human and dog blood. *Am J Physiol*. 1989;256:C799-C806. doi:10.1152/ajpcell.1989.256.4.c799
83. Crosson JE, Etheridge SP, Milstein S, Hesslein PS, Dunnigan A. Therapeutic and diagnostic utility of Adenosine during tachycardia evaluation in children. *Am J Cardiol*. 1994;74(2):155-160. doi:10.1016/0002-9149(94)90089-2
84. Till J, Shinebourne EA, Rigby ML, Clarke B, Ward DE, Rowland E. Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children. *Br Heart J*. 1989;62(3):204-211. doi:10.1136/hrt.62.3.204
85. DeGroff CG, Silka MJ. Bronchospasm after intravenous administration of adenosine in a patient with asthma. *J Pediatr*. 1994;125:822-823. doi:10.1016/S0022-3476(06)80191-5
86. Ellenbogen KA, Thames MD, DiMarco JP, Sheehan H, Lerman BB. Electrophysiological effects of adenosine in the transplanted human heart: evidence of supersensitivity. *Circulation*. 1990;81(3):821-828. doi:10.1161/01.CIR.81.3.821
87. Hage K, Fischer C, Knebel NG, Bühl K. Estimation of the absolute bioavailability of flecainide using stable isotope technique. *Eur J Clin Pharmacol*. 1995;48(1):51-55. doi:10.1007/BF00202172
88. Nace GS, Wood AJJ. Pharmacokinetics of long acting propranolol implications for therapeutic use. *Clin Pharmacokinet*. 1987;13(1):51-64. doi:10.2165/00003088-198713010-00003
89. Liedholm H, W»hlin-Boll E, Melander A. Mechanisms and variations in the food effect on propranolol bioavailability. *Eur J Clin Pharmacol*. 1990;38(5):469-475. doi:10.1007/BF02336686
90. Paul T, Pfammatter JP. Adenosine: an effective and safe antiarrhythmic drug in pediatrics. *Pediatr Cardiol*. 1997;18:118-126. doi:10.1007/s002469900129
91. Hegenbarth MA, Snodgrass W, Frattarelli D, et al. Preparing for pediatric emergencies: drugs to consider. *Pediatrics*. 2008. doi:10.1542/peds.2007-3284
92. Bauer LA. Applied clinical pharmacokinetics. 2nd ed. McGraw-Hill Education; 2008.
93. Weinberg L. Pharmacokinetics and pharmacodynamics of lignocaine: a review. *World J Anesthesiol*. 2015;4(2):17-29. doi:10.5313/wja.v4.i2.17
94. Lehnert A, Foissac F, Bouazza N, et al. Amiodarone/N-desethylamiodarone population pharmacokinetics in paediatric patients. *Br J Clin Pharmacol*. 2022;88(12):5369-5377. doi:10.1111/bcp.15458
95. Singh S, Gelband H, Mehta AV, Kessler K, Casta A, Pickoff AS. Procainamide elimination kinetics in pediatric patients. *Clin Pharmacol Ther*. 1982;32(5):607-611. doi:10.1038/clpt.1982.210
96. Tjandra-Maga T, Verbesselt R, van Hecken A, Mullie A, De Schepper P. Flecainide: single and multiple oral dose kinetics, absolute bioavailability and effect of food and antacid in man. *Br J Clin Pharmacol*. 1986;22(3):309-316. doi:10.1111/j.1365-2125.1986.tb02892.x

How to cite this article: Geanacopoulos AT, Zielonka B, Fox MT, et al. Pediatric antiarrhythmics and toxicity: A clinical review. *JACEP Open*. 2024;5:11111. https://doi.org/10.1002/emp2.13090