Amiodarone–an "old" drug with new recommendations

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Amiodarone has gained recognition as an antiarrhythmic medication after recent publication of the newly revised American Heart Association guidelines for pediatric resuscitation. Although support for the widespread use of amiodarone in adults has been supported by research, the few pediatric studies demonstrate limited efficacy and highlight the need for additional data. Because of the nature of the need for this type of resuscitation medication, controlled prospective studies will be difficult to obtain if not morally contraindicated. This article reviews the properties of amiodarone and the pertinent pediatric studies to provide healthcare providers supplemental information regarding amiodarone when choosing antiarrhythmics for acute resuscitation. Individual providers need to discern whether the pediatric data available supports widespread acceptance into current treatment regimens. Curr Opin Pediatr 2003, 15:193–199

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Current Opinion in Pediatrics 2003, 15:193–199

Abbreviations

AHA	American Heart Association
AV	atrioventricular
ECG	electrocardiogram
JET	junctional ectopic tachycardias
SVT	supraventricular tachycardia
Vfib	ventricular fibrillation
VT	ventricular tachycardia

ISSN 1040–8703

Antiarrhythmic medications have varied indications in the treatment of cardiac arrhythmias. Current practice draws on these medications to terminate arrhythmias acutely, to use as maintenance therapy, or to use as an adjunct to other treatments (*eg*, defibrillation, ablation, or pacing). Amiodarone has been used to treat supraventricular tachycardia (SVT); junctional ectopic tachycardias (JET); atrial fibrillation or atrial flutter or atrial ectopic tachycardia; and ventricular tachycardia (VT) or ventricular fibrillation (Vfib)[1–11••]. The efficacy in treating each of these arrhythmias ranges from anecdotal reports to small study populations with variable methods and success in the pediatric population.

Antiarrhythmic medication classification

The different classes of antiarrhythmics are subdivided by their mechanism of action, summarized in the Vaughn-Williams classification system (Table 1)[12]. The effects on cardiac electrophysiology are seen as varying conduction delays or the depression of automaticity. Most antiarrhythmics exert their effect through channel blockade or receptor blockade or regulation. Figure 1 illustrates the relationship between ion channel flux and action potential phases [13].

Amiodarone is most often referred to as a class III antiarrhythmic (potassium channel blocker), which prolongs phase 3, thereby prolonging the effective refractory period. Whereas class III is its traditional classification, it is interesting to note that amiodarone has activity in multiple classes. Amiodarone also has properties of sodium and calcium channel blockade [14] as well as decreasing beta-adrenoreceptors producing effectual beta blockade [15–19]. The principal effects are the delay in repolarization by prolonging the action potential duration and effective refractory period [20].

Amiodarone is available in two preparations, oral and intravenous (IV). The route of administration, coupled with duration of therapy and physical properties of each form, effect somewhat different results and is summarized in Table 2 [21]. Generally speaking, the IV form lacks two important effects: minimal antithyroid action [22] and its metabolite is not accumulated in serum or tissue sufficiently to generate remarkable action [23].

Emphasis should be placed on the American Heart Association (AHA) guidelines for use of amiodarone *or* an

Table 1. Vaughn-Williams classification system

Class I: Na channel blockers; depress phase 0, increase refractory period, delay return of excitability, and resting membrane potential may be depressed
IA: quinidine, procainamide, disopyramide
IB: lidocaine, mexilitine, tocainide
IC: flecainide, propafenone, encainide
Class II: beta blockers; inhibit catecholamine dependent spontaneous depolarization of phase 4 (automaticity is slowed as is AV conduction)
Propanolol, timolol, esmolol, atenolol
Class III: K channel blockers; prolong phase 3, prolong the effective refractory period
Amiodarone, sotalol, bretylium, NAPA, ibutalide
Class IV: Ca channel blockers; prolong conduction and increase nodal and bundle of His refractory time
Verapamil, diltiazem, nifedipine
Class V: miscellaneous
Adenosine: slows sinus rhythm and AV conduction
Digoxin: at high doses, increases phase 4 slope and decreases resting membrane potential, decreases conduction velocity, increases vagal tone, and decreases sympathetic tone

Adapted with permission from [32].
Na, sodium; AV, atrioventricular; K, potassium; Ca, calcium.

alternative antiarrhythmic. All healthcare providers should avoid concurrent use of amiodarone with a class I antiarrhythmic (procainamide or lidocaine) because all of these medications can prolong the QT interval.

Pharmacology and physical properties

Amiodarone is primarily metabolized in liver with primary excretion in bile and less than 1% renal excretion. It is highly protein bound, therefore not removed by dialysis. No current recommendations exist to alter dosing in light of hepatic or renal insufficiency. Its primary metabolite, *N*-desethylamiodarone, is equipotent as its parent compound for sodium channel blockade and a less potent calcium channel antagonist [18].

Serum amiodarone displays kinetics of rapid distribution and decline. Serum levels drop to 10% of peak value within 30 to 45 minutes from the end of infusion. It is highly lipophilic and rapidly distributes from plasma to peripheral tissues, such as fatty tissue, and erythrocyte membranes [18].

Adverse effects are variable and seen in multiple organ systems. Among the most concerning are amiodarone's cardiac effects—bradycardia and its proarrhythmic properties (Torsades de pointes, Vfib, sustained VT, and increased resistance to cardioversion) [2–4,6,7,20,24–26]. Other adverse effects include hypotension [5–7,9,26], thyroid dysfunction [1–4,27•], pulmonary toxicity [28–30], keratopathy, fever, nausea, local phlebitis, photosensitivity, skin discoloration, and hepatotoxicity [2,31]. Amiodarone decreases cytochrome P450 enzyme activity (CYP3A-mediated deethylation)[32]. This pharmacologic characteristic can result in increased serum concentrations of lidocaine, flecainide, digoxin, procainamide, warfarin, quinidine, phenytoin, and cyclosporin. It is incompatible with aminophylline, cefazolin, mezlocillin, heparin, and sodium bicarbonate. The latter incompatibility necessitates reconstitution of amiodarone in 5% dextrose water solution.

Recommended dosing and administration

The AHA guidelines [33] recommend amiodarone be dosed as a 5 mg/kg loading dose (IV or via intraosseous line) with a maximum of 15 mg/kg/d. The rate of infusion is dependent on which algorithm is followed—rapid bolus in pulseless Vfib or VT; otherwise, over 20 to 60 minutes for perfusing tachycardias. These dosing recommendations in children are derived from a number of case series and the adult literature.

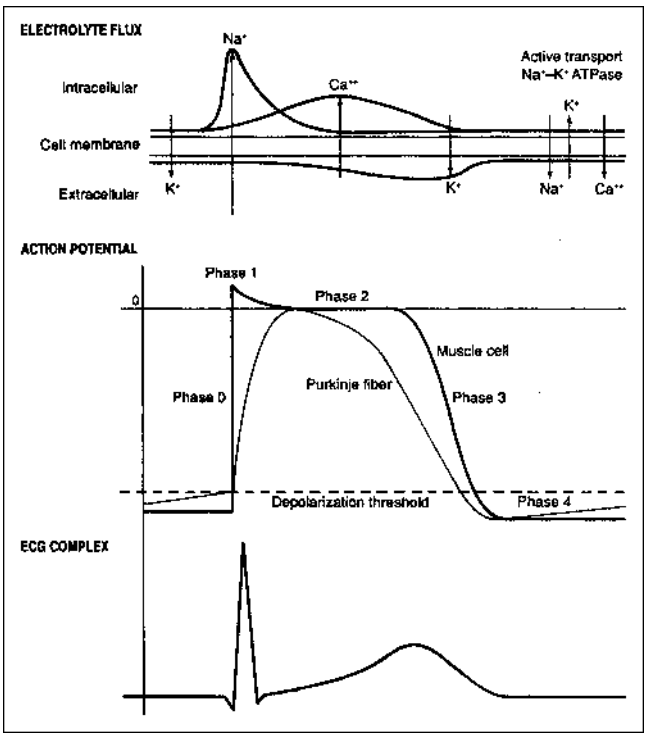
Both the concentration of the suspension and protection from light require specific considerations. The concentration of amiodarone should not exceed 2 mg/mL to reduce the risk of local phlebitis. Amiodarone should be stored in light protected ampules, but light protection is no longer needed once it has been reconstituted. It is stable in polyolefin or polyvinyl chloride (PVC) (if used within 2 hours) and glass (preferred for use longer than 2 hours duration). Reconstitution in evacuated flasks is not advised because of a buffer, which can cause precipitation [18].

Indications for supraventricular tachycardias

Amiodarone has indications for multiple SVT, both with and without adequate perfusion. Its role ranges from first-line therapy to adjunct therapy. The pharmacologic management of pediatric SVT is summarized in Table 3.

Atrial arrhythmias include flutter, fibrillation, and ectopic tachycardia. Fibrillation is best treated by direct current (DC) cardioversion if thrombus evaluation is negative. Amiodarone treatment for fibrillation is considered as equally effective as flecainide with controversial efficacy when compared with quinidine. Atrial flutter treatments include digoxin and cardioversion. Atrial ectopic tachycardia treatment includes digoxin or beta-blockers with amiodarone as an alternative. Patients with aflutter or sick sinus syndrome have been noted to develop significant bradycardia after treatment with amiodarone [2,6].

Figure 1. Cardiac electrophysiology



Ion channel flux and action potential phases correlation to ECG signal. Published with permission [13].

Junctional ectopic tachycardia is seen both as a congenital and a postoperative phenomenon. Postoperative JET (pJET) is a manifestation of atrioventricular (AV) block, with trauma usually at or near the bundle of His in conjunction with endogenous or administered catecholamines [31]. Seen in postoperative repairs of ventriculoseptal defect (VSD), AV canal, tetralogy of Fallot, and a Fontan procedure. Nonpharmacologic treatments include corporal cooling, removal of pressors, and overdrive pacing. Postoperative JET is exacerbated by propanolol and verapamil by reducing vagal tone, systemic vascular resistance, and myocardial contractility. Recent amiodarone efficacy cited with rapid IV infusion and low need for maintenance continuous infusion [7,9]. Congenital JET treatment includes amiodarone as an alternative after beta-blockers or digoxin; some success has been seen in infants with or without propanolol as an adjunct [11••].

Pediatric studies

Amiodarone studies in the pediatric population have been cited for several decades. The profiles of the populations studied and global results vary widely. The following are synopses of the major pediatric studies, with emphasis within each study focusing on key features of that particular study. Table 4 is a summary of these studies included for quick review and rapid comparison.

- Coumel and Fidelle [1]: 135 patients' responses to oral amiodarone therapy for idiopathic and postoperative arrhythmias with 55% of these resistant to other antiarrhythmics. The arrhythmias were a combination of atrial (69%), junctional (16%), and ventricular (15%). An oral load of 800 mg/d scaled by body surface area was given to patients 0 to 15 years of age for a mean of 4.1 months. Complete electrocardiographic (ECG) control was noted in 60% and partial control or clinical improvement was noted in 33%. No notable relation was seen to location, resistance to other drugs, or the presence of cardiomegaly. Side effects included thyroid dysfunction (2.2%), increased PR interval (30%), Wenckebach (2.2%), increased QRS duration (1.5%), corneal deposits (2.2%), and photosensitivity (3%).
- Garson *et al.* [2]: 39 patients, 6 weeks to 30 years of age, with resistant arrhythmias, including postoperative patients and patients with congenital heart disease. The population studied had atrial flutter (41%), VT (36%), or SVT (23%). Oral amiodarone, given at a starting dose of 10 mg/kg/day divided twice daily for a minimum of 3 days, was continued at a mean dose of 8.2 mg/kg/day. Oral amiodarone was found to be completely effective in 79% of patients overall, with success in 94% of those with atrial flutter, 79% of those with VT, and 71% of those with reentrant SVT. Three patients (7.7%) developed bradycardia requiring a pacemaker, all of whom had either atrial flutter or sick sinus syndrome. Side effects included rash, headache, nausea, neuropathy, corneal deposition, ECG changes, and thyroid dysfunction.
- Costigan *et al.* [3]: 15 patients with refractory arrhythmias (40% atrial, 27% ventricular, 33% combined). Of these patients, 40% had previously had cardioversion and 53% had congenital heart disease. These patients, aged 0.5 to 19.5 years, received a mean IV amiodarone load of 16.3 mg/kg for those patients

Table 2. Electropharmacologic effects of amiodarone

	Effect	
Cardiac effect	Oral amiodarone	IV amiodarone
Prolongation of AP duration in atrial and ventricular myocardium	+++	+
Na channel blockade	+++	++
Sinus node slowing of phase 4 depolarization	+++	+
Ca channel blockade	+++	+++
AV node ERP	↑↑↑	↑↑↑
Atrial ERP	↑↑↑	↑
Ventricular ERP	↑↑↑	↑
QRS interval	↑↑	↑
QT_c duration	↑↑↑	↑/–
Heart rate	↓↓	↓/–
Interaction with thyroid axis	+++	–

Adapted with permission from [19].
IV, intravenous; AP, action potential; Na, sodium; Ca, calcium; AV, atrioventricular; ERP, effective refractory period; QT_c, corrected QT.

Table 3. Pediatric SVT pharmacologic management

Arrhythmia	First-line agent	Alternative
Aflutter	Infant: (cardioversion), digoxin Child: digoxin	β-blocker, procainamide/quinidine, amiodarone, flecainide
Afib	Digoxin	β-blocker, procainamide/quinidine
AET	β-blocker ± digoxin	Amiodarone, propafenone, flecainide
JET		
pJET	IV amiodarone (± digoxin)	Propafenone
cJET	β-blocker or digoxin	Procainamide/quinidine, amiodarone/flecainide, propafenone

Adapted with permission from [29].
SVT, supraventricular tachycardia; Aflutter, atrial flutter; Afib, atrial fibrillation; AET, atrial ectopic tachycardia; JET, junctional ectopic tachycardia; pJET, postoperative JET; cJET, congenital JET; IV, intravenous.

older than 6 years of age with a significant, dramatic range for those patients less than 6 years of age. Mean maintenance therapy for those older than 5 years of age was 7.5 ± 1.2 mg/kg/day, again with a dramatic range for those less than 5 years of age. A satisfactory response was noted in 87% of patients, including prompt abolition in 53%. Clinical status was improved or delayed in 33%. Amiodarone was discontinued in 13% of these patients because of the development of a rash or Vfib. The Vfib developed during the treatment of atrial flutter. Hypothyroidism was noted in 20% of patients and cited to be a similar incidence to that in adults in iodine sufficient areas. This study commented on how amiodarone affects thyroid metabolism by two mechanisms: competitive inhibition of 5′-monodeiodinase centrally and peripherally and by direct effect because of its high iodine content (Wolff-Chaikoff effect).

- Pongiglione *et al.* [4]: 47 patients aged 23 weeks (mother treated for fetal tachycardia in 1) to 29 years

Table 4. Select pediatric amiodarone studies

Study, year	IV/PO	n	Idiopathic	Postop	CHD	WPW	S/p CV	Resistant	Success	Partial	Failure	Dc'd
Coumel and Fidelle, 1980	PO	135	28	82	0			74	81	45	9	0
	Atrial	93										
	Junctional	22										
	Ventricular	20										
Garson *et al.*, 1984	PO	39		14	35				31	3	5	0
	Aflutter	16							15			
	VT	14							11			
	Reentrant SVT	9							5			
Costigan *et al.*, 1986	IV	15			8		6		8	5	0	2
	Atrial	6										
	Ventricular	4										
	Combination	5										
Pongiglione *et al.*, 1991	PO	47							21	11	15	0
	VT	7										
	Syncope	16										
	Atach postop	11										
	SVT	13										
Perry *et al.*, 1993	IV	10					?		6	1	3	0
	VT	7							4			
	Atach	1							1			
	Jtach	1							1			
	Multiple	1										
Figa *et al.*, 1994	IV	30			18				21	7	2	0
	SVT	18										
	VT	12										
Soult *et al.*, 1995	IV	23			5	3			20	3?	3?	
	PSVT	23										
Perry *et al.*, 1996	IV	40		25				40	24	8	8	
	VT	7							5		2	
	AT	11							10		1	
	JET	14							5	8	1	
	SVT	3							2		1	
	VT/VF	5							2		3	

Summary presentation adapted with permission from [1–9].
CHD, congenital heart disease; WPW, Wolff-Parkinson-White; S/p CV, status-post cardioversion; Resistant, arrhythmia resistant to alternate therapy; Dc'd, amiodarone discontinued; PO, by mouth; Aflutter, atrial flutter; Vtach, ventricular tachycardia; SVT, supraventricular tachycardia; IV, intravenous; Atach, atrial tachycardia; Jtach, junctional tachycardia; PSVT, paroxysmal supraventricular tachycardia.

of age. These patients had either VT (15%), syncope of unknown etiology (34%), postoperative primary atrial tachycardia (23%), or SVT (28%). They were treated with an oral amiodarone load of 10 to 20 mg/kg, followed by maintenance therapy of 5 to 10 mg/kg/day for an average duration of 12 months. Amiodarone was cited as clinically useful in 68% (effective in 45% as a sole agent, ineffective but continued as an adjunct in 23%) and ineffective and withdrawn in 32%. Notable sequelae included Torsades de pointes and cardiac arrest in one patient each after 9 and 14 days of treatment.

- Perry *et al.* [5]: 10 patients with an age range of 6 days to 26 years treated with IV amiodarone for resistant life-threatening arrhythmias (70% Vtach, 10% each junctional tachycardia, atrial tachycardia, and multiple arrhythmia). Previous therapies included oral and IV medications and cardioversion. Intravenous amiodarone was loaded in 5 × 1 mg/kg aliquots over 5 to 10 minutes with 5 to 10 minutes between aliquots and subsequent maintenance therapy of 10 mg/kg/day for an average of 3 days. The arrhythmias showed complete resolution in 60% and slowing of Vtach in 1 patient to allow surgical cure of a hamartoma. The average loading dose at time of beneficial effect was 4.8 mg/kg. Both patients with a hamartoma had VT, neither of whom was cured with amiodarone alone. Hypotension developed in 40% during the loading phase, all of whom were responsive to volume or low-dose calcium bolus.
- Figa *et al.* [6]: 30 patients (31 episodes) with life-threatening tachyarrhythmias (SVT 60%, VT 40%). These patients, 1 day to 14 years of age (mean age 14 months), received an IV amiodarone load of 5 mg/kg over 1 hour followed by maintenance of 7.2 to 21.6 mg/kg/day for a mean of 5 days. Amiodarone was used as first-line therapy for 3 arrhythmias, in combination with digoxin in 15 and in the remaining 13 arrhythmias amiodarone was used after 1 to 5 medications. Amiodarone was found effective in 71% or partially effective in 23% (total of 94%) without predilection for arrhythmia or structurally normal heart. Bradycardia requiring pacing was noted in 10% during treatment with amiodarone alone. When amiodarone was used in conjunction with propafenone (Class I), ECG changes were noted in 17%: increased QT_c, QRS, and sick sinus syndrome progression. Bradycardia was noted in an additional 13% (4 of 30 patients) and 1 each of first- and third-degree blocks.
- Raja *et al.* [7]: 16 patients with JET associated with significant hemodynamic impairment after cardiopulmonary bypass. None of the patients studied had Wolff-Parkinson-White or rhythm abnormality preoperatively. The patients, 6 days to 14 years of age, received IV amiodarone loaded as 5 mg/kg over 1 hour, followed by 5 mg/kg over 12 hours and a repeat dose in some portion as needed for persistent JET. On average, the JET rates decreased 30 beats per minute (bpm) by 2 hours and 47 bpm at 24 hours. The average increase in systolic blood pressure (SBP) was 15 mmHg. "Late" bradycardia with hypotension and "late" asymptomatic bradycardia were reported in several patients, yet no hypotension was noted during the loading phase. Atrial pacing to provide AV synchrony was provided patients (63%).
- Soult *et al.* [8]: 23 patients, 9 days to 11 years of age, with paroxysmal supraventricular tachycardia (PSVT) received IV amiodarone loaded as 5 mg/kg over 5 minutes with repeat dosing in 15 minutes, as needed, then 10 mg/kg over 12 to 24 hours. A return to sinus rhythm was reported in 87% by 35 minutes with a cumulative dose of 12.75 ± 5.25 mg/kg. An additional 13% showed slowing of the tachycardia without resolution; 52% exhibited an unspecified hemodynamic instability.
- Perry *et al.* [9]: 40 patients (mean age 5.4 years, with 60% less than 2 years of age) received amiodarone treatment for resistant early postoperative tachycardia (VT 30%, atrial tachycardia 27.5%, JET 35%, SVT 7.5%). Intravenous amiodarone was loaded as 5 × 1 mg/kg aliquots over 5 to 10 minutes, then an afterload bolus of 1 to 5 mg/kg after 30 minutes (total mean load 6.3mg/kg) with a subsequent maintenance of 10 to 15 mg/kg/day. Amiodarone was not the first-line agent for any patient and no concurrent use of a class IC antiarrhythmic was reported. Postoperative tachycardia was reported in 25 of the 40 patients, with successful treatment with amiodarone in 21 of 25 (84%). Treatment of JET was notable in 13 of the 14 patients studied and a beneficial effect was noted during the initial amiodarone bolus where 5 converted to sinus rhythm and 8 slowed to allow improved function using atrial or AV sequential pacing. Four patients developed hypotension during the load and one patient developed bradycardia requiring temporary pacing.

The methodology in each of these studies varies significantly. Both studies by Perry *et al.* and that by Figa *et al.* most closely approximate the current dosing recommendations of a 5 mg/kg loading dose, however, the duration of infusion or subdivision into 5 × 1 mg/kg aliquots provide varied methods and differ from the current AHA guidelines. The population in each of these studies may have included postoperative patients, patients with congenital heart disease, patients with arrhythmia refractory to "first-line" agents, and patients who had prior cardioversion. The most notable adverse effects of the amiodarone used in these studies includes hypothyroidism, bradycardia requiring pacing, hypotension requiring fluid or calcium bolus, prolongation of several ECG in-

dices (PR, QRS, QT_c), and proarrhythmia (Torsades de pointes, cardiac arrest, sick sinus syndrome).

Amiodarone is a medication with varied function and roles when used to treat arrhythmias. The lack of a controlled prospective study guided the AHA recommendations as class indeterminate. However, given the circumstances in which we must use this medication, healthcare providers may find little leeway to stray from the current AHA guidelines. One must be prepared for the possible development of hypotension, bradycardia, or other arrhythmias in an acute situation warranting immediate intervention and possible termination of amiodarone therapy. Certain clinical scenarios might warrant lower threshold to empiric placement of pacing wires for postoperative management (atrial flutter) or pacemaker implantation (sick sinus syndrome). Intravascular fluid bolus with normal saline or calcium chloride bolus to address hypotension should be readily available. Special care must be taken to avoid concurrent use of amiodarone along with a class I antiarrhythmic. Lastly, healthcare providers are advised that amiodarone is one choice among several agents in the current AHA guidelines.

Conclusion

Amiodarone is an antiarrhythmic with a multifaceted mechanism of action lending itself to treating numerous supraventricular and ventricular arrhythmias. The current AHA recommendations to use amiodarone find little evidence substantiated by pediatric clinical studies, hence the class indeterminate designation by the AHA. Healthcare providers who include amiodarone in their acute treatment of SVT and VT or Vfib must do so with the caveat of a strong potential for adverse effects, ranging from bradycardia to hypotension to other cardiac abnormalities including arrest. The numerous side effects noted in the adult population will most likely bear out in the pediatric population as well once we have expanded our usage of amiodarone.

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