Intravenous amiodarone for acute pharmacological conversion of atrial fibrillation in the emergency department

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia seen in patients presenting to the emergency department (ED). Pharmacological conversion of atrial fibrillation to normal sinus rhythm (NSR) may be a feasible management strategy in selected patients. Recent guidelines have recommended intravenous amiodarone, a class III antiarrhythmic agent, for the conversion of AF to NSR. The purpose of this review is to examine the published evidence for the efficacy of IV amiodarone for the acute conversion of AF to NSR in the ED. Currently available data from 11 randomized, controlled trials and 3 meta analyses do not support the use of conventional doses of IV amiodarone for acute conversion in the ED. High dose IV or combined IV and oral administration may be effective as early as 8 hours in patients with recent-onset AF of ≤48 hour duration in patients without contraindications to these high dose regimens. There are no data to support the use of IV amiodarone for acute conversion in patients with an ejection fraction of <40% or clinical heart failure, so its use in these scenarios should be limited to symptomatic patients who are refractory to electrical conversion. More well-designed studies are required to determine the role of IV amiodarone for the acute conversion of AF in the ED.

Key words: amiodarone, atrial fibrillation, conversion, antiarrhythmic agents

RÉSUMÉ

La fibrillation auriculaire (FA) est l'arythmie la plus couramment rencontrée chez les patients se présentant au département d'urgence (DU). La conversion pharmacologique de la fibrillation auriculaire en rythme sinusal normal (RSN) pourrait se révéler une stratégie de prise en charge réalisable chez des patients sélectionnés. Des lignes directrices récentes ont recommandé le recours à l'amiodarone, un antirarythmique de classe III, pour la conversion de la FA en RSN. La présente revue avait comme objectif d'examiner les articles publiés traitant de l'efficacité de l'amiodarone IV pour la conversion d'une crise aiguë de FA en RSN au DU. Les données présentement disponibles provenant de 11 essais contrôlés randomisés et de trois méta-analyses n'étayent pas le recours à des doses conventionnelles d'amiodarone IV pour la conversion d'une crise aiguë au DU. L'administration IV à fortes doses ou l'administration combinée per os et IV d'amiodarone peut donner des résultats aussi tôt que huit heures après son administration pour des cas d'AF d'apparition récente, soit moins de 48 heures, chez des patients ne présentant aucune contre-indication pour ces traitements à fortes doses. Il n'existe aucune donnée qui appuie le recours de l'amiodarone IV pour la conversion d'une crise aiguë chez des patients dont la fraction d'éjection est inférieure à 40 % ou qui sont atteints d'insuffisance cardiaque. Son utilisation dans de telles circonstances devrait se limiter aux patients symptomatiques qui sont réfractaires à la conversion électrique. Des études mieux conçues s'imposent pour déterminer le rôle de l'amiodarone IV pour la conversion de crises aiguës de FA au DU.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of 2% in the general population.[1–3] Approximately 2.2 million people in the United States have AF.[1,4] The prevalence of AF is 0.5% in patients 50–59 years old and increases to 9% in patients 80–89 years of age.[1] In the Framingham Study, 1.7% of women and 2.2% of men developed AF during 38 years of follow-up.[5] With our aging population, AF prevalence is predicted to rise to more than 5.6 million by the year 2050, dramatically increasing the impact of AF-related symptoms, morbidity, mortality and health care costs.[3]

AF is the most common arrhythmia in patients presenting to the emergency department (ED), accounting for 35.1% of acute care visits for dysrhythmias. In addition, it is a concurrent problem in 6%–7% of medical and 5% of cardiovascular-related admissions from the ED.[6,7] Hospital admission rates are 50%–83% for patients with acute AF, with a mean length of stay of 1.7–5.0 days, and mean hospital costs of US$1989–$6692 per patient.[6–9] In patients who require admission, AF is associated with an increase in length of stay of 2.3–2.5 days, and higher medical costs.[10–12] Patients with uncomplicated AF can, however, be successfully treated and discharged home safely from the ED, with shorter mean lengths of stay and lower treatment costs.[13] Broader application of evidence-based pharmacotherapy for patients with acute AF presenting to the ED will ensure the safest, most effective and least costly treatment.

Therapeutic goals for acute AF may include 1) ventricular rate control with AV nodal blocking agents, 2) prevention of thromboembolic events with anticoagulants, and 3) conversion to normal sinus rhythm (NSR) with Vaughan Williams Class Ia, Ic, or III antiarrhythmic drugs.[14–18] Emergent electrical cardioversion is the modality of choice in hemodynamically unstable AF patients with serious signs or symptoms such as presyncope, hypotension, pulmonary edema or an acute coronary syndrome.[14–16] Thus, pharmacological methods of conversion are advised only in patients without emergent symptoms, or in patients who are refractory to electrical cardioversion.

Although amiodarone administered intravenously (IV) is effective for the acute management of ventricular dysrhythmias and is the agent of choice in several advanced cardiac life support (ACLS) algorithms,[15,19,20] the evidence for its use to convert acute AF is less convincing, and its inclusion in recent AF guidelines is controversial.[14–16,18,21–26] The 2000 ACLS Guidelines consider IV amiodarone (150-mg IV load over 15 min, followed by 60 mg/h for 6 hours, then 30 mg/h with repeat boluses of 150 mg IV as needed up to a maximum of 2.0 g/d) a Class IIa recommendation for conversion of AF of <48-h duration in patients with a normal ejection fraction, and a Class IIb recommendation for those with an ejection fraction of <40% or clinical heart failure.[15] Recently published international guidelines consider IV amiodarone (5–7 mg/kg over 30–60 min, followed by 1.2–1.8 g/d as a continuous IV infusion) a Class IIa recommendation for conversion of recent-onset AF of ≤7 days.[16] The purpose of this review is to systematically examine the best published evidence to determine the efficacy of IV amiodarone for the acute conversion of nonsurgical AF to normal sinus rhythm.

Pharmacology and pharmacokinetics

Amiodarone is highly lipophilic with a large volume of distribution (40–84 L/kg) due to extensive tissue uptake.[27] It is hepatically metabolized via CYP3A4 enzymes to an active metabolite called desethylamiodarone (DEA), which has unique antiarrhythmic properties.[27] Due to a long elimination half-life ranging from 20–47 days, steady state may not be achieved for months, so loading doses given over a prolonged period are required to rapidly achieve therapeutic serum concentrations and clinical effects.[27]

Although amiodarone is considered a Class III antiarrhythmic agent, it also possesses sodium, calcium, potassium and beta-blocking properties. The parent compound and DEA metabolite have unique electrophysiological properties that contribute to its clinical effects. Oral and IV amiodarone prolong the effective refractory period (ERP) at the AV node and slow intranodal conduction; however, only chronic oral dosing causes prolongation of the QTc interval and the atrial and ventricular ERP.[27,28] Accumulation of the active DEA metabolite with chronic dosing may prolong atrial ERP more than the parent compound, which may translate into significantly higher conversion rates.[25,29]

Although amiodarone is thought of as one of the safest antiarrhythmic agents in patients with a low ejection fraction or clinical heart failure, it has negative inotropic effects that can cause hypotension in patients with pre-existing left ventricular dysfunction. Those most susceptible include postcardiac surgery patients, critically ill patients in shock, and heart failure patients with an ejection fraction less than 35%.[30–32]

Clinical evidence

The efficacy of IV amiodarone for the acute conversion of AF has been studied in 14 randomized placebo- or rate-

controlled trials and in 3 meta analyses (Table 1).[33–46] Eleven of the 14 studies targeted patients with recent-onset AF of ≤7 days duration; however, it is important to note that all of the trials discussed actually enrolled patients within 48 hours of AF onset, a population of practical interest to ED practitioners.

Conventional dose trials

Five randomized, placebo- or rate-controlled trials have evaluated conventional doses of IV amiodarone (≤1600 mg/d) in patients with recent-onset AF (Table 1).[33–37] Noc and colleagues showed that a 5 mg/kg bolus of amiodarone converted significantly more patients than IV verapamil at 3 hours.[33] Cowan and coworkers studied patients with re-

cent-onset AF complicating myocardial infarction and found that 24-h conversion rates were no better with amiodarone (7 mg/kg bolus followed by an infusion rate up to 1500 mg/d) than with IV digoxin.[34] Donovan and cohorts found no difference in conversion rates between amiodarone (7 mg/kg) and placebo after 2 and 8 hours.[35] Galve and colleagues conducted the largest trial of conventional IV dosing, in which 100 patients were randomized to amiodarone (5 mg/kg IV over 30 min, followed by 1200 mg IV over 24 hours) or saline placebo.[36] At 24 hours there was no difference in conversion rates, and the groups had similar 2-week recurrence rates: 12% with amiodarone and 10% with placebo.[36] The only trial using sequential dosing with conventional IV loading and oral doses of amio-

Table 1. Randomized, placebo- or rate-controlled trials of intravenous amiodarone for acute conversion of recent-onset atrial fibrillation

Author, year, ref. no.	Onset	Mean duration	Agent(s)	Total dose (first 24 h)	N	End-point time	Success rate, %	Conversion time
Noc, 1990[33]	≤2 d	NR	Amiodarone	350 mg	13	3 h	A: 77*	Range
			Verapamil		11		V: 0	10-175 min
Cowan, 1986[34]	<48 h complicating MI	NR	Amiodarone	1500 mg	18	24 h	A: 83	NR
			Digoxin		16		D: 75	
Donovan, 1995[35]	≤72 h	11.5 h	Amiodarone	490 mg	32	2 h	A: 34, PL: 22	NR
		8.9 h	Placebo		32	8 h	A: 59, PL: 56	
Galve, 1996[36]	≤7 d	25 h	Amiodarone	1550 mg	50	24 h	A: 68	328 min
		18 h	Placebo		50		V: 60	332 min
Joseph, 2000[37]	<24 h	NR	Sotalol iv, po		40	4 h	S: 40, A: 31, D: 25	13.0 h†
			Amiodarone iv, po	1150 mg	39	24 h	S: 80,† A: 69, D: 50	18.1 h†
			Digoxin		36	48 h	S: 88,† A: 77, D: 58	26.9 h
Capucci, 1992[38]	≤7 d	28 h	Flecainide po		22	3 h	F: 68,*‡ A: 16, PL: 29	169 min*‡
		30 h	Amiodarone	2150 mg	19	8 h	F: 91,*‡ A: 37, PL: 48	217 min
		27 h	Placebo		21	12 h	F: 91,* A: 47	234 min
						24 h	F: 95, A: 89	
Hou, 1995[39]	Recent	14 h	Amiodarone	1620 mg	20	24 h	A: 95	2.5 h
		4 h	Digoxin		19		D: 74	6.5 h
Boriani, 1998[40]	≤7 d	29 h	Flecainide po		69	1 h	F: 13, PR: 8, A: 6, PL: 9	161 min
		31 h	Propafenone po		119	3 h	F: 57,‡ PR: 45,‡ A: 25, PL: 18	181 min
		29 h	Amiodarone	2150 mg	51	8 h	F: 75,‡ PR: 76,‡ A: 57,‡ PL: 37	225 min*‡
		30 h	Placebo		121			181 min
Cotter, 1999[41]	≤48 h	NR	Amiodarone	3000 mg	50	8 h	A: 62, PL: 58	NR
			Placebo		50	24 h	A: 92,‡ PL: 64	
Kochiadakis, 1998[42]	≤48 h	16 h	Amiodarone iv, po	3500 mg	48	24 h	A: 83‡	7 h‡
		18 h	Placebo		49		PL: 55	13 h
Vardas, 2000[43]	Recent, persistent and chronic	24 h	Amiodarone iv, po	2300 mg	108	1 h	A: 38,‡ PL: 25 (OR 1.84; 95% CI 1.01-3.33)	NR
		28 h	Placebo		100	24 h	A: 61,‡ PL: 40 (OR 2.35; 95% CI 1.35-41.1)	
						30 d	A: 81,‡ PL: 40 (OR 6.21; 95% CI 3.33-11.57)	

*p < 0.05 for comparison between agents; †p < 0.05 for comparison v. digoxin; ‡p < 0.05 v. placebo
AF = atrial fibrillation; NR = not reported; A = amiodarone; V = verapamil; D = digoxin; PL = placebo; S = Sotalol; iv = intravenous; po = by mouth; F = flecainide; PR = propafenone

darone found no benefit at 4, 24 or 48 hours compared to digoxin, prior to electrical cardioversion.[37] In summary, conventional doses of amiodarone appear to have no effect on the acute conversion of recent-onset AF to NSR.

High dose trials

Six trials have evaluated high-dose IV amiodarone (>1600 mg/d) either by administering larger IV doses or by combining IV and oral administration (Table 1).[38–43] In a small trial, Capucci and colleagues compared a 5-mg/kg IV amiodarone bolus followed by a 75-mg/h infusion (1800 mg/d) vs. a single dose of flecainide or placebo.[38] In this study, amiodarone was no more effective than placebo at any point within 24 hours, and was significantly less effective than flecainide at 3, 8 and 12 hours.

Boriani and coworkers compared the same amiodarone regimen to oral flecainide and oral propafenone in a larger trial involving 360 patients.[40] At 8 hours, amiodarone was more effective than placebo but less effective than flecainide or propafenone, although statistical significance was not assessed for the latter comparisons.[40]

One randomized trial[39] investigated a tailored infusion of high-dose IV amiodarone in recent-onset AF in an attempt to attain therapeutic plasma concentrations within 1 hour and maintain them for 24 hours. This study showed that, while IV amiodarone controlled ventricular response rates better than digoxin from 1–8 hours, it was no more effective in achieving 24-h conversion.

Cotter and cohorts compared a high-dose amiodarone infusion (125 mg/h) to placebo and found no difference at 8 hours, but higher conversion rates at 24 hours with amiodarone.[41] Kochiadakis and colleagues found that amiodarone (300-mg bolus plus 20-mg/kg/d infusion, with concomitant oral amiodarone at 600 mg three times daily) led to significantly higher 24-h conversion rates than placebo.[42] Vardas and colleagues showed that this IV amiodarone regimen, with a lower oral dosage (200 mg, 3 times daily) was associated with more successful conversions than placebo at 1 and 24 hours in a mix of recent-onset and chronic AF patients;[43] however, benefit was limited to patients with recent-onset AF, as none of the chronic AF patients converted to NSR within 24 hours.[43] In summary, high-dose amiodarone, using larger daily IV doses or combining oral and IV doses, is more effective than placebo for converting recent-onset AF to normal sinus rhythm. It is important to note that the high-dose amiodarone trials had strict enrollment criteria similar to those for Class Ic agents, and excluded patients with NYHA (New York Heart Association) Class II–IV functional status.[38,40–43]

Meta analyses

Three meta-analyses have examined the use of IV amiodarone for conversion of AF to NSR.[44–46] Miller and colleagues included data from 3 randomized placebo- or rate-controlled trials that examined the use of antiarrhythmic agents for conversion of nonsurgical AF prior to May 1998.[44] Assuming a spontaneous conversion rate of 30%, IV amiodarone conferred a strong trend toward increased conversion (odds ratio [OR] = 5.7; 95% confidence interval [CI], 1.0–33.4).[44] Hilleman and cohorts conducted a meta analysis of randomized trials published before March 2001, comparing amiodarone to placebo or active controls (including digoxin and verapamil) in the conversion of surgical and nonsurgical AF of <7 days duration.[45] Intravenous amiodarone was associated with significantly higher conversion rates (82.4%; 95% CI, 61%–92%) than placebo (59.7%; 95% CI, 49%–60%), with a corresponding number needed to treat (NNT) of 5 ($p = 0.03$).[45] Conversely, the data showed no significant difference between IV amiodarone and "active" control agents. Finally, Nichol and colleagues analyzed randomized controlled trials published up to August 2001 that compared various antiarrhythmic agents to placebo for conversion of AF.[46] Pooled together, class III agents, including IV and oral amiodarone, sotalol, ibutilide and dofetilide, were significantly more effective than placebo in achieving NSR in studies with short-term (<7 day) follow-up (absolute risk reduction [ARR] = 17.3%; 95% CI, 9.6%–25%; $p = 0.0002$; NNT = 6) and long-term (≥7 day) follow-up (ARR = 17.6%; 95% CI, 3.3%–31.9%; $p = 0.03$; NNT = 6).[46] This study failed to show that IV or oral amiodarone was associated with significantly different conversion rates than other "active" agents, including digoxin, verapamil, quinidine, procainamide, flecainide and propafenone (ARR = 2.7%; 95% CI, –51.2%–56.7%; $p = 0.64$).

Adverse effects

Amiodarone has been well tolerated in randomized controlled trials, causing mostly minor adverse drug reactions (ADRs) such as bradycardia, phlebitis and mild hypotension sometimes requiring IV fluids.[33,36,38–40,43] Serious ADRs causing drug discontinuation included symptomatic hypotension requiring fluids and inotropes,[35] congestive heart failure in a patient with underlying ventricular dysfunction,[39] significant bradycardia,[41] cardiac arrest in a critically-ill patient[39] and an allergic reaction.[42] There were, however, no statistically significant differences between amiodarone and placebo in minor or major ADRs, or withdrawals due to ADRs in any of the randomized trials. In

the meta analysis by Hilleman and colleagues, IV amiodarone was associated with significantly higher ADR rates (27%; 95% CI, 17%–35%) than placebo (11%; 95% CI, 9%–15%), with a number needed to harm (NNH) of 7 (*p* = 0.02).[45]

Limitations of the evidence

Utilization of antiarrhythmic therapy has historically been based on presumed mechanisms of action, pathophysiological rationale, unsystematic observations, intuition and clinical experience rather than evidence from high-quality clinical trials. Due to the high rate of spontaneous conversion with recent-onset AF, early studies without placebo comparators perpetuated the belief that digoxin may be effective for the conversion of AF.[18] Subsequent placebo-controlled trials have established that neither digoxin, beta-blockers nor calcium-channel blockers are effective for AF conversion, and that these drugs can be used as control agents in conversion studies.[18,24]

Despite the inclusion of only randomized placebo- or rate-controlled clinical trials in this review, there are some important limitations to the literature. Many of the trials were small and lacked the statistical power to show a difference between the agents studied. Some of the studies were unblinded and others enrolled poorly defined patient groups. Most did not report confidence intervals or specify the precision of the absolute treatment effect. Furthermore, most of the trials had a short period of follow-up, so the duration of conversion and overall clinical importance of the pharmacological intervention could not be assessed. Adverse drug reactions and withdrawals were often poorly reported, and most trials did not define criteria for withdrawals due to ADRs.

The meta-analyses also have serious limitations. The study by Miller and cohorts failed to identify and include 3 published placebo-controlled trials,[35,36,38] analyzed statistically heterogeneous data and assumed a 30% spontaneous conversion rate rather than using actual conversion rates from published clinical trials.[44] Hilleman and coworkers utilized a limited search strategy, failed to identify and include 3 published placebo-controlled trials,[37,40,42] included surgical and nonsurgical AF patients, failed to assess study quality, incorporated data from both AF and atrial flutter patients, included rate control agents in "active" treatment comparisons for conversion, and did not report results of statistical heterogeneity testing.[45] Nichol and colleagues pooled studies designed to assess conversion and maintenance therapy, and only reported the proportion of patients in NSR at the time of latest follow-up. In addition, these investigators included surgical and nonsurgical AF patients, incorporated data from both AF and atrial flutter patients, included rate control agents in "active" treatment comparisons for conversion, and did not report results of statistical heterogeneity testing.[46]

Many questions remain unanswered. In particular, there is a lack of well-designed studies of antiarrhythmic interventions for patients with heart failure.[47,48] Despite being given a Class IIb recommendation for conversion of recent-onset AF in patients with an ejection fraction of <40% or clinical heart failure, no acute conversion study has examined the use of IV amiodarone in this population. Moreover, no studies of sufficient power have clarified the optimal dose of IV amiodarone for acute conversion, or evaluated ED duration of treatment, admission rates, length of stay, or pharmacoeconomic endpoints with its use.

Emergency medicine perspectives

Unlike many other acute dysrhythmias, AF often reverts spontaneously to sinus rhythm, and observational studies suggest cumulative spontaneous conversion rates of 47%–68% by 24 hours.[8,49] The median (and range) spontaneous conversion rates in randomized placebo- and rate-controlled studies of recent-onset AF ≤7 days are 13% (3%–28%) at 1 hour, 11% (8%–22%) at 2 hours, 18% (10%–29%) at 3 hours, 25% (17%–33%) at 4 hours, 31% (17%–47%) at 6 hours, 39% (24%–58%) at 8 hours, 38% (14%–58%) at 12 hours, 58% (27%–88%) at 24 hours, and 67% (41%–76%) at 48 hours after presentation (Figure 1).[25] Consequently, in order to demonstrate a statistically significant effect on acute conversion, antiarrhythmic agents must work rapidly, before spontaneous conversion rates in placebo groups nullify their effect over time, and clinical trials must incorporate placebo or rate control comparators to determine whether antiarrhythmic agents are actually converting AF to NSR. Recent evidence-based international guidelines base their recommendations on less stringent levels of evidence developed for life-threatening dysrhythmias.[15,16,25] This may lead to an overestimation of the value of antiarrhythmic agents for acute conversion of AF and promote widespread utilization of unproven therapies.

Based on current evidence, there are no data to support the use of conventionally dosed IV amiodarone for the acute conversion of AF to NSR in the ED. High-dose IV or combined IV and oral administration may be effective as early as 8 hours in patients with recent-onset AF in patients who do not have contraindications to these regimens. The cost of amiodarone is substantial (Can$160.65
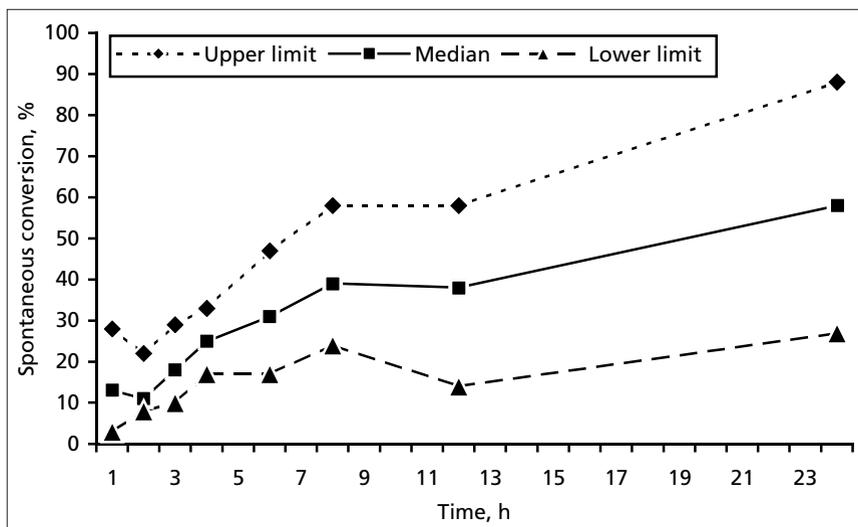
Fig. 1. Spontaneous conversion rates in placebo or rate-controlled studies of patients with recent-onset atrial fibrillation ≤7 days

for a 5-mg/kg load and 75-mg/h infusion for 8 hours), and it is important to note that patients without contraindications to high-dose amiodarone are also candidates for other less costly agents that effectively convert recent-onset AF to NSR.

Oral propafenone has been studied more than any other antiarrhythmic agent for the acute conversion of recent-onset AF, and is effective as early as 3 hours after a single 600-mg dose, at a cost of Can$2.86.[15,16,25,50,51] Based on one placebo-controlled trial, IV procainamide is also effective as early as 1 hour, at a cost of Can$6.05.[15,16,25,52] Importantly, there are no data to support the use of IV amiodarone for acute conversion in patients with an ejection fraction of <40% or clinical heart failure. Its use in these scenarios should be limited to symptomatic patients who are refractory to electrical cardioversion.

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