Clinical Use of Intravenous Amiodarone for Ventricular Arrhythmias

Introduction

- Current emergent therapy for cardiac arrhythmias often involves the use of intravenous antiarrhythmic agents, but their value in improving survival to the hospital has been questioned.[1]
- Neither lidocaine nor bretylium has been shown in controlled clinical trials to improve out-of-hospital survival in the resuscitation setting.
- Amiodarone has gained increased acceptance recently because of its diverse antiarrhythmic activity. Because of the strong evidence supporting amiodarone, it has been added to the guidelines for Advanced Cardiovascular Life Support (ACLS).[2]
- Amiodarone is the only antiarrhythmic agent that shows antiarrhythmic properties from all four Vaughan Williams classes (Figure 1).[1,3]

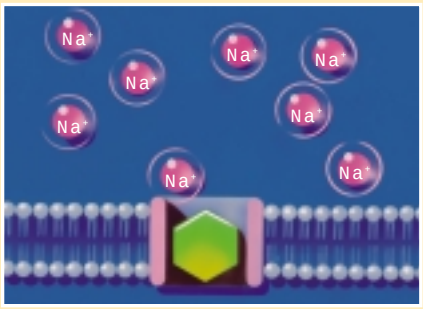
Amiodarone Pharmacology

- The diverse pharmacological actions of amiodarone also produce many important hemodynamic effects.[1,3]
  - Dilates coronary arteries
  - Increases coronary blood supply
  - Causes peripheral arterial vasodilation
  - Decreases systemic vascular resistance
  - Improves cardiac pump performance in patients with impaired LV function

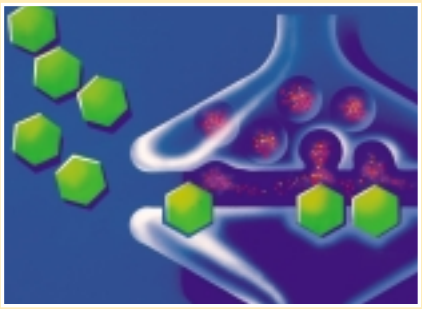
Figure 1

Vaughan Williams Classification of Antiarrhythmic Drugs

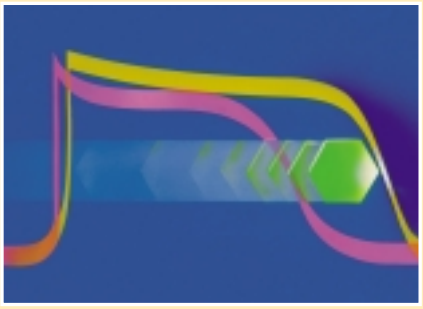
Class I effect
Sodium channel blockade



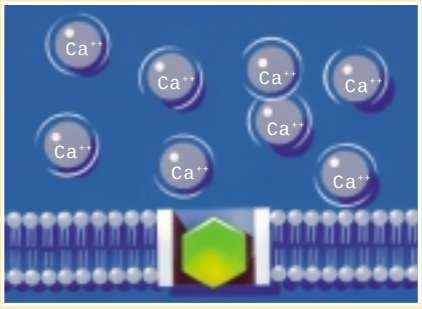
Class II effect
Noncompetitive alpha- and beta-blockade



Class III effect
Potassium channel blockade

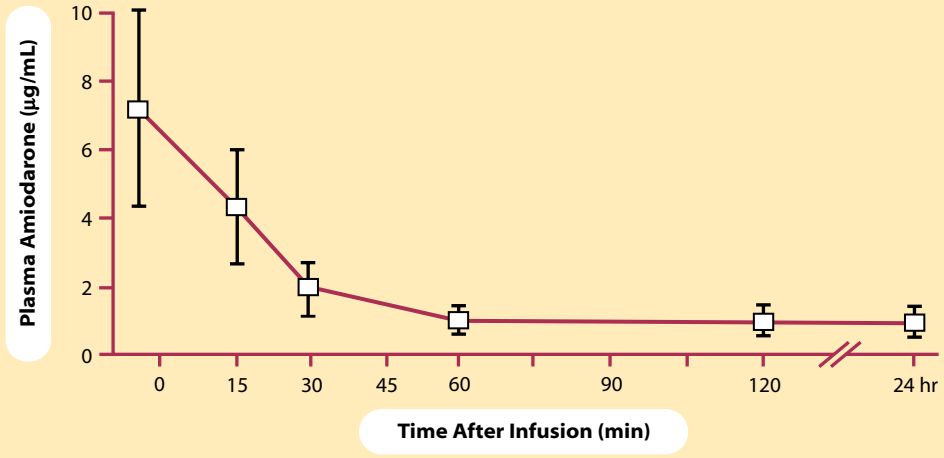


Class IV effect
Calcium channel blockade



- Amiodarone displays unique, complex pharmacokinetics.[1,3]
  - Highly bound to plasma proteins (96%)
  - Rapidly distributed throughout adipose tissue
  - Wide intersubject variability in dose-concentration relationship and in thresholds of safety and toxicity
  - Extended elimination half-life (16–180 days) because of extensive storage in the peripheral compartment
  - Principal active metabolite (desethylamiodarone or DEA) with electrophysiological/antiarrhythmic properties similar to parent compound
  - Age, sex, hepatic disease, or renal insufficiency do not have marked effects on pharmacokinetics
  - Rapid decrease in serum concentrations within 30–45 minutes after the end of an infusion (Figure 2)

Figure 2 **Plasma Concentrations of Amiodarone After IV Administration (n = 9)**



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- Although efficacy has been noted with serum concentrations ranging from 1 to 2 µg/mL, there is wide intersubject variability in the dose–concentration relationship and in concentrations associated with efficacy or toxicity.[1,3]

Key Clinical Studies of Intravenous Amiodarone

- The efficacy of amiodarone in treating malignant ventricular arrhythmias has been established in a number of clinical studies (Table 1).[1,3]

Table 1 **Summary of Uncontrolled Studies of IV Amiodarone for Serious Ventricular Arrhythmias**

Study	Patients	Previous Treatments Per Patient	Outcome
Helmy et al	46	3.2	33 responded
Klein et al	13	3.3	7 suppressed 2 suppressed with procainamide added
Mooss et al	35	3 to 7	22 responded
Morady et al	15	2 to 5	12 responded
Ochi et al	22	3.7	14 responded within 48 hr
Schutzenberger et al	26	2 to 5	8 of 19 with spontaneous VT terminated 12 of 15 with VF/VT responded
Williams et al	14	0 to 3	11 of 14 survived resuscitation

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- **Scheinman et al**[4] determined a dose response among three regimens in patients with refractory, recurrent VF/VT. A significant (*P* = 0.043) decrease from baseline in arrhythmia event rates was observed with increasing doses:

Dose	Median events/hr
125 mg/24 hr (n = 117)	0.07
500 mg/24 hr (n = 119)	0.04
1,000 mg/24 hr (n = 106)	0.02

- **Investigators also noted:**
  - A significant dose-related increase in the time to first VT/VF event (*P* = 0.025)
  - A significant dose-related decrease in number of supplemental IV infusions (150 mg) required (*P* = 0.043)
  - 26% of patients experienced hypotension; therapy was discontinued because of adverse events in only 5% of patients
- **Kowey et al**[5] studied two doses of IV amiodarone in comparison with IV bretylium in patients with refractory ventricular arrhythmias.
  - >50% of the bretylium-treated patients discontinued blinded therapy before hour 16 and crossed over to open-label amiodarone
  - Patients receiving bretylium experienced significantly more drug-related adverse events (58% vs. 42%) and significantly more hypotension (32% vs. 20%)
  - IV amiodarone (1.8 g, n = 105) and IV bretylium (4.7 g, n = 103) achieved comparable reductions in arrhythmia event rate (the primary end point) during the first 48 hours
- **Kudenchuk et al**[6] in the ARREST trial evaluated the efficacy of IV amiodarone versus placebo in 504 patients experiencing out-of-hospital cardiac arrest due to pulseless VT or VF refractory to three initial countershocks; IV amiodarone improved survival to hospital admission (the primary end point) by 29% compared with placebo (*P* = 0.03; see Poster 3).

- **Kentsch et al**[7] performed a study that randomized 20 consecutive patients with out-of-hospital cardiac arrest and VF (refractory to three DC countershocks, sodium bicarbonate, and 100 mg lidocaine) to receive either intravenous amiodarone (300 mg push) or an additional 100 mg dose of lidocaine.
  - After administration of study drug, a further countershock restored a stable rhythm in 6 of 10 patients in the amiodarone group (60%) as compared with 2 of 10 (20%) in the lidocaine group ($P < 0.05$)
  - More patients who received amiodarone were admitted to the hospital in a stable hemodynamic condition (8 of 10 [80%] vs. 2 of 10 [20%] in the lidocaine group; $P < 0.05$); patients in the amiodarone group also required fewer countershocks than patients receiving lidocaine
  - The results suggested a beneficial effect for amiodarone as compared with lidocaine in out-of-hospital VF

Side Effects and Contraindications

- Overall, amiodarone has shown a clinically manageable side-effect profile.[3]
  - The most common adverse event seen with IV amiodarone is hypotension, which may be related to the rate of infusion
  - In clinical trials, most important treatment-emergent adverse effects were hypotension (16%), bradycardia (4.9%), liver function test abnormalities (3.4%), cardiac arrest (2.9%), VT (2.4%), congestive heart failure (2.1%), cardiogenic shock (1.3%), and AV block (0.5%)
- IV amiodarone is contraindicated in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block in the absence of a functioning pacemaker.[3]

Dosing

- Amiodarone shows considerable interindividual variation in response; therefore, although a starting dose adequate to suppress life-threatening arrhythmias is necessary, close monitoring with adjustment of dose as needed is essential (Table 2).[3]

Table 2 Recommendations for IV Amiodarone Dosing: First 24 Hours[2,3]

Loading infusions

First Rapid:	**150 mg over the FIRST 10 minutes (15 mg/min).** Add 3 mL of IV amiodarone (150 mg) to 100 mL D_5W (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes. (**Note:** In cardiac arrest due to shock-refractory VF/pulseless VT, the initial dose should be 300 mg, IV push, as recommended in the VF/pulseless VT algorithm in the 2000 ACLS guidelines[2]) PVC* or glass† container
Followed by Slow:	**360 mg over the NEXT 6 hours (1 mg/min).** Add 18 mL of IV amiodarone (900 mg) to 500 mL D_5W (concentration = 1.8 mg/mL) Glass† or polyolefin container Flush with 10 mL D_5W or normal saline
Maintenance Infusion‡	**540 mg over the REMAINING 18 hours (0.5 mg/min).** Decrease the rate of the slow loading infusion to 0.5 mg/min.
Supplemental infusion§	**Add 150 mg to 100 mL D_5W; administer over 10 minutes (15 mg/min).**

* <10% loss after 2 hours.

† Use of evacuated glass containers for admixing IV amiodarone is not recommended, as incompatibility with a buffer in the container may cause precipitation.

‡ After the first 24 hours, the maintenance infusion rate of 0.5 mg/min (720 mg/24 hr) should be continued utilizing a concentration of 1–6 mg/mL; concentrations greater than 2 mg/mL should be administered via a central venous catheter, infusions for longer than 3 weeks have not been studied. Transition to oral therapy is recommended at the earliest possible time.

§ For the management of breakthrough episodes of life-threatening VT or VF. Alternatively, the rate of the maintenance infusion may be increased.

Must use volumetric pump when administering IV amiodarone; an in-line filter is recommended.

Store ampuls in cartons until ready for use to protect from light.

Prepared solutions should not be kept for more than 24 hours.

Concentrations greater than 3 mg/mL in D_5W have been associated with a high incidence of peripheral vein phlebitis.

For infusions longer than 1 hour, IV amiodarone concentrations should not exceed 2 mg/mL unless a central venous catheter is used.

IV amiodarone has been found to leach out plasticizers, including DEHP, from intravenous tubing (including PVC tubing). The degree of leaching increases when infusing IV amiodarone at higher concentrations and lower flow rates than provided in the Dosage and Administration section of the Prescribing Information.

Hypotension is the most common adverse effect seen with IV amiodarone and may be related to the rate of infusion.

- The various studies of IV amiodarone show a rapid onset of action, which is crucial to the success of out-of-hospital CPR, when antiarrhythmic agents must be administered while there is still hope for return of spontaneous circulation (ROSC).
- "The oral form of the drug is poorly absorbed, which makes acute therapy by the oral route largely impractical."[2]
- Storage:
  - Amiodarone for injection should be maintained at room temperature, 15°C to 25°C (59°F to 77°F), and protected from excessive heat[3]
  - Amiodarone must be protected from light during storage before admixture (but not during administration)[3]

Y-Site Injection Incompatibility

- Intravenous amiodarone in D_5W is incompatible with the drugs shown below (Table 3).[3]

Table 3 **Y-Site Injection Incompatibility**

Drug	Vehicle	Amiodarone Concentration	Comments
Aminophylline	D_5W	4 mg/mL	Precipitate
Cefamandole Nafate	D_5W	4 mg/mL	Precipitate
Cefazolin Sodium	D_5W	4 mg/mL	Precipitate
Mezlocillin Sodium	D_5W	4 mg/mL	Precipitate
Heparin Sodium	D_5W	—	Precipitate
Sodium Bicarbonate	D_5W	3 mg/mL	Precipitate

Summary

- Antiarrhythmic therapy in prehospital CPR must be initiated quickly (while there is still hope for ROSC).
- In the ARREST trial, IV amiodarone improved survival to hospital admission.
- Amiodarone has not been shown to increase mortality.
- Data from the ARREST trial suggest an important role for IV amiodarone in emergency antiarrhythmic therapy in patients with cardiac arrest due to VF/pulseless VT.

IV amiodarone is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.

IV amiodarone can also be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication.

IV amiodarone is contraindicated in patients with cardiogenic shock, marked sinus bradycardia, and second- or third-degree AV block in the absence of a functioning pacemaker.

IV amiodarone should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, who are thoroughly familiar with the risks and benefits of amiodarone therapy, and who have access to facilities adequate for monitoring the effectiveness and side effects of treatment.

Hypotension is the most common adverse effect seen with IV amiodarone and may be related to the rate of infusion. Hypotension should be treated by slowing the infusion or with standard therapy: vasopressor drugs, positive inotropic agents, and volume expansion.

In clinical trials, the most important treatment-emergent adverse effects were hypotension (16%), bradycardia (4.9%), liver function test abnormalities (3.4%), cardiac arrest (2.9%), VT (2.4%), congestive heart failure (2.1%), cardiogenic shock (1.3%), and AV block (0.5%).

Please see Prescribing Information available at this display.

REFERENCES

1. Gonzalez ER, Kannewurf BS, Ornato JP. Intravenous amiodarone for ventricular arrhythmias: overview and clinical use. *Resuscitation.* 1998;39:33–42.
2. American Heart Association. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiac Care. *Circulation.* 2000;102:(suppl):I–86–I–165.
3. Cordarone® I.V. (amiodarone HCl) Prescribing Information.
4. Scheinman MM, Levine JH, Cannom DS, et al. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. *Circulation.* 1995;92:3264–3272.
5. Kowey PR, Levine JH, Herre JM, et al. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. *Circulation.* 1995;92:3255–3263.
6. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med.* 1999;341:871–878.
7. Kentsch M, Berkel H, Bleifeld W. Intravenose amiodaron-applikation bei therapierefraktarem kammerflimmern. *Intesivmedizin.* 1988;25:70–74.

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