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Amiodarone-Induced Toxicities: Mechanisms, Timing, and Monitoring

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April 6th, 2023

Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Clyde Marquez, PharmD:**
    - None
  - **CE mentor(s), Irene Pan, PharmD, BCCP:**
    - None
- Off-Label Uses of Medications
  - Amiodarone

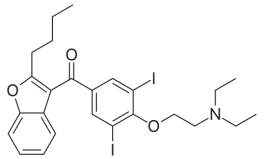
Learning Objectives – Pharmacists

1. Differentiate between the pathophysiology of each amiodarone-induced toxicity
2. Describe the clinical presentation and treatment of amiodarone-induced toxicities
3. Recognize the incidence of different toxicities and the general timeline when each may occur
4. Formulate baseline testing and monitoring strategies for different toxicities

Learning Objectives – Technicians

1. Identify appropriate indications for amiodarone
2. Distinguish between sound-alike/look-alike medications and recognize amiodarone as an ISMP High-Risk medication
3. Examine and recall major drug-drug interactions between amiodarone and other medications

Background



History of Amiodarone

- Derived from the plant *Ammi visnaga;* found in Mediterranean countries
- Synthesized during the early 1960s in Belgium as an anti-anginal agent
- Anti-arrhythmic properties described in the 1970s by researchers such as Bramah Singh, MD, Miles Vaughan Williams, and Maurico Rosenbaum, MD
- FDA-approved in 1985 for ventricular and supraventricular arrhythmias

Place in Clinical Practice

- **Oral** administration
  - Prevent recurrent atrial fibrillation (AF) or atrial flutter
  - Rate control of AF of atrial flutter with rapid ventricular rate (RVR) or supraventricular tachycardias (SVT)
  - Pharmacological cardioversion of AF or atrial flutter
  - Wolff–Parkinson–White syndrome
- **Intravenous** administration
  - Shock-refractory ventricular fibrillation or pulseless ventricular tachycardia
  - Rate control of AF with RVR or SVT when urgent control is needed
  - Treatment of electrical storm or incessant ventricular tachycardia

Pharmacokinetics

Absorption	Distribution	Metabolism	Elimination
• Bioavailability ~50% • Oral time to peak = 3-7 hours	• ~96% protein bound • Volume of distribution = ~60 L/kg	• Hepatic via **CYP3A4** and CYP2C8 to DEA*	• **t½ = ~58 days** (15-142 days) • Excretion via feces • Not dialyzed

DEA = *N*-desethylamiodarone

Mechanism of Action

- Blocks K^+ channels
- Blocks Na^+ Channels
- Blocks Ca^{2+} Channels
- Blocks β-receptors
- Blocks α-receptors

Drug-Drug Interactions

- Mechanism:
  - CYP3A4, CYP2C9, and CYP2D6 inhibitor
  - P-glycoprotein (P-gp) inhibitor

Medication	Metabolism	Clinical Effect
Warfarin	Primarily CYP2C9	↑ warfarin concentration
Digoxin	Mostly independent of CYP enzymes. effluxed by P-gp	↑ digoxin concentration
Colchicine	Primarily CYP3A4, effluxed by P-gp	↑ colchicine concentration

ISMP Information on Amiodarone

- List of Confused Drug Names:
  - amantadine vs. amiodarone
- List of High-Alert Medications in Acute Care Settings
  - If given in error, can cause arrhythmias, bradycardia, or hypotension
- Medication Safety Alert October 24, 2019:
  - IV Nicardipine (Cardene®) vs. IV Amiodarone (Nexterone®)

Personal Safety and Handling

- Amiodarone is **not** classified as a hazardous drug by the National Institute for Occupational Safety & Health (NIOSH)
- Category 2 for carcinogenicity and reproductive toxicity (suspected cause)
  - If eye contact is possible, wear safety glasses or goggles
  - If skin contact is possible, wear impervious gloves and protective clothing (e.g., nitrile)

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Knowledge Check 1

In which of the following clinical scenarios would you NOT use amiodarone?

- A • Atrial fibrillation
- B • Ventricular tachycardias
- C • Major Depressive Disorder
- D • Pharmacologic cardioversion of atrial flutter

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Knowledge Check 2

Based on the ISMP List of Confused Drug Names, which of the following is confused with amiodarone?

- A • Amitriptyline
- B • Amantadine
- C • Amoxicillin
- D • Anastrozole

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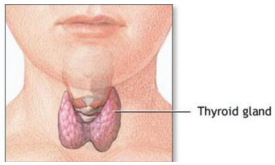

Thyroid Toxicity

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Amiodarone-Induced Hypothyroidism (AIH)

- Incidence up to 26%
- Patients present with cool and dry skin, fatigue, cold intolerance, constipation, weight gain, bradycardia, or myxedema coma (rare)
- AIH risk depends on patient specific factors; onset is 2 weeks to 39 months
- Thyroid function labs reveal elevated thyroid stimulating hormone (TSH) and normal to low thyroxine (T4)
- Risk factors:
  - Additional exogenous iodine intake
  - Presence of thyroid autoantibodies
  - Females

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Amiodarone-Induced Hyperthyroidism (AIT)

- Incidence depends on region/prevalence of iodine-deficiency
- Patients present with restlessness, weight-loss, low-grade fever, tachycardia, heat intolerance, or new onset of supraventricular arrhythmias
- Some data estimate median onset at ~2 years, but appears unpredictable
- **Presents as either Type 1 or Type 2**
- Thyroid function labs reveal elevated triiodothyronine (T3) and T4 with a low TSH
- Risk factors:
  - Low dietary iodine intake
  - Pre-existing thyroid disease
  - Males

Differentiating Between AIT Types

	Type 1	Type 2
Underlying thyroid disease?	Yes	No
Ultrasound findings	Diffuse or nodular goiter	Normal gland
Pathogenesis	Iodine-induced	Destructive thyroiditis
Spontaneous remission?	No	Possible
Subsequent hypothyroidism	No	Possible
Subsequent therapy for underlying thyroid disease?	Likely	No
Prevalence	Most common in iodine-deficient regions outside U.S. (10-12%)	Most common in U.S. (3-5%)

Mechanism of Thyroid Toxicity

- **Hypothyroidism**
  - Thought to occur from inability to escape the Wolff-Chaikoff effect, direct inhibition of Type I and Type II 5'-monodeiodinases, and impaired T4 and T3 entry into different cell lines
- **Hyperthyroidism**
  - Type 1: Abnormal thyroid glands (e.g., Toxic nodular goiter, Graves') increase synthesis of thyroid hormones due to increased iodine levels
  - Type 2: Direct cytotoxicity of amiodarone and excessive iodine causes excess release of T3 and T4 from normal thyroid glands

Hypothyroidism Management

- **Screening**
  - Assess baseline underlying thyroid function and engage in risk/benefit discussions prior to starting therapy
- **Treatment**
  - Replete with T4 to normalize thyroid function
  - Higher doses may be required to restore normal TSH levels
  - Ok to continue amiodarone
- **Monitoring**
  - Baseline TSH, T3, and T4
  - If initiating treatment, assess thyroid labs in 4-8 weeks

AIT Type 1 Management

- **Screening**
  - Identify patients with risk factors for thyrotoxicosis and engage in risk/benefit discussions
- **Treatment**
  - Methimazole (up to 40-60 mg/day) or equivalent propylthiouracil dose
  - Ok to continue amiodarone
- **Monitoring**
  - Repeat thyroid function tests every 3-6 months until euthyroid
  - If continuing amiodarone, may need prolonged thionamides

AIT Type 2 Management

- **Screening**
  - Identify patients with risk factors for thyrotoxicosis and engage in risk/benefit discussions
- **Treatment**
  - Start prednisone at 0.5 mg/kg/day; once thyroid levels normalize reduce by 0.1 mg/kg every 7-14 days
  - Ok to continue amiodarone
- **Monitoring**
  - Continue prednisone until T3/T4 normalizes, then taper
  - Patients often respond despite continuing amiodarone

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Knowledge Check 3

Where would you expect AIT Type 2 to be more prevalent?

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A	• Western Africa
B	• India
C	• South Asia
D	• North America

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Case – Thyroid Toxicity

An 80 kg 65M presents to their PCP clinic with symptoms of restlessness, weight loss, and tachycardia. He is 1 year into amiodarone treatment for suppression of recurrent ventricular tachycardia. His thyroid function tests show an elevated T3 and T4, with a low TSH. A provider consults you, the pharmacist, asking for a recommendation. Which of the following interventions would be reasonable to recommend, along with referral to an endocrinologist?

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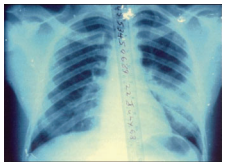
A	• Start methimazole 30 mg daily
B	• Start prednisone 40 mg daily
C	• Discontinue amiodarone
D	• Start levothyroxine 50 mcg daily



Pulmonary Toxicity

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Clinical Manifestations

- Typically presents as non-specific symptoms (e.g., non-productive cough, dyspnea, pleuritic pain, fever, malaise, weight-loss)
- Pulmonary function tests (PFTs) reveal restrictive or mixed restrictive/obstructive airway disease and reduced diffusion capacity
- Typically manifests as an interstitial pneumonitis, but other pulmonary complications possible
- Toxicities can develop in as little as 2 days and up to several months after starting therapy
- Chest X-ray findings: new or localized diffuse opacities

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Epidemiology and Risk Factors

- Incidence is ~5% (2-17%)
- Risk factors:
  - Daily dose (>200-400 mg) and cumulative dose (>100 g)
  - >60 years old
  - Duration of therapy (>6 months)
  - Pre-existing lung disease
    - Starting amiodarone in patients with pre-existing lung disease requires a risk/benefit discussion

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Mechanism of Pulmonary Toxicity

- Thought to occur through **direct cytotoxicity** and **indirect immune reactions**
- Amiodarone-lipid complexes accumulate in lung tissues and interfere with metabolic pathways causing cell death
  - Characteristic pathological finding: Lipid-rich macrophages seen in alveolar spaces
  - Amiodarone may generate radical oxygen species that are cytotoxic
- Lymphocytic infiltration and recruitment of cytotoxic T-cells also observed

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Management

- **Screening**
  - Identify patients with risk factors for pulmonary toxicity and engage in risk/benefit discussions
- **Treatment**
  - Discontinue amiodarone, if possible
  - Case report data suggests 40-60 mg of prednisone followed by a gradual taper may help improve symptoms in patients with dyspnea at rest requiring oxygen
- **Monitoring**
  - Baseline chest x-ray, then yearly
  - Baseline PFTs, then as needed
  - Amiodarone blood concentrations are not predictive of toxicity

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Knowledge Check 4

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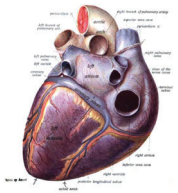
A primary care provider calls your clinic about a patient who was recently started on amiodarone after a hospital admission. Which of the following monitoring strategies for pulmonary toxicity be appropriate to recommend?

A	• Baseline potassium and magnesium, replete as needed
B	• Baseline serum TSH, T3, and T4 levels
C	• Baseline and annual chest x-ray and PFTs
D	• Amiodarone concentrations every 3 months



Cardiac Toxicity

Sinus Bradycardia and Atrioventricular Blockade

- Cardiac toxicity is rare, but results from potentiation of expected pharmacological properties of amiodarone
- Bradycardia incidence is ~2-5%
- Presentation (if symptomatic or 2nd or 3rd degree block): presyncope, syncope, lightheadedness, fatigue
- Risk factors:
  - Concomitant negative inotropic medications (e.g., diltiazem, β-blockers)
  - ≥ 65 years old with a history of myocardial infarction

Arrhythmia Exacerbation

- Incidence is ~2-5%
- Potential for new arrhythmias:
  - Ventricular fibrillation
  - Incessant ventricular tachycardia (VT)
  - Increased defibrillation threshold
  - Polymorphic VT associated with torsades de pointes (TdP), rare (<1%)
- Mostly occurs in an unpredictable fashion
- Risk factors:
  - Hypokalemia and hypomagnesemia
  - ≥2 medications that prolong the QT interval

Mechanism of Cardiotoxicity

- **Sinus bradycardia and AV block**
  - Occurs due to reduced AV nodal conduction, a consequence of β-receptor and calcium channel inhibition
- **Torsades de Pointes (rare)**
  - Occurs due to potassium channel inhibition prolonging the effective refractory period, thus prolonging the QT interval and leaving patients susceptible to development of TdP
    - Proposed mechanisms include ↑ action potential duration by β-blockade and ↓ early afterdepolarizations by calcium channel blockade

Management

- **Screening**
  - Monitor heart rate diligently if heart rate (HR) <70 beats per minute when initiating therapy or during therapy
  - Consider dose adjustment of contributing medications (if possible) when baseline HR is low
- **Treatment**
  - Symptomatic bradycardia or high-grade AV block: discontinue or dose reduce amiodarone, discontinue or dose reduce contributing agents
  - TdP:
    - Treatment: IV magnesium + positive chronotrope/anti-arrhythmics as needed
    - Prevention: maintain K >4, Mg >2, similar treatment as above
- **Monitoring**
  - Baseline potassium and magnesium (replete as needed)
  - Baseline electrocardiogram (ECG) and may consider repeating when additional QT-prolonging agents are added. HR throughout therapy

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Knowledge Check 5

Which of the following medications does NOT have a major drug-drug interaction with amiodarone?

A	• Acetaminophen
B	• Digoxin
C	• Colchicine
D	• Warfarin

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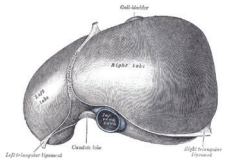

Hepatic Toxicity

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Clinical Presentation

- Transient elevations occur in 15-50% of patients upon initiation of amiodarone
- About 1-3% of patients develop amiodarone-associated liver injury
  - Presents as fatigue, nausea, weight loss, no jaundice, and hepatomegaly
- Acute toxicity can manifest within a day, chronic toxicity after ≥1 year of therapy
- Elevations usually mild-to-moderate but may presents in 2 ways:
  - Hepatocellular injury pattern -> Severe alanine transaminase (ALT) increase
  - Cholestatic pattern -> Minor ALT increase with prominent alkaline phosphatase increase
- Risk factors:
  - Chronic toxicity:
    - Cumulative dose
  - Acute toxicity:
    - Higher doses, IV administration, or older adults

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Mechanism of Hepatotoxicity

- Amiodarone directly damages the phospholipid bilayer and inhibits phospholipase A, leading to accumulation of lipids in lysosomes
  - This can cause apoptosis of hepatocytes, leading to fibrosis and Mallory body formation
- Polysorbate 80 (found in IV formulations) can destabilize cell membranes and predispose patients to steatosis

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Management

- **Screening**
  - Consider a risk/benefit discussion if starting amiodarone during liver injury or baseline LFTs are elevated
- **Treatment**
  - Acute or chronic LFT elevations: monitor for symptoms of hepatitis
  - Symptomatic hepatitis or LFTs persistently > 2-5x ULN*: discontinue amiodarone
- **Monitoring**
  - Baseline LFTs, then every 6 months

*ULN = upper limit of normal, LFT = liver function test

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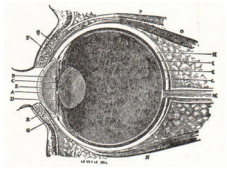

Ocular Toxicity

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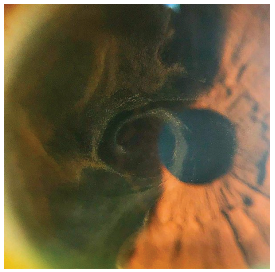
Corneal Microdeposits

- Incidence of *symptomatic* deposits is ~1.5%
  - Patients with more deposits report blue-green rings or halos around lights
  - Corneal opacities evident in both eyes on exam
  - Presence of deposits rarely leads to vision loss
- Typically form within 1-30 months of starting therapy
  - Often resolves over several months after discontinuing therapy
- Higher doses may be associated with greater deposition
- Risk factor: extended duration of therapy



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Optic Neuropathy

- Incidence is ~0.3-2%
- Patients present with mild reversible vision loss to permanent blindness
- Most cases present with ≥12 months of therapy
- Limited data on risk factors
  - Generally thought to occur in a dose-dependent manner and with longer durations of therapy
  - There is no screening protocol or defined risk stratification strategy for amiodarone-associated optic neuropathy (AAON)

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Mechanism of Ocular Toxicity

- **Corneal Deposits**
  - Amiodarone-lipid complexes accumulate inside the corneal epithelium
- **Optic Neuropathy**
  - Similarly, accumulated lamellar bodies have been observed in large optic nerve axons, leading to decreased axoplasmic flow and optic disc swelling

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Management

- **Treatment**
  - Most cases of corneal microdeposits require no intervention
  - If vision is impaired, discontinue or dose reduce amiodarone
  - Possible laser treatment if significant corneal deposits present
  - If optic neuropathy is suspected, amiodarone should be discontinued upon discussion with a cardiologist
- **Monitoring**
  - Baseline eye exam, then yearly

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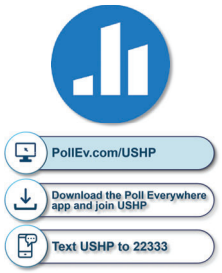
Knowledge Check 6



What is a mechanism of ocular toxicity with amiodarone? Select all that apply.

A	• Inability to escape the Wolff-Chaikoff effect can lead to permanent blindness
B	• Lamellar bodies accumulate in optic nerves, leading to optic nerve swelling
C	• Amiodarone-lipid complexes accumulate inside the corneal epithelium
D	• Amiodarone blocks potassium channels in the eye, leading to optic nerve damage

Other Toxicities

Dermatologic

- Incidence ~2% when higher doses were used, now exceedingly rare
- **Photosensitivity** occurs with or without associated rash
- **Hyperpigmentation and Blue man syndrome:**
  - Caused by accumulation of lipofuscin in lysosomes of dermal cells
  - Extent of pigmentation appears to be dose-related, with pigmentation improving with dose reductions
- For either scenario, avoid excessive sun exposure and use sunscreen to protect the skin
- Onset typically with longer duration of therapy (≥12 months)

Neurologic

- Presents broadly as a tremor, gait ataxia, cognitive impairment, peripheral neuropathy, and as rare cases of Parkinson disease or myopathy
- Incidence is ~1.6%
- Primary risk factor appears to be duration of therapy (≥12 months)
- Risk remains low with lower doses
- Clinically, amiodarone should be considered a possible culprit after other diagnoses have been ruled out

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Safety in Pregnancy and Breastfeeding

- May increase the risk of neonatal hypo- and hyperthyroidism, bradycardia, neurodevelopmental abnormalities, preterm birth, and fetal growth restriction
- Not a first-line option for chronic management of arrhythmias (such as AF)
- Concentrations in breast milk vary (3.5-45%)
  - Package insert recommends avoiding breastfeeding, but some evidence supports continuing with appropriate infant thyroid and cardiac monitoring

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Acute Overdose Toxicity

- Ingestions often present with exacerbated electrophysiological effects; subsequent cardiovascular collapse may occur
  - Presentation: bradycardia (AV blockade, SA node dysfunction), prolonged QT interval, malignant tachycardias, hypotension, and cardiac arrest
- Management:
  - Immediate supportive measures required (securing airway if needed)
  - Fluids +/- vasopressors to manage hypotension
  - Enact acute cardiac life support measures as needed
  - Consult poison control for further management/stabilization

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Conclusion

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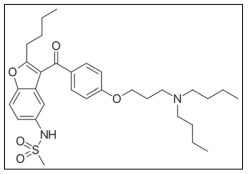
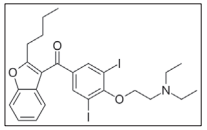
What about dronedarone?

- Lack of iodine reduces thyroid effects
  - May be reasonable to switch in thyroid toxicity
- Contraindicated in patients with previous **lung** or **liver** toxicity secondary to amiodarone (carries its own risk for these toxicities)
- Contraindicated in New York Heart Association Class III or IV or recent (<4 week) hospitalization for decompensated heart failure

Dronedarone Chemical Structure



Amiodarone Chemical Structure



Key Takeaways

- Presently, **amiodarone toxicity is rare** as maintenance doses are much lower than were commonly prescribed in the 1980s (~600 mg daily)
- Most mechanisms are caused by cellular damage from amiodarone-lipid complexes accumulating within different cell types throughout the body
- Baseline and routine imaging and laboratory tests should be obtained in every patient to monitor for development of toxicities
- Patients should be thoroughly educated on the risks of amiodarone therapy and symptoms of toxicity

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