
Amiodarone Toxicities

— Student Rounds Review —

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Amiodarone

- Use: Antiarrhythmic agent
 - Supraventricular and ventricular tachycardia
 - Favourable for HF patients due to minimal inotropic effects and less likelihood to induce ventricular arrhythmias
- Primary MOA: blocks potassium and inactivated sodium channels
 - K: Prolongs refractory period of action potential (prolongs the QT interval)
 - Na: Prevents depolarization of the action potential
- Other effects
 - Blocks Beta-receptors → reduces SNS stimulation → reduce spontaneous depolarization
 - Blocks L-type calcium channels → reduces firing in SA and AV nodes

Properties of Amiodarone

- Poor oral absorption + lipophilicity → uptake by tissues, large volume of distribution
- Elimination half-life is **long!** (60-140 days)
- Serum amiodarone levels have no clinical utility for monitoring therapeutic efficacy, or toxicity
- High Iodine content
- Inhibits CYP3A4, drug interactions with CYP3A4 substrates

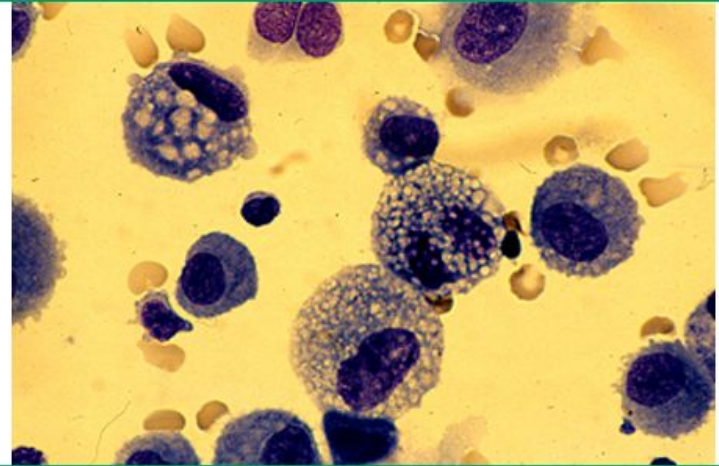
Toxicity

- Likelihood of toxicity increases the longer the drug is used
- Due to accumulation of the drug in the following tissues:
 - Pulmonary, thyroid, ocular, neurological and skin
- Less common with IV therapy
- Lower doses decreases the risk of toxicity
 - Reported rates increase when doses $\geq 400\text{mg/day}$ used

Pulmonary toxicity

- Occurs with higher *cumulative* doses - slow onset (weeks - years)
- Manifests routinely as foamy macrophages present in lung air spaces, filled with amiodarone - phospholipid complexes

BAL in amiodarone pulmonary toxicity



Bronchoalveolar lavage (BAL) cytopreparation smear with normal differential and marked foamy appearance of alveolar macrophages.

Courtesy of Talmadge E King Jr, MD.

Pulmonary toxicity

- May present as interstitial pneumonitis (most common), bronchitis, respiratory distress, lung nodules or masses, alveolar hemorrhage, eosinophilic pneumonia
- Signs and symptoms:
 - Pleuritic chest pain, dyspnea, cough, fever, weight loss, bilateral crackles
- Typically a diagnosis of exclusion
 - Lung biopsy, chest imaging, broncheolar lavage may be performed
- Resolved by stopping drug, or using corticosteroids (if can't stop)
 - Will be slow to improve
 - Avoid future use

Thyroid disturbances

- Occurrence is only 3-4% if low doses are used (up to 20% at high doses)
- Hypothyroidism and hyperthyroidism may occur
- Varies based on underlying thyroid abnormalities and iodine intake
- 3mg of iodine per 100mg dose (2 iodine atoms/amiodarone)
- Suggested to monitor thyroid function Q3-4 months while on treatment
- If discontinuing amiodarone, check thyroid function up to 1 year out for late-onset presentation (long elimination half-life)
- Warfarin is increased by thyrotoxicosis, reduced in hypothyroidism
 - **Monitor INR closely!**

Mechanism

- Reduces deiodination of T4 to T3
- Blocks T3 from binding with nuclear receptors and gene transcription
- Directly cytotoxic to thyroid cells
- Amiodarone displaces T3, T4 from thyroid binding globulin - increases free fraction
- Affects TSH secretion

Hyperthyroidism - amiodarone induced thyroidtoxicosis (AIT)

- Type 1 - Iodine Induced
 - Onset within months of starting
 - Underlying thyroid disease (goiter, or antibodies/Grave's disease)
 - Increased iodine load → synthesize more thyroid hormone (T4, T3)
 - Treat with high dose thionamides and monitor closely
- Type 2 - Thyroiditis
 - Onset more common after months-years of use, or after discontinuation
 - Likely normal underlying thyroid physiology
 - Thyroid tissue destroyed, releases large amounts of hormone into circulation
 - Treat with high dose corticosteroids for 1-3 months, then taper
- May appear as development of arrhythmia, heart failure, tachycardia
- Only continue if required for control of life-threatening arrhythmias

Hypothyroidism

- More likely in patients with antibodies or Hashimoto's thyroiditis
- Presents as fatigue, weight gain, bradycardia, coarse hair, cold intolerance, periorbital edema, etc.
- Diagnose with serum TSH levels
- Treat with levothyroxine
- Resolves when amiodarone is stopped (discontinuation is not required)

Hepatotoxicity

- Occurrence in 25% of patients
- Increase in LFTs when first starting drug
 - Recommended monitoring at baseline, and every 6 months
- Stop drug if 2x baseline levels
- Rare complications: cholestasis, jaundice, hepatitis, cirrhosis and liver failure
- Clinical presentation similar to alcoholic liver disease (due to phospholipids)

Ocular changes

- **Microdeposits** on surface of cornea
 - Secreted by lacrimal glands, appear as brown spots
 - Unlikely decrease in visual acuity
 - Rare disturbances: halo, photophobia, blurred vision
 - Reversible
- **Optic neuropathy**
 - Damage to nerve axons by lipid accumulations
 - Vision loss that can progress to blindness
 - Discontinue drug if possible
 - Prevalence not well studied

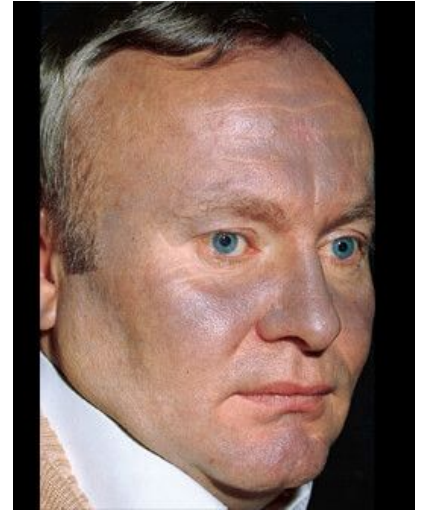
Skin

Ceruloderma

- Blue/ slate grey tinge to skin
- 1-10%, less likely at low doses
- Lipofuscin is deposited in macrophages and skin cells
- Reversible (slow resolution)

Photosensitivity

- 25-75%
- Avoid sun exposure and wear sunscreen



Other effects

- Cardiac:
 - Bradycardia (calcium channel blockade) 5%
 - Ventricular arrhythmias, TdP (K⁺ channel blockade) <1%
- Neurologic - tremor, ataxia, neuropathy
- Genitourinary - sexual dysfunction, epididymitis
- Gastrointestinal - no more than placebo

Drug Interactions

- ★ Run an interaction check through Lexicomp!

Table 2 Major Amiodarone Drug Interactions

Drug	Interaction
Digoxin	Increased concentration and effect with sinus and AV node depression and gastrointestinal tract and neurologic toxicity
Warfarin	Increased concentration and effect
Quinidine, procainamide, disopyramide	Increased concentration and effect; torsades de pointes ventricular tachycardia; bradycardia and AV block
Diltiazem, verapamil	Bradycardia and AV block
β-blockers	Increased concentration and effect
Flecainide	Increased concentration and effect
Phenytoin	Hypotension and bradycardia
Anesthetic drugs	Increased concentration and effect
Cyclosporine	Promote liver function abnormalities
Statins	Myalgias, myopathy, rhabdomyolysis

AV = atrioventricular.

Toxicities Summary

Table 1 Adverse Reactions to Amiodarone

Reaction	Incidence, %	Diagnosis	Management
Pulmonary	2	Cough or dyspnea (or both), especially with focal or diffuse opacities on high-resolution CT scan and decrease in D _L CO from baseline	Usually discontinue drug; corticosteroids may be considered; occasionally, continue drug if levels high and abnormalities resolve; rarely, continue drug with corticosteroid if no other option
Gastrointestinal tract	30	Nausea, anorexia and constipation	Symptoms may decrease with decrease in dose
	15-30	AST or ALT level >2× normal	If hepatitis considered, exclude other causes
	<3	Hepatitis and cirrhosis	Consider discontinuation, biopsy, or both to determine whether cirrhosis is present
Thyroid	4-22	Hypothyroidism	L-thyroxine
	2-12	Hyperthyroidism	Corticosteroids, propylthiouracil or methimazole; may need to discontinue drug; may need thyroidectomy
Skin	<10	Blue discoloration	Reassurance; decrease in dose
	25-75	Photosensitivity	Avoidance of prolonged sun exposure; sunblock; decrease in dose
Central nervous system	3-30	Ataxia, paresthesias, peripheral polyneuropathy, sleep disturbance, impaired memory and tremor	Often dose dependent, and may improve or resolve with dose adjustment
Ocular	<5	Halo vision, especially at night	Common and does not require drug discontinuation
	≤1	Optic neuropathy	Discontinue drug and consult an ophthalmologist
	>90	Photophobia, visual blurring, and microdeposits	Corneal deposits common, indicate that drug is being taken, and do not require discontinuation.
Heart	5	Bradycardia and AV block	May need permanent cardiac pacing
	<1	Ventricular proarrhythmia	Usually discontinue drug
Genitourinary	<1	Epididymitis and erectile dysfunction	Pain may resolve spontaneously

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AV = atrioventricular; CT = computed tomography; D_LCO = diffusion capacity for carbon monoxide.

Monitoring

Amiodarone monitoring and recommendations

System	Monitoring		Possible adverse effect	Recommendation
	Baseline	Follow-up		
Cardiac	ECG (at baseline and during loading dose)	Yearly	QT prolongation; torsade de pointes	Reduce amiodarone dose or discontinue use
			Symptomatic sinoatrial or conduction system impairment	
Dermatologic	Physical examination	As needed for signs/symptoms	Photosensitivity to UV light	Avoid sunlight; use sunscreen
			Blue-gray skin discoloration	Reduce amiodarone dose or discontinue use
Endocrine	Thyroid function tests	Every 6 months	Hyperthyroidism	Discontinue amiodarone; refer to endocrinologist
			Hypothyroidism	Treat with levothyroxine
Hepatic	AST or ALT	Every 6 months	AST or ALT elevation $\geq 2x$ upper limit of reference range	Reduce amiodarone dose or discontinue use
Neurologic	Physical examination	As needed for signs/symptoms	Ataxia, dizziness, fatigue	Reduce amiodarone dose or discontinue use
Ophthalmologic	Eye examination	As needed for signs/symptoms	Corneal microdeposits	Continue amiodarone treatment
			Optic neuropathy	Discontinue treatment
Pulmonary	Pulmonary function tests	As needed for signs/symptoms	Pulmonary toxicity (cough, fever, dyspnea)	Discontinue amiodarone immediately; consider corticosteroid treatment
	Chest radiograph	Yearly		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ECG: electrocardiogram.

References

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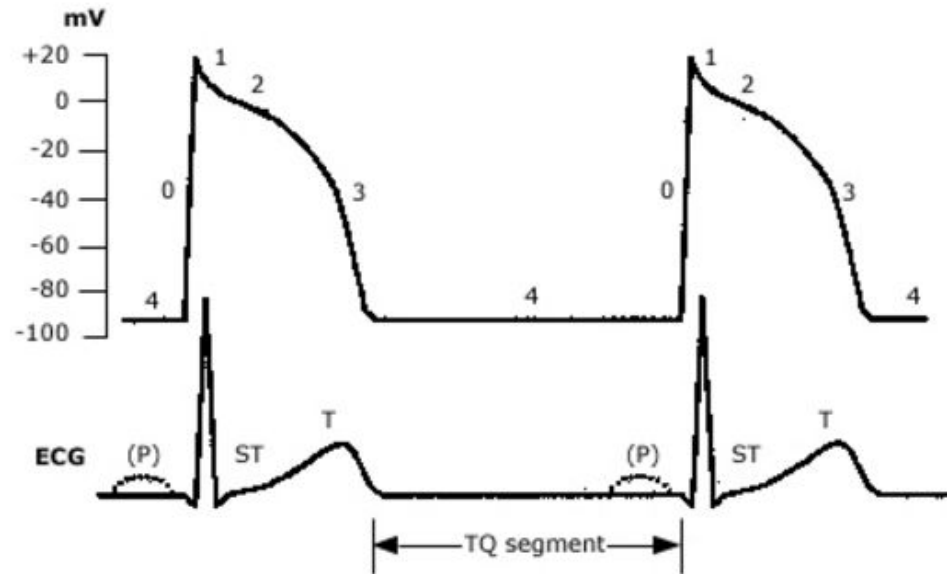
Relationship between myocardial action potential and surface electrocardiogram

Mechanism of action

- Sodium - Phase 0
- Potassium - Phase 2

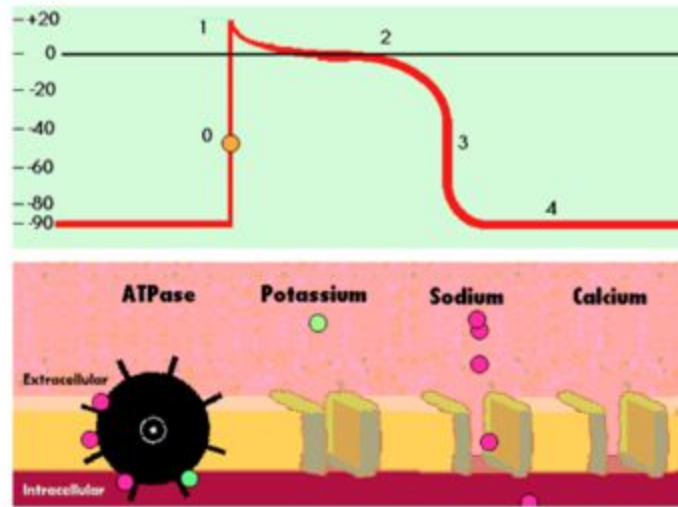
Cumulative effects:

- Reduced automaticity
- Prolongs refractory period



Each phase of the myocardial action potential (numbers, upper panel) corresponds to a deflection or interval on the surface electrocardiogram (lower panel). Phase 4, the resting membrane potential, is responsible for the TQ segment; this segment has a prominent role in the ECG manifestations of ischemia during exercise testing.

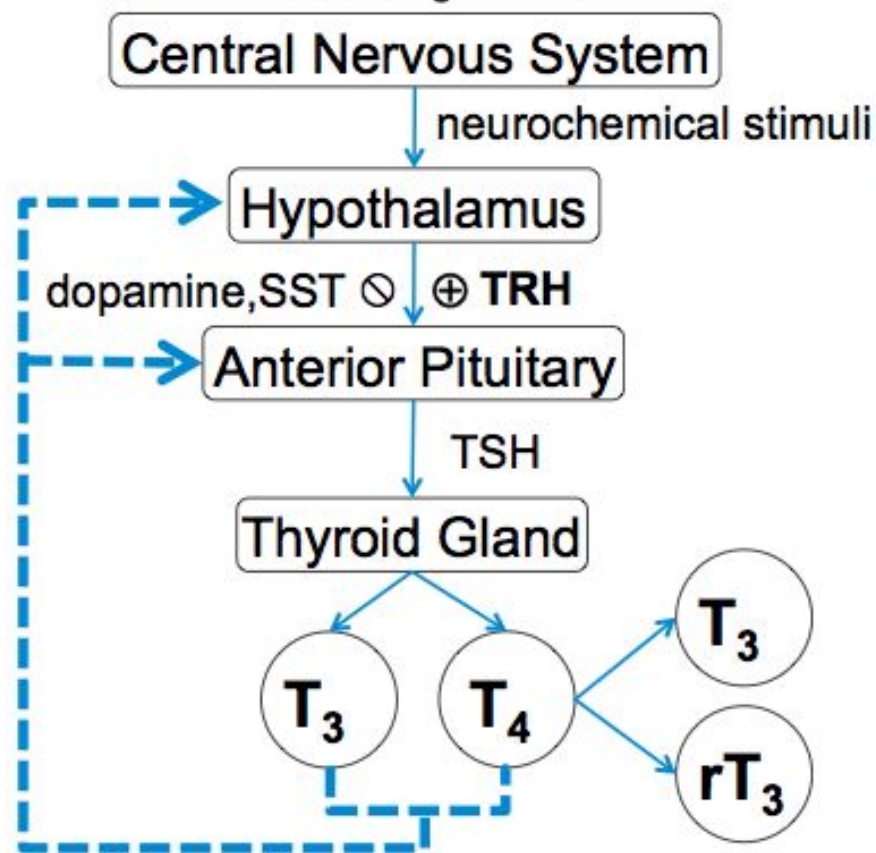
Generation of the fast action potential in myocardial cells



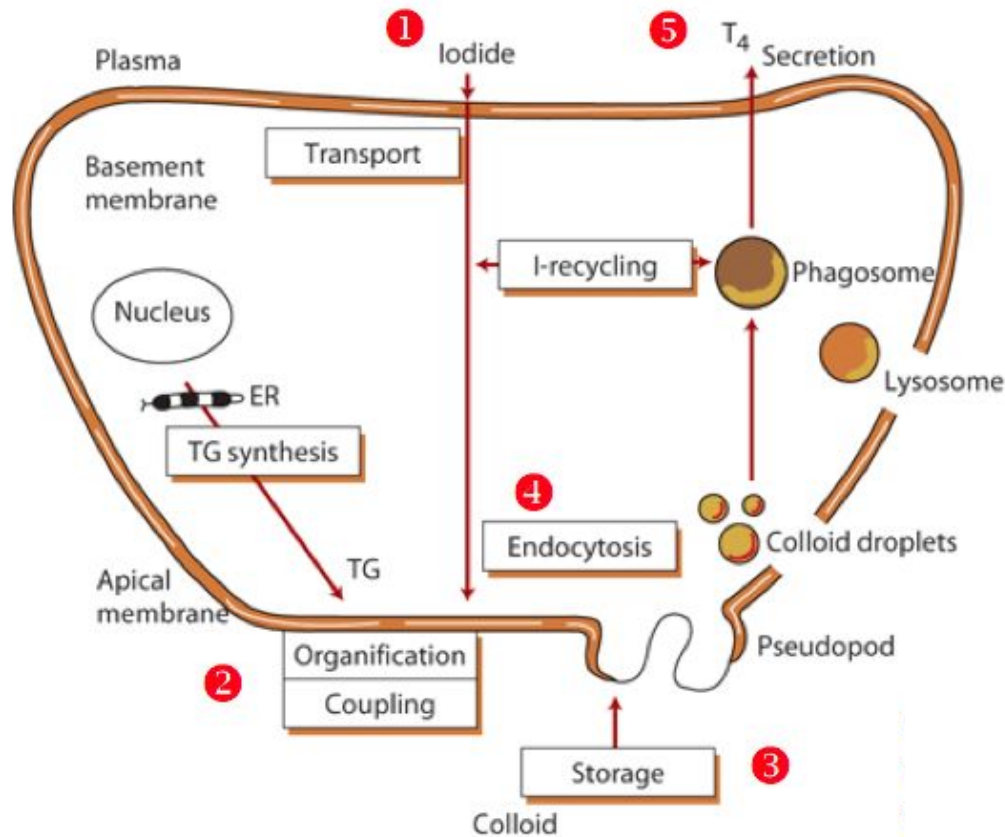
Schematic representation of the ionic events during the different phases of the fast action potential. The resting membrane potential (phase 4) is maintained by an energy-dependent ATPase sodium-potassium mechanism which pumps potassium (green spheres) into the cell in exchange for sodium (magenta spheres) which is extruded. Rapid depolarization during phase 0 is characterized by opening of voltage-dependent sodium channels and rapid entry of sodium ions into the cell. This is followed by delayed opening of slow calcium channels and influx of calcium ions (blue spheres). The calcium channels remain open during phase 2 (early repolarization) and there is also opening of potassium channels and efflux of potassium ions which results in late repolarization (phase 3) and a return to resting membrane potential (phase 4).

Courtesy of Entropy, Inc.

Adapted from: Chapter 52. Thyroid Disorders. *Applied Therapeutics: The Clinical Use of Drugs*. 10th ed



high circulating thyroid hormone levels block further production by inhibiting TSH release.



- 1** Iodide is transported from the plasma, through the cell, to the apical membrane
- 2** Iodide is organified and coupled to the thyroglobulin synthesized within the thyroid cell.
- 3** Hormone stored as colloid
- 4** Stored hormone reenters the cell through endocytosis and moves back toward the basal membrane
- 5** thyroxine (T₄) is secreted.