



Clinical Pearl: Safe Use of Dronedarone

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Learning Objectives

- Compare dronedarone to amiodarone with respect to chemical structure, electrophysiologic effects, and pharmacokinetics
- List contraindications and precautions for use of dronedarone
- Describe drug/drug and drug/food interactions associated with dronedarone use
- Discuss the role of the pharmacist in facilitating the safe use of dronedarone

Dronedaronone: Indications

- Reduces risk of cardiovascular hospitalization in patients with recent episodes of atrial fibrillation (AF) or atrial flutter (AFL), and cardiovascular risk factors
 - Age > than 70
 - Hypertension
 - Diabetes
 - Prior cerebrovascular accident (CVA)
 - Left atrial diameter \geq 50 mm
 - Left ventricular ejection fraction < 40%

Dronedarone versus Amiodarone: Structural Comparison

- Dronedarone chemical structure contains no iodine
 - Benzofuran derivative of amiodarone
- Dronedarone contains a methane-sulfonyl group
 - Lower lipophilicity
 - Shorter half-life
 - Less tissue accumulation
 - Structural changes made to dronedarone reduce the risk of pulmonary and thyroid adverse events that may occur with amiodarone therapy

Dronedarone versus Amiodarone: Pharmacokinetic Comparison

• Dronedarone

- Steady state achieved at 5-7 days
- Protein binding > 98%
- Active metabolite (debutyldronedarone)
- Elimination half-life is 24-31 hours of the parent compound; for the metabolite 20-24 hours

• Amiodarone

- Steady state achieved at 1-5 months
- Protein binding > 99%
- Active metabolite (N-desethyl-amiodarone)
- Elimination half-life is 26-107 days (mean 53 days)

Dronedarone versus Amiodarone: Electrophysiology

- Both inhibit potassium, sodium, and calcium channels
- Both possess anti-adrenergic properties
- Dronedarone has a negative inotropic effect

Dronedarone:

Contraindications

- Class IV heart failure or symptomatic Class II-III heart failure with recent decompensation or referral to specialized heart failure clinic
 - Increased mortality in ANDROMEDA trial
- Second- or third-degree AV heart block or sick sinus syndrome (except when pacemaker is in place)
- Bradycardia (defined as heart rate less than 55 beats per minute)

Dronedarone:

Contraindications (cont)

- Concomitant use of medications known to prolong QT_c interval
- Concomitant use of medications that strongly inhibit cytochrome P-450 (CYP) 3A4
- QT_c Bazett interval ≥ 500 ms
- Severe hepatic impairment
- Pregnancy (category X)
 - Fetal harm in animal studies at doses consistent with approved dose
- Breast feeding

Dronedarone:

Precautions

- New or worsening heart failure
- Prolonged QT_c interval
- Teratogenicity
 - Effective contraception is imperative for women of child bearing age
- Increased serum creatinine
 - Serum creatinine typically increases 0.1 mg/dl within a week after starting dronedarone
- Hypokalemia and hypomagnesemia
 - Caution with diuretic therapy

Dronedarone:

Drug Interactions

- Avoid concomitant antiarrhythmics
- Calcium channel blockers and beta blockers
 - Start with low doses, monitor for bradycardia, and assess tolerability by EKG
- CYP 3A inducers decrease levels of dronedarone
 - Rifampin, carbamazepine, phenytoin, St. John's Wort
- Strong inhibitors of CYP 3A4 significantly increase dronedarone concentration
 - Ketoconazole, itraconazole, clarithromycin, erythromycin, ritonavir

Dronedarone:

Drug Interactions (cont)

- Moderate CYP 3A inhibitors
 - Diltiazem or verapamil may increase dronedarone concentration
- Concomitant use of digoxin increases digoxin levels
 - Consider reducing dose of digoxin by half or discontinuing
- Avoid medications known to prolong QTc interval
 - Haloperidol, amitriptyline, ciprofloxacin, thioridazine

Dronedarone:

Drug Interactions (cont)

- CYP 3A substrates
 - Dronedarone may increase levels of certain statins (such as simvastatin)
 - Careful monitoring recommended for narrow therapeutic index substrates (tacrolimus and sirolimus)
- Concomitant use with warfarin did not produce clinically significant increases in INR
- No effect on oral contraceptives containing ethinylestradiol and levonorgestrel

Dronedarone: Food Interactions

- Grapefruit juice
 - Moderate inhibitor of CYP 3A
 - Concomitant use of grapefruit juice with dronedarone resulted in dronedarone levels that were three times higher than when dronedarone was used without grapefruit juice
 - Avoid drinking grapefruit while taking dronedarone

Safety with Use of Dronedaronone: Role of the Pharmacist

- Approved under a risk evaluation and mitigation strategy (REMS)
 - mPACT
- Create standard documentation tool
 - Compliance with REMS
 - Monitor electrolytes, vital signs, QT_c
 - Assess medication profile for drug interactions
 - Evaluate for signs/symptoms of worsening heart failure
 - Provide patient education

