Dronedarone
Basic Pharmacology and Clinical Use

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KEYWORDS

• Dronedarone • Atrial fibrillation • Rhythm control • Antiarrhythmic drug

KEY POINTS

- Dronedarone is an amiodarone derivative shown to moderately reduce arrhythmia recurrence, decrease ventricular rate, and prevent hospitalizations in patients with nonpermanent atrial fibrillation (AF).
- In contrast, it increases all-cause mortality in patients with permanent AF and those with moderate to severe heart failure.
- Through CYP3A4 and P-glycoprotein inhibition, dronedarone has numerous drug interactions. Its use in combination with digoxin should be avoided or carefully monitored.
- Dronedarone is less effective than amiodarone, but has less thyroid and neurologic toxicity; direct comparison with other antiarrhythmic drugs and AF ablation is limited.
- Low-dose dronedarone with ranolazine seems to be promising for rhythm control, but a larger clinical trial is needed to assess its effect on cardiovascular outcomes.

INTRODUCTION

Atrial fibrillation (AF) is a highly prevalent arrhythmia with substantial morbidity and associated costs.[1] Drug therapy remains the cornerstone of AF management for the majority of patients and consists of anticoagulation and arrhythmia management (rate with or without rhythm control). In contrast with the approval and widespread clinical use of several novel anticoagulants for AF in the last decade, antiarrhythmic drug (AAD) development has been much less fruitful. Challenges facing AAD development in AF include (1) the complexity of AF pathophysiology, including multiple electrical and structural determinants,[2] (2) the lack of any clear-cut clinical benefit associated with a strategy of rhythm control when compared with the simpler approach of ventricular rate control,[3,4] (3) the toxicities associated with AADs, including ventricular proarrhythmia,[5] and (4) the "competition" with the rapid development of AF ablation.[6] Only a single new AAD has obtained approval by the US Food and Drug Administration (FDA) since 2000. Dronedarone was developed as an amiodarone derivative with less toxicity. Like amiodarone, dronedarone is a multichannel blocker. Randomized controlled trials (RCTs) of dronedarone involving nearly 10,000 patients have established the usefulness of the drug in AF but also highlighted its dangers in certain patient populations. Postapproval studies reiterate the benefits and risks of dronedarone use in "real life." This review summarizes the available pharmacologic and clinical data on dronedarone and discusses its place in the AF rhythm management armamentarium.

Disclosures: None (R. Tadros and S. Nattel); J.G. Andrade is supported by a Michael Smith Foundation Clinical Scholar award (Award No: 5963).

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Card Electrophysiol Clin 8 (2016) 453–465
http://dx.doi.org/10.1016/j.ccep.2016.02.008
1877-9182/16/$ – see front matter

BASIC PHARMACOLOGY

Molecular Structure: An Amiodarone Derivative

Dronedarone was designed based on the structure of amiodarone, with the objective of reducing side effects and decreasing its elimination half-life (**Fig. 1**).[7] Thyroid toxicity was eliminated by the removal of the 2 iodine atoms from amiodarone, and the reduction of half-life was accomplished by reducing lipophilicity through the addition of a methylsulfonamide group.

Pharmacokinetics

Peak dronedarone concentration is reached within approximately 4 hours of oral administration.[8] Although its absorption is good when taken with food, the oral bioavailability is only approximately 15% because of first-pass metabolism. Plasma protein binding exceeds 98%. Plasma steady state is reached within 7 days of oral administration of 400 mg twice daily (BID). Dronedarone elimination is predominantly through fecal excretion of metabolites formed by the cytochrome P450 CYP3A4. In contrast with amiodarone's long elimination half-life (several weeks), the lower lipophilicity of dronedarone reduces its half-life to approximately 24 hours.

Pharmacodynamics: Ion Channel Blockade

Similar to amiodarone, dronedarone is a multichannel blocker, which explains the broad range of its electrophysiologic effects. At progressively higher concentrations, it blocks the L-type calcium current (I_{CaL}), the rapid then slow components of the delayed rectifier potassium current (I_{Kr}, I_{Ks}), and the inward rectifier potassium current (I_{K1}).[9] Dronedarone also effectively blocks the cardiac sodium current (I_{Na}) in isolated human atrial myocytes, with minimal effects on its kinetics.[10] Bogdan and colleagues[11] demonstrate that I_{Na} and I_{CaL} blockade increases with a less polarized (less negative) holding potential. Such state-dependent block possibly contributes to dronedarone's atrial-selective properties, because atrial myocytes are less polarized at

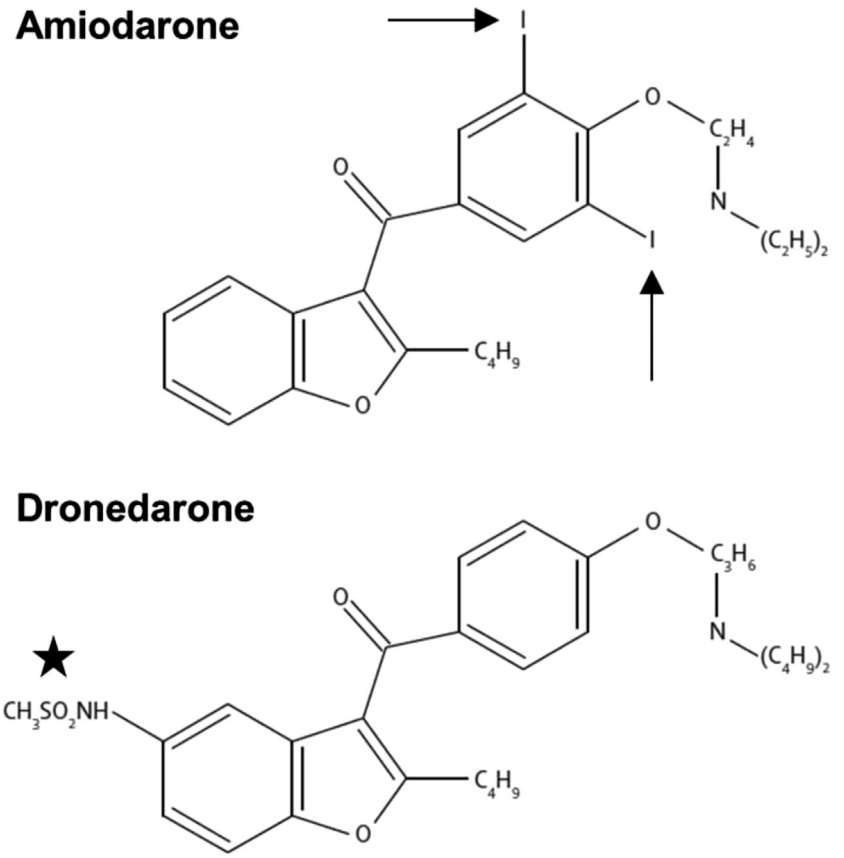

Fig. 1. Molecular structure of amiodarone and dronedarone. Dronedarone is derived from amiodarone by removing the iodine atoms (*arrows*) and adding a methylsulfonamide moiety (*star*). (*Adapted from* Dobrev D, Nattel S. New antiarrhythmic drugs for treatment of atrial fibrillation. Lancet 2010;375:1214; with permission.)