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Assessing the Risk for Peripheral Neuropathy in Patients Treated With Dronedarone Compared With That in Other Antiarrhythmics

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ABSTRACT

Purpose: There are few data on the risk for peripheral neuropathy associated with dronedarone, a newer antiarrhythmic medicine. The objective of this study was to assess whether dronedarone is potentially associated with an increased risk for peripheral neuropathy compared with other antiarrhythmics, including amiodarone, sotalol, flecainide, and propafenone.

Methods: The MarketScan database was used for identifying patients who were at least 18 years of age, had atrial fibrillation or flutter, and had not been diagnosed with peripheral neuropathy in the 180-day period prior to or on the date of the first prescription of an antiarrhythmic between July 20, 2009, and December 31, 2011. Peripheral neuropathy that occurred during the treatment period for a study drug was ascertained using ICD-9-CM diagnostic codes. For each antiarrhythmic, the incidence rate of peripheral neuropathy was calculated. The adjusted hazard ratio (aHR) for peripheral neuropathy for dronedarone compared with another antiarrhythmic was obtained, with control for age, sex, diabetes mellitus status, and the presence of other comorbidities.

Findings: The study population included 106,933 patients treated with dronedarone (n = 12,989), amiodarone (n = 45,173), sotalol (n = 22,036), flecainide (n = 14,244), or propafenone (n = 12,491). The incidence rates (per 1000 person–years) of peripheral neuropathy were 1.33 for dronedarone, 2.38 for amiodarone, 1.20 for sotalol, 1.08 for flecainide, and 1.97 for propafenone. The aHRs for peripheral neuropathy for dronedarone relative to other drugs ranged from 0.53 (95% CI, 0.21–1.34) compared with propafenone, to 0.94 (95% CI, 0.38–2.30) compared with sotalol. A new-user analysis showed similar results.

Implications: The risks for peripheral neuropathy were not significantly different between dronedarone and other antiarrhythmics. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: amiodarone, dronedarone, flecainide, peripheral neuropathy, propafenone, sotalol.

INTRODUCTION

Dronedarone is an antiarrhythmic medicine first approved in the United States in 2009 with indication to treat atrial fibrillation or atrial flutter.[1,2] Dronedarone demonstrates electrophysiologic characteristics of all of the 4 Vaughan-Williams classes of antiarrhythmics, and it mainly has a Class III effect and, to a limited extent, a Class I effect.[1]

While peripheral neuropathy is considered a class effect (amiodarone-like effect), data from the dronedarone clinical program did not suggest it as a signal.[1] In the postmarketing period, it is of interest to further monitor the risk for peripheral neuropathy in clinical practice. In addition, there have been limited data in the literature on the relative risk for peripheral neuropathy in patients treated with antiarrhythmics. For amiodarone, a Class III antiarrhythmic, several case reports have described the development of peripheral neuropathy,[3–8] and a few case-series studies have examined the risk for peripheral neuropathy.[9,10] For flecainide, a Class I antiarrhythmic, there were 2

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case reports of peripheral neuropathy.[11,12] However, there is a lack of population-based epidemiologic data examining the risk for peripheral neuropathy associated with antiarrhythmics, including dronedarone, which is a newer antiarrhythmic drug.[2]

Therefore, a retrospective cohort study was undertaken to examine whether dronedarone is potentially associated with a higher risk for peripheral neuropathy compared with other frequently prescribed major Class III and I antiarrhythmics, including amiodarone and sotalol (Class III antiarrhythmics), as well as flecainide and propafenone (Class I antiarrhythmics), using data from a large claims database.

MATERIALS AND METHODS

Database

The data source was the Truven Health MarketScan Research Database (Truven Health Analytics; http://marketscan.thomsonreuters.com/marketscanportal). This database covers the claims records of >165 million patients recorded since 1995 in the United States. In the MarketScan database, outpatient prescription-drug data are linked with inpatient and outpatient claims files by unique encrypted patient identifiers. The data used in this study were deidentified.

Study Population

The study population was identified using the MarketScan database. Patients who had a prescription for dronedarone, amiodarone, sotalol, flecainide, or propafenone filled between July 20, 2009 (the launch date of dronedarone in the United States), and December 31, 2011, were identified. The earliest exposure to a study drug determined the assignment of index study cohort, and the date of the first exposure to the study medication on or after July 20, 2009, was defined as the *index date*.

Excluded from the cohort were patients with any of the following conditions: (1) age of <18 years on the index date; (2) <180 days of continuous enrollment prior to the index date; (3) no diagnosis of atrial fibrillation or atrial flutter based on *International Classification of Diseases, Ninth Revision–Clinical Modification* (ICD-9-CM) diagnostic codes (427.31 for atrial fibrillation and 427.32 for atrial flutter) in any practice setting in the *baseline period,* defined as the 180 days prior to and including the index date; or (4) a diagnosis of the specific outcome event of interest during the baseline period.

Exposure Measurement

The exposure of interest was on-drug treatment with a study drug. The National Drug Code was used for identifying the 5 study drugs, dronedarone, amiodarone, sotalol, flecainide, and propafenone, in the MarketScan database. For each study drug, the first treatment episode in the study period started on the index date (when the drug was first dispensed) and continued for the duration of the days supplied. A 30-day or shorter gap between the end of the days' supply of a prescription and the dispensing date of the subsequent prescription was counted as *continuous*. For a study drug, a switch to a different study drug also ended its treatment episode on the date immediately prior to the date on which the second study drug was dispensed.

Follow-Up Period

For a patient in a particular study drug cohort, the follow-up period began on the index date and ended with one of the following events, whichever occurred first: (1) end of the first treatment episode; (2) end of enrollment in the MarketScan database; (3) end of the study period (December 31, 2011); or (4) occurrence of the outcome of interest, peripheral neuropathy.

Outcome of Interest

The outcome of interest was the first diagnosis of peripheral neuropathy after the index date and while on treatment with a study drug. Peripheral neuropathy was ascertained based on ICD-9-CM diagnostic codes from any practice setting (see **Supplemental Appendix I** in the online version at https://doi.org/10.1016/j.clinthera.2018.01.015).

Confounders

A number of potential confounders were considered in this study. These variables included age, sex, cohort entry year (year of index date), concurrent use of statins (defined on the index date), and history of comorbidities such as congestive heart failure, diabetes mellitus, hypertension, stroke, myocardial infarction, and renal failure. The comorbidities were defined based on ICD-9-CM diagnostic codes (see **Supplemental Appendix II** in the online version at https://doi.org/10.1016/j.clinthera.2018.01.015) from