Dofetilide dose reductions and discontinuations in women compared with men

Sean D. Pokorney, MD, MBA,*† Debbie C. Yen, PharmD,* Kristen B. Campbell, PharmD,* Nancy M. Allen LaPointe, PharmD, MHS,† Shubin Sheng, MS,† Laine Thomas, PhD,† Tristram D. Bahnson, MD, FHRS,* James P. Daubert, MD, FHRS,* Jonathan P. Picini, MD, MHS, FHRS,*† Kevin P. Jackson, MD,* Kevin L. Thomas, MD,*† Sana M. Al-Khatib, MD, MHS, FHRS*†

*From the *Electrophysiology Section, Division of Cardiology, Duke University Medical Center, Durham, North Carolina, and †Duke Clinical Research Institute, Durham, North Carolina.*

BACKGROUND Compared with men, women have longer corrected QT (QTc) intervals, lower clearance of dofetilide, and higher rates of drug-induced torsades de pointes, but the dofetilide dosing algorithm is the same for men and women.

OBJECTIVE The purpose of this study was to evaluate the tolerability of the 500 μg twice daily dose of dofetilide for men and women.

METHODS Men and women admitted to Duke University Medical Center (January 1, 2006, to October 19, 2012) for the initiation of dofetilide 500 μg twice daily were matched 1:1 on age and estimated creatinine clearance. Electrocardiograms throughout dosing were analyzed, and rates of dofetilide discontinuations and dose reductions were compared in unadjusted and adjusted analyses.

RESULTS For 220 matched men and women, the median age was 62.5 years (interquartile range 55–69 years) and the median eCrCl was 98.1 mL/min (interquartile range 77.6–126.2 mL/min). Women were less likely than men to have hypertension and interventricular conduction delay but were otherwise similar. During dofetilide initiation, women were more likely than men to have their dofetilide dose discontinued or reduced (55% vs 32%; $P < .001$). In most women (82%) and men (69%), the reason for dose adjustment was significant QTc prolongation. In the adjusted analysis, female sex was associated with higher rates of dofetilide dose discontinuations or reductions (odds ratio 3.01; 95% confidence interval 1.58–5.71; $P < .01$).

CONCLUSION More than half of women who initiated on 500 μg twice daily of dofetilide required medication discontinuations or dose reductions, mostly because of QTc prolongation. Additional studies are needed to evaluate the optimal dosing algorithm of dofetilide in women.

KEYWORDS Atrial fibrillation; Dofetilide; QT prolongation; Rhythm control; Women

(Heart Rhythm 2018;15:478–484)

Introduction

Professional society guidelines for atrial fibrillation (AF) recommend antiarrhythmic drug therapy for patients with symptomatic recurrent paroxysmal AF and recurrent persistent AF despite rate control.[1] Dofetilide has been shown to be effective in cardioversion of AF and maintenance of sinus rhythm in 2 randomized controlled clinical trials,[2,3] and as a result, dofetilide is the only antiarrhythmic agent that is recommended as a first line therapy for a wide range of patients with AF—those with and those without structural heart disease (coronary artery disease or heart failure).[1]

Dofetilide is a Vaughan Williams class III antiarrhythmic medication that blocks the rapid-delayed outward rectifier potassium current (I_{Kr}) during repolarization, which can result in a dose-related prolongation of the action potential duration and corrected QT (QTc) interval on an electrocardiogram (ECG).[4,5] Dofetilide is primarily excreted by the kidneys (70%–80%).[6] The Food and Drug Administration–

Dr Pokorney reports research support from the Food and Drug Administration, Bristol-Myers Squibb, Janssen Pharmaceuticals, Gilead, and Boston Scientific and consulting for Boston Scientific, Medtronic, and Bristol-Myers Squibb. Dr LaPointe reports salary from Premier Inc. Dr Bahnson reports research funds from Medtronic and St. Jude Medical and consulting fees and honoraria from Boehringer Ingelheim, ChanRX, Sequel Pharma, and Sanofi Aventis. Dr Daubert reports research support from Biosense Webster, Boston Scientific, Gilead, Medtronic, and St. Jude Medical; he is a consultant to and an advisory board member of Arca Biopharma, Biosense Webster, Biotronik, Boston Scientific, Gilead, Medtronic, St. Jude Medical, and VytronUS. Dr Picini receives funding for clinical research from ARCA biopharma, Boston Scientific, Gilead, Janssen Pharmaceuticals, Spectranetics, and St. Jude Medical and serves as a consultant to Allergan, Amgen, GlaxoSmithKline, Johnson & Johnson, Medtronic, and Spectranetics. Dr Jackson reports consulting for Medtronic. Dr Thomas reports consulting for Bristol-Myers Squibb, Janssen Pharmaceuticals, and Pfizer. **Address reprint requests and correspondence:** Dr Sean D. Pokorney, Electrophysiology Section, Division of Cardiology, Duke University Medical Center, DUMC 3845, Durham, NC 27710. E-mail address: sean.pokorney@duke.edu.

1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2018.01.027

approved dose selection algorithm for dofetilide is based on the estimated creatinine clearance (eCrCl; as determined using the Cockcroft-Gault equation). Lower initiation doses are selected for those with poorer renal function with the intent of minimizing the risk of QTc prolongation and torsades de pointes.[7] Women have a longer baseline QTc interval than do men,[8] and female sex has been associated with at least a 2-fold higher rate of torsades de pointes with class III antiarrhythmic drugs[9]; however, no differential dosing adjustment is recommended for women with the same eCrCl as men.

The purpose of this analysis was to explore the tolerability of the 500 μg twice daily dose of dofetilide that is the recommended initiation dose for both men and women with eCrCl >60 mL/min by comparing changes in QTc interval, adverse events, and rates of dose discontinuations or reductions between men and women.

Methods

Study population

This retrospective study included adult patients at Duke University Medical Center, initiating dofetilide for treatment of AF for the first time between January 1, 2006, and October 19, 2012, with a dose of 500 μg twice daily. Patients were identified through the Duke Enterprise Data Unified Content Explorer (DEDUCE), which is a research database of data collected through patient care at Duke University Medical Center. Manual chart abstraction was used to collect comorbid conditions, actual body weight, baseline QTc intervals, and QTc intervals after each of the first 5 doses of dofetilide, dofetilide discontinuations, dofetilide dose reductions, reasons in the chart for dofetilide dose discontinuations or reductions, adverse drug reactions, and electrophysiology procedures performed. Patients were excluded for the following reasons: previous treatment with dofetilide, reinitiation of dofetilide, or initiation of dofetilide at a dose less than 500 μg twice daily. As per hospital policy, all patients were monitored for at least the first 5 doses of dofetilide on continuous telemetry with daily electrolyte and renal function monitoring, as well as ECGs before the first dose of dofetilide and 2–3 hours after each dose. Patients were monitored by cardiologists or electrophysiologists who were certified dofetilide prescribers.

All women initiated on dofetilide for the first time at a dose of 500 μg twice daily during the study period were included in the analysis. These women were matched 1:1—on age and eCrCl—with men who were admitted during the study period for initiation of 500 μg twice daily of dofetilide for the first time. Serum creatinine on the day of or day before the initiation of dofetilide and actual body weight on admission were used to calculate the eCrCl by using the Cockroft-Gault equation. Patients in the analysis had eCrCl > 60 mL/min, so they were dosed appropriately with the 500 μg twice daily dose.

End points

Measurements of baseline QTc intervals and the QTc intervals after each dose of dofetilide were performed manually using the Bazett formula by a single cardiologist (S.D.P.). The ECG reader was blinded to patient sex, whether the ECG was taken at baseline or after one of the dofetilide doses, previous and future QTc interval values for a given patient, and patient outcomes (adverse events, dose modifications, or medication discontinuation). Measurements of QTc intervals were retrospective and independent of clinical care measurements. The QT interval was measured from the onset of the QRS complex to the intersection of the line of the maximal slope of the t wave and the TP baseline. The QTc interval measurement for an ECG in sinus rhythm was determined by a single beat in the limb leads. The QTc interval measurement for an ECG in AF was based on the average of 3 QTc interval measurements, including the shortest R-R interval in any lead, the longest R-R interval in any lead, and an intermediate R-R interval in the limb leads.[10]

Dofetilide discontinuations or dose reductions were determined through manual chart review. Dofetilide discontinuation was defined as initiation of the dofetilide 500 μg dose with subsequent discharge off dofetilide. *Dofetilide dose reductions* were defined as initiations of the dofetilide 500 μg twice daily dose with subsequent discharges on a dose less than 500 μg twice daily. *Dofetilide discontinuations* were defined as initiations of the dofetilide 500 μg twice daily dose with subsequent discharges off dofetilide. Decisions to modify the doses of dofetilide, either by medication discontinuations or by dose reductions, were made by the certified dofetilide prescriber who were clinically caring for the patients. Adverse events such as torsades de pointes, bradycardia-requiring pacemaker implantation, and in-hospital death were determined through chart abstraction. Recurrence of AF was evaluated 1 year after dofetilide initiation, and AF recurrence was defined as patient reported symptomatic recurrence of AF, ECG documented AF, or AF documented on Holter monitor.

Statistical methods

Men were identified for the analysis by matching them 1:1 to women on age and eCrCl. Patients were first matched on age with the goal of obtaining an exact match whenever possible. Patients were then matched on eCrCl, and women and men were a match if their eCrCl were within 10% of each other. If there were no matches based on eCrCl for patients of the same age, a match was then pursued for women and men with ages with a maximum of 5-year difference while maintaining the 10% difference in eCrCl; if there was still no match, the unmatched women (n = 2) were excluded from the analysis. If more than 1 match was identified, the matched pair with the closest eCrCl was used.

Baseline characteristics were compared between men and women. Categorical variables were summarized as counts and percentages and were compared using the Pearson χ^2 test. Continuous variables were summarized as medians and interquartile ranges and were compared using the Kruskal-Wallis test. The unadjusted number and prevalence of dofetilide discontinuations or dose reductions by sex during in-hospital initiation were reported. Logistic regression modeling assessed the adjusted association between sex and dofetilide