Dofetilide usage and effects on QT-prolongation in patients receiving concomitant QT-prolonging medications

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**Background**

- Dofetilide is a Vaughan-Williams Class III antiarrhythmic agent approved for the acute termination of atrial fibrillation or flutter and prevention of recurrence.
- Dofetilide has the potential to prolong the QT-interval via potassium channel blockade causing extension of the ventricular repolarization phase. There is a linear relationship between dofetilide concentration and the extent of QT-prolongation observed. The presence of QT-prolongation carries the risk of serious adverse events, including Torsade de Pointes (TdP).1,3
- Concomitant use of multiple agents with the potential to prolong the QT-interval may increase risk via pharmacodynamic (additive QT-prolonging effects) or pharmacokinetic (inhibitor/inducer relationships, effect on clearance of QT-prolonging agent, etc.) mechanisms.4
- Dofetilide prescribing information denotes eight absolutely contraindicated medications and multiple other medications listed as "cautionary." There is a paucity of data examining the clinical consequence of concurrent use of these cautionary medications with dofetilide.

**Objectives**

**Primary Objective**

- Determine the effect of the use concomitant cautionary medications on the change in the QT-interval during dofetilide initiation

**Secondary Objectives**

- Determine the rate of occurrence of TdP in patients receiving concomitant cautionary medications
- Determine the rate of occurrence of cardiac adverse events in patients receiving concomitant cautionary medications
- Determine the rate of occurrence of any adverse events in patients receiving concomitant cautionary medications
- Describe the effect of concomitant cautionary medications on the success of dofetilide initiation

**Study Design**

- Institutional Review Board (IRB) approved, retrospective, single-center study at a tertiary academic medical center

**Subject Selection**

- All potential subjects for inclusion have been identified via a query of the Duke Enterprise Data Unified Content Explorer (DEDUCE) database.
- The study population will include patients being newly initiated on dofetilide and receiving concomitant therapy with cautionary medications. These patients will be compared to a control group matched by sex, age, and renal function being newly initiated on dofetilide, but not receiving concomitant cautionary medications.

**Methods**

**Table 1. Cautionary Medications Included**

<table>
<thead>
<tr>
<th>Cautionary Medications</th>
<th>TCA's</th>
<th>Triamterene</th>
<th>Methadone</th>
<th>SSRI's</th>
<th>Amlodipine</th>
<th>Digoxin</th>
<th>Atypical Antipsychotics</th>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Chlorthalidone</td>
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<td></td>
<td>Metformin</td>
</tr>
</tbody>
</table>

**Figure 1. Study Population**

- Patients newly initiated on dofetilide July 15, 2013 through August 31, 2016

**Table 2. Study Inclusion and Exclusion Criteria**

**Inclusion Criteria**

- Age ≥ 18 years of age
- Initiation of dofetilide between July 18, 2013 and August 31, 2016
- Concomitant use of cautionary medications during initiation of dofetilide therapy
- ECG’s performed before, during, and after dofetilide initiation

**Exclusion Criteria**

- Intermittent use of cautionary medications or other potential QT-prolonging agents during dofetilide initiation
- Creatinine clearance less than 20 mL/min by Cockcroft-Gault formula
- Incomplete medical record

**Endpoints**

**Primary Endpoints**

- Absolute and percent change in QT-interval (milliseconds) after the first and fifth doses of dofetilide received during initiation in patients receiving concomitant cautionary medications, as compared to a control group not receiving cautionary medications

**Secondary Endpoints**

- Rate of occurrence of the following in patients receiving concomitant cautionary medications versus control group:
  - TdP
  - Any cardiac adverse events
  - Any adverse events
  - Dofetilide initiation failure (patient unable to tolerate medication for any reason)

**Data Collection and Analysis**

**Data Collection**

- Demographic and clinical data including age, sex, race, weight, serum creatinine, and medications will be collected
- Currently in process

**Statistical Analysis**

- Mixed analysis of covariance (ANCOVA) will be used to compare the change in QT-interval from baseline between groups. Two-sided 95% confidence intervals will be constructed with an upper bound of 10 milliseconds.
- Rates of dofetilide initiation failure will be compared using an independent samples t-test.
- Rates of adverse cardiac events, adverse events, and TdP will be analyzed using descriptive statistics.
- The QT-interval will be adjusted for heart rate using Bazett’s formula (QTc=QT/R). The QT-interval will be used if heart rate is < 60 beats per minute.

**Disclosures**

Authors of this presentation have the following conflicts of interest to disclose regarding personal or financial relationships with commercial entities that may have influenced the content or subject matter of this presentation.

- Cody Carson, PhD: Nothing to disclose
- Kristen Bova Campbell, PharmD: Nothing to disclose
- James Daubert, MD: Nothing to disclose

**References**

5) Thysv8/Package Insert. New York: Pfizer; 2013

**Figure 1**

- Study Cohort: Patients receiving concomitant cautionary medications
- Matched by: Sex, Age (+5 years), Renal Function (Cockroft Gault, ≥ 20 mL/min)
- Control Group: Patients not receiving concomitant cautionary medications