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Practice variation in the re-initiation of dofetilide: An observational study

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ABSTRACT

Background: Dofetilide is a class III antiarrhythmic drug that has been reported to be safe and efficacious in the treatment of atrial dysrhythmias with a known initial risk of QT prolongation and torsades de pointes (TdP). As a result, the Federal Drug Administration (FDA) mandated in-hospital dofetilide initiation and adherence to a common dosing protocol. However, there is a lack of clarity on how to manage dofetilide re-initiation.
Methods: An observational survey was performed including 347 cardiologists in the United States and worldwide to evaluate the deviations from approved manufacturer's protocol during dofetilide initiation and re-initiation among practicing cardiologists.
Results: Most practicing cardiologists were cautious about outpatient dofetilide use and adhered to the manufacturer's in-patient dofetilide protocol during *de-novo* initiation and reported low incidence of TdP in clinical practice. There were substantial differences among practicing cardiologists with deviation from the manufacturer's protocol during re-initiation of dofetilide. About 21% cardiologists always admitted patients to the hospital while 37% admitted patients < 10% of the time for dofetilide re-initiation. Only 4% reported major adverse events with outpatient dofetilide re-initiation. There was also wide variation regarding monitoring of electrolytes and QT interval as an outpatient with dofetilide.
Conclusion: There is significant practice pattern variation in the use of dofetilide for the management of AF. This degree of variation noted is concerning and is a reflection of the current lack of substantial clinical evidence in the re-initiation dofetilide protocol to help direct the provider.

1. Introduction

Atrial fibrillation (AF) is the most common significant cardiac dysrhythmia seen in clinical practice and is often associated with symptomatic impairment, decreased quality of life, an increased risk of stroke/systemic thromboembolism, heart failure (HF) and mortality [1–3]. Dofetilide is a class III antiarrhythmic agent that is currently recommended for maintenance of sinus rhythm in patients with atrial dysrhythmias such as AF, atrial flutter/atrial tachycardia [1] based on data from placebo-controlled trials [4–6]. Often times it is also used to treat paroxysmal atrial arrhythmias when other AADs have failed or patient has intolerance to them.

Although dofetilide has demonstrated to be safe and effective in the maintenance of sinus rhythm for various atrial dysrhythmias, including patients with congestive heart failure and coronary artery disease, [5] its associated initial risk of QT prolongation and possible TdP [7] have raised concerns in the medical community. As a result of which FDA, clinicians and the manufacturer has mandated in-hospital dofetilide initiation and adherence to a common dosing protocol in all patient populations [1,8]. Although there is a risk of TdP with QT prolongation, clinical studies have demonstrated discrepancy regarding dofetilide induced QT prolongation and TdP [4,9–12] especially when following the standard manufacturer's recommended dosing protocol [8]. While the practice guidelines for the *de-novo* initiation of dofetilide are relatively well established and followed, re-initiation of the same drug after a

Abbreviations: AF, Atrial Fibrillation; EKG, Electrocardiogram; AAD, Antiarrhythmic drug; VT, Ventricular tachycardia; ICD, Implantable Cardioverter Defibrillator; TdP, Torsades de pointes.

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patient has been "off" of it for a given time period is less standardized. There is a significant variability in clinical practice among physicians. Often times it is left to the interpretation of the physician.

However, we have noted some exceptions to standard dofetilide protocols by experienced prescribing cardiologists in routine clinical practice. Individual hospital protocols may dictate practice patterns at a given medical center with lack of available universal guidelines. Furthermore, there are no established guidelines or agreement among practicing cardiologists regarding protocols on dofetilide re-initiation if the dose was discontinued for a few days.

The aim of this study was to evaluate the variations from approved manufacturer's protocol during dofetilide initiation and re-initiation among practicing cardiologists and if there are any adverse effects from such deviation in routine clinical practice as reported by clinicians who use this drug regularly.

2. Methods

A survey was emailed to approximately 3500 cardiologists including fellows-in-training, general cardiologists, interventional cardiologists and electrophysiologists in the United States and worldwide to study their practice preferences regarding initiation and re-initiation of dofetilide and responses were received. The survey was emailed to the subscribers of a popular cardiovascular journal through their online edition and listserv of the American College of Cardiology Board of Governors to be distributed to their respective constituents. The survey was conducted online using a survey website www.surveymonkey.com. Dofetilide Usage Questionnaires (Appendix-1) were accompanied by a letter describing the purpose of the research and also emphasizing the importance of providing realistic answers based on the cardiologist's experience with dofetilide. Reminders were sent *via* email if there was no response within 1 month. A link to the survey was also displayed on the website the Journal of Atrial Fibrillation. The survey included questions about physician experience in prescribing dofetilide, any deviation from the drug standard protocol and any reported adverse events. The online survey is configured to not collect any identifying information of the respondent. All responses were collected by January 2016. All responses obtained were stored in a secure server.

2.1. Statistical analysis

The results are presented as absolute numbers as reported by the respondents. All the variables were categorical and expressed as percentages. The percentages were not adjusted for missing values. Statistical analyses were performed using the IBM SPSS (version 21.0, New York) statistical software program.

3. Results

3.1. Demographic and practice details of physicians

347 physicians completed the questionnaire (10%). Majority of the physicians were form North America (87%). A small group of physicians (13%) were from 5 other continents (South America, Europe, Australia, Africa and Asia). Demographic and practice details of physicians who completed the questionnaire are detailed in Table 1. Majority of the physicians were practicing electrophysiologists (67%), followed by general cardiologists (22%), interventional cardiologists (7%) and fellows-in-training (2%). Majority of the responders (85%) were part of a physician group that included >5 cardiologists. A total of 220 cardiologists (64%) had 15 or more years in practice. The majority (56%) of the clinical volumes of the respective practices consisted of at least 30% of AF.

Table 1
Demographics and practice details of physicians who completed the survey.

Demographic variables	$N = 347$
Specialty	
• General Cardiology	77(23%)
• Interventional Cardiology	25(7%)
• Electrophysiology	233(67%)
• Fellow-in-training	8 (2%)
• No response	4(1%)
Cardiologists'practice size	
• <5	48 (14%)
• 5–20	157(45%)
• 20–40	89 (26%)
• >40	47 (14%)
• No response	6 (1%)
Years in practice	
• <5	31(9%)
• 5–15	87 (25%)
• 15–25	121(35%)
• >25	99(28.5%)
• No response	9 (2.5%)
Geographic practice location	
• North America	303(87%)
• South America	3 (0.9%)
• Europe	26 (7.5%)
• Australia	3 (0.9%)
• Africa	3 (0.9%)
• Asia	4 (1%)
• No response	5 (1%)
Type of practice	
• Academic	138(40%)
• Private	140(40%)
• Hybrid	60(17%)
Type of patient population	
• Urban	167(48%)
• Rural	33(10%)
• Suburban	144(41.5%)
• No response	3(0.5%)
What % of clinical volume consists of patients with AF	
• <10	18(5%)
• 10–30	131(38%)
• 31–50	121(35%)
• >50	72(21%)
• No response	5 (1%)

3.2. Dofetilide initiation practice of physicians

Tables 2 and 3 demonstrate the dofetilide initiation practice of physicians who completed the survey. Approximately 80% (276/347) cardiologists have been prescribing dofetilide for >5 years in clinical practice. Dofetilide was not the first antiarrhythmic choice for most cardiologists (86%) for persistent AF. About 69% of cardiologist reported that <10% of their total AF patients were on dofetilide. Despite the fact that 50% of the cardiologists believe that the initiation of dofetilide has a low incidence of TdP, they were cautious or concerned regarding prolonged QT and were reluctant to initiate dofetilide as an outpatient (even if the patient had an implantable cardioverter defibrillator). Dofetilide would not be initiated in patients with a QTc >480 ms irrespective of the baseline wide complex QRS (>120 ms) on EKG [by 66% of respondents if baseline QRS > 120 ms and by 65% of respondents if baseline QRS < 120 ms]. The majority of the cardiologists (67%) reported that they deviated from the manufacturers protocol <5% of time and less often when there was drug related adverse events.

About 70% of the cardiologists reported that they would wait for at least 1 month after stopping amiodarone for amiodarone washout yet 61% reported that they would not check an amiodarone drug level prior to starting dofetilide. Only 5% of the cardiologist reported they would continue dofetilide with a lower doe and close follow up in patients who developed any polymorphic ventricular tachycardia irrespective of potassium (K+) and magnesium (Mg + 2) levels. About 25% reported monitoring of creatinine clearance, K+ and Mg + 2

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