Safety of Inpatient Dofetilide Initiation per Cardiology Services: A Retrospective Review

Carrie Cicirale, PharmD: PGY1 Pharmacy Resident at Mercy Medical Center – Canton, Ohio

- Corresponding author
- carrieLcicirale@yahoo.com
- Mercy Medical Center 1320 Mercy Dr NW Canton, OH 44708
- Personal address: 2909 Parklane St NW Apt B Canton, OH 44709

Jennifer Jackson, PharmD: Clinical Cardiology Pharmacist at Mercy Medical Center – Canton, Ohio

David Gothard: Statistician at Mercy Medical Center – Canton, Ohio

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Abstract

Introduction

Dofetilide is an antiarrhythmic medication that has the potential to cause life threatening arrhythmias, such as Torsade de pointes. The 2014 ACC/AHA/HRS guidelines for the management of patients with atrial fibrillation state that patients need to meet certain criteria to be initiated on dofetilide. Patients who are not initiated on this therapy according to the guideline criteria are likely to be at higher risk of adverse reactions.

Methods

This is a single center, retrospective chart review of patients who were initiated on dofetilide from July 2016-December 2019. Patients included in the study were initiated on dofetilide as a new antiarrhythmic and monitored inpatient for three days. The primary outcome was a composite of incidence of cardiac arrhythmias, cardiac arrest, cardiac death, and cardiac related hospital readmission.

Results

There were 224 patients included in the analysis: 190 patients who were initiated on dofetilide inappropriately and 34 that were initiated appropriately. The primary outcome (composite of cardiac arrhythmia, cardiac arrest, cardiac death, and hospital readmission) was statistically significant with more patients experiencing an outcome in the group initiated inappropriately.

Conclusions

Patients are placed at a higher risk of adverse reactions when this potentially dangerous antiarrhythmic medication is not used according to the protocol set forth by the guidelines. Practitioners should use caution when prescribing dofetilide. Other antiarrhythmic medications or non-pharmacologic options should be considered due to the incidence of these dangerous adverse reactions.

Keywords: antiarrhythmic, atrial fibrillation, dofetilide, Torsade de pointes, cardiology

Introduction

Dofetilide is a class III antiarrhythmic medication that is used for patients with atrial fibrillation and atrial flutter to maintain normal sinus rhythm. It selectively blocks potassium channels on the heart, which delays repolarization and increases the action potential, which slows conduction and converts arrhythmias into a normal rhythm. Dofetilide also can cause serious adverse reactions, such as Torsade de pointes, a heart rhythm that can lead to cardiac death. The Mercy Medical Center dofetilide initiation protocol, which is based off the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines for the management of patients with atrial fibrillation, states that patients who have had atrial fibrillation for more than one week can be initiated on dofetilide therapy after they convert to normal sinus rhythm if they meet certain criteria. These criteria include having a QTc interval ≤440 milliseconds (or ≤500 milliseconds in ventricular conduction abnormalities), appropriate dosing of the medication based on the patient's renal function, not having concurrent QTc prolonging agents, and being on continuous ECG monitoring for three days after initiation. Doses should then be adjusted based on further ECG readings and CrCl changes. [1] Despite having this protocol in place, patients are receiving dofetilide therapy who do not meet the protocol's criteria, therefore placing the patient at risk of Torsade de pointes, other life threatening arrhythmias, and sudden cardiac death.

According to the guidelines for the treatment of atrial fibrillation, dofetilide is a class IA recommendation for antiarrhythmic therapy, along with other agents such as flecainide, propafenone, and ibutilide. Initiating dofetilide outside of the hospital is a class IIIB recommendation for harm of the patient because of the increased risk of Torsade de pointes due to QTc prolongation. Contraindications to this medication include prolonged QTc, severe renal insufficiency, hypokalemia, hypomagnesemia, concomitant diuretic therapy, and therapy with other QTc prolonging agents. If transitioning from amiodarone to dofetilide, patients must wait at least three months in order for amiodarone to be eliminated from the body.

Absolute contraindicated drug interactions include verapamil, hydrochlorothiazide, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol.[1]

There are various large trials that prove the efficacy and safety of dofetilide in patients with atrial fibrillation who need to be pharmacologically converted into normal sinus rhythm. In the SAFIRE-D trial, which compared dofetilide to placebo in patients with atrial fibrillation or atrial flutter, dofetilide was found to be moderately effective in converting and maintaining normal sinus rhythm in patients followed for one year. It was also shown to be safe when used appropriately and was associated with a small, but potentially dangerous, proarrhythmic risk. There were two cases of Torsade de pointes and one case of cardiac death out of the 105 patients enrolled in this study.[2] Another ground breaking trial regarding the use of dofetilide was the DIAMOND-CHF trial, which evaluated the safety of dofetilide in patients with heart failure with reduced ejection fraction ≤35%. This study proved that use of dofetilide in these patients was safe and effective in both converting patients into normal sinus rhythm as well as preventing hospitalizations due to heart failure exacerbations.[3] Options for antiarrhythmic therapy for patients with heart failure with reduced ejection fraction are limited to amiodarone and dofetilide, which provides a challenge for providers when treating patients with systolic heart failure in addition to arrhythmias.
A study that was conducted at Cleveland Clinic evaluated the safety of dofetilide in patients who were initiated on therapy from 2008-2012. In this time, they included 1404 patients in their evaluation, and found that 17 of these patients (1.2%) experienced Torsade de pointes during their initiation period. Ten of the patients (0.7%) experienced cardiac arrest, one of whom died during this arrest. The patient characteristics that were associated with a higher incidence of Torsade de pointes were female sex, doses of 500 mcg, reduced ejection fraction, and prolonged QTc. The most common reasons for discontinuation in this study were asymptomatic QTc prolongation, ineffectiveness of the medication, and occurrence of arrhythmias.[4] On March 9th, 2016, the Risk Evaluation and Mitigation Strategies (REMS) program that was available for dofetilide was eliminated. Researchers discovered the risk associated with dofetilide was

lower than previously thought and did not differ much from other antiarrhythmic agents available. Since these other agents did not have a REMS program associated with their use and carried the same risk of arrhythmias, the REMS program was then eliminated and providers were able to prescribe dofetilide as freely as other medications. Since this program was removed, providers were encouraged to reference the criteria found in the 2014 guidelines in order to initiate this medication on appropriate patients.[5,6] With the guidelines in place and the REMS program gone, health care providers were entrusted to prescribe dofetilide appropriately based on the resources available to them. Unfortunately, this medication is often still prescribed inappropriately, putting patients at risk of harmful arrhythmias, and the question remains just how harmful these adverse reactions can be for patients who are initiated on this therapy against the recommendations of the guidelines.

Methods

This study was a single center, retrospective chart review of patients who were initiated on dofetilide from July 2016-December 2019 at Mercy Medical Center. Patients were included in the study that were initiated on dofetilide as a new antiarrhythmic therapy and admitted for three days on continuous electrocardiogram (ECG) monitoring. Patients were excluded if they were initiated on dofetilide as a continuation of a home medication, if they were less than 18 years old, or if they were pregnant. The primary outcome of this study was a composite of incidence of Torsade de pointes or other cardiac arrhythmias, cardiac arrest, cardiac death, or readmission within 30 days for a worsening cardiac condition. Secondary outcomes included each of these outcomes separately in order to evaluate which outcome might drive the data. Other data that was collected was QTc intervals before and after initiation of therapy, discontinuation or dose adjustments of the medication, maintenance of normal sinus rhythm before discharge, differences among male and female patients, differences among patients with other cardiac conditions, use of other antiarrhythmic medications before dofetilide, and magnesium and potassium levels during initiation period.

Statistical Analysis

Data were imported into SPSSv25.0 software (IBM Corp, Armonk, NY) and analyzed using $p<0.05$ considered statistically significant via two-sided testing. Categorical comparisons including all primary and secondary outcomes were determined via Pearson chi-square or Fisher's exact tests depending on cell sample sizes. Mean comparisons between the appropriate and inappropriate dichotomy were performed via independent samples Student's t tests. Finally an exploratory ROC curve was determined for baseline QTc value and the primary composite outcome. Youden's J index was calculated for each value and the maximum value was determined as the cut point for increased risk of the primary outcome.

Results

A total of 224 patients initiated on dofetilide were included in the analysis: 190 patients were initiated on this medication inappropriately according to the policy, while only 34 patients were initiated appropriately on dofetilide. Baseline characteristics were comparable among groups, therefore demonstrating a reduced risk of selection bias that could confound the results. Baseline age, gender, body mass index (BMI), arrhythmic diagnosis, cardiac history, and renal function (measured by creatinine clearance) are outlined in table 1.

The primary outcome, a composite of cardiac arrhythmias, cardiac arrest, cardiac death, and cardiac related readmission within 30 days, had a significantly higher percentage of outcomes occurring in patients who were initiated on dofetilide inappropriately (45.8% vs. 5.9%, $p<0.001$). Initiating a patient on dofetilide inappropriately places them at a 13.5 times higher relative risk of experiencing one of these negative cardiac outcomes compared to patients who are initiated on therapy appropriately according to the guidelines and protocol (RR 95% CI [3.15-58.0]). Secondary outcomes, each of these composite constituencies evaluated on their own, showed statistically significant differences in cardiac arrhythmias

and cardiac related readmission. No patient experienced cardiac death during their initiation period of dofetilide. There were four cases of cardiac arrest in the inappropriate use group, while there were no cases of cardiac arrest in patients who were initiated appropriately on therapy. There was also a significantly higher percentage of patients who were readmitted to the hospital for a cardiac related condition in the inappropriate use group compared to patients in the appropriate use group (21.1% vs. 5.9%, p=0.037). These results are outlined in table 2.

Other data that was collected and analyzed was regarding QTc changes, incidence of acute kidney injury (AKI), and potassium and magnesium levels during initiation. An AKI was defined as an increase of serum creatinine (SCr) ≥0.3 mg/dL. The baseline QTc intervals and post initiation QTc intervals were collected and averaged, and the difference between these values was calculated and recorded as change in QTc. There were statistically significant differences detected in each of these values between both of the groups. There was no statistically significant difference in incidence of AKI between each group. The potassium and magnesium levels also did not show a statistically significant difference among groups. These results are summarized in table 3.

Discontinuation of dofetilide during the initiation period occurred in 17/224 (7.6%) of patients, and dose changes occurred in 76/224 (33.9%) of patients. The most common reasons for dose changes during initiation included QTc changes and renal function changes, which is guided by the protocol. Some doses were increased due to the patient's rhythm remaining in atrial fibrillation or atrial flutter. Most common reasons patients were discontinued on therapy included experiencing adverse reactions to the medication, asymptomatic QTc prolongation, incidence of AKI, and ineffectiveness of the medication. A few patients discontinued therapy on their own due to inability to afford the medication. The most disturbing statistic is that out of the 57 patients who experienced life threatening cardiac arrhythmias during their initiation period, only three of these patients had their dofetilide discontinued, and out of the four patients who experienced cardiac arrest, only one of them had dofetilide discontinued. The other

three were discharged on this antiarrhythmic medication that could have contributed to these harmful outcomes.

In terms of efficacy in converting to and maintaining normal sinus rhythm, 23/224 patients were not maintained in normal sinus rhythm and had either constant continuation of their arrhythmias or were in and out of their arrhythmias before discharge. 172/224 (76.8%) of patients were previously treated with other antiarrhythmic medications or nonpharmacological interventions that ended up failing to convert them into normal sinus rhythm before attempting dofetilide. The remaining 52 patients were using rate controlling agents to treat their atrial fibrillation before deciding to be treated with antiarrhythmic agents. The most common antiarrhythmic medications and other interventions that patients attempted before dofetilide initiation are highlighted in table 4.

One of the criteria for dofetilide initiation stated in the guidelines and outlined in the protocol is not having concomitant use of other QTc prolonging agents. This was one of the reasons many patients were considered to be initiated inappropriately, along with high QTc intervals and not being dosed appropriately based on their renal function. Along with QTc prolonging medications, other medications that can affect the renal elimination of dofetilide are also contraindicated in these patients. The most common example of this is the use of hydrochlorothiazide, which can increase the serum concentration of dofetilide and lead to further QTc prolongation and dangerous arrhythmias. Table 5 highlights the medications that patients were on that were contraindicated with dofetilide use. Note that some patients were concurrently taking more than one of these medications along with dofetilide.

A receiver operation characteristic (ROC) curve (table 6) was determined to evaluate the QTc interval in relation to the risk of experiencing a cardiac outcome. The area under the curve was significantly greater than 0.5 indicating a significant association (AUC=0.657, $p<0.001$). A baseline QTc of 467.5 or greater was associated with an 88% increased relative risk of experiencing cardiac arrhythmias, cardiac arrest, cardiac death, or cardiac related readmission.

Discussion

Based on these results, when providers are initiating patients on dofetilide inappropriately based on the protocol criteria, they are placing patients at an increased risk of adverse reactions to the medications that could place them at harm. There were other factors taken into account and recorded in order to assure that these results were due to inappropriate use of these medications and nothing else. Potassium and magnesium levels were important data points to collect in this patient population. These electrolyte values are important in patients being initiated on dofetilide because hypokalemia and hypomagnesemia are both risk factors for developing arrhythmias such as Torsade de pointes. Development of an AKI could also contribute to increased risk of adverse reactions of dofetilide because the medication would not be sufficiently eliminated by the kidneys. Because incidence of AKI and potassium and magnesium levels did not differ in each group, this proves that these factors are not contributing to cardiac outcomes, and that going against the protocol is mainly what is leading to worsening outcomes.

The outcome that is least directly related to dofetilide use is cardiac related readmissions. Cardiac related readmissions can include a wide range of conditions and diagnoses, therefore the specific reasons were recorded as well. The most common reason for readmission that occurred was worsening atrial fibrillation or atrial flutter, which occurred in 34/42 (81.0%) of the patients who were readmitted within 30 days. 3/42 (7.1%) patients were readmitted due to both worsening atrial fibrillation along with heart failure exacerbations. The remaining 5/42 (11.9%) were admitted due to chest pain and ultimately were diagnosed with acute coronary syndromes.

Because the most common reason patients were returning to the hospital was due to worsening arrhythmias, this speaks more to the efficacy of the medication rather than its safety. The conclusion can be drawn that dofetilide is only moderately effective in maintaining normal sinus rhythm in these patients, which is consistent with the large trials regarding the use of this medication.

Conclusions

There are several limitations to this study. First, the nature of the study being a retrospective evaluation of patients who were initiated on dofetilide does not have as much internal validity as a prospective study. Additionally, the study only followed patients during their admission to Mercy Medical Center and did not follow up on patients when they were discharged, except for those who were readmitted to the same institution within 30 days. This does not allow for outcomes that could have occurred outside of the hospital to be recorded and included in the analysis. Also patients who may have presented at other institutions would not have been detected by electronic health records. This may alter the results of the study. However, this could have potentially increased the amount of outcomes that were recorded. The events that did occur during hospitalization were enough to detect a statistically significant difference. Another limitation included this being a single center study, which decreases the external validity and generalizability of the results. However, there were not strict inclusion and exclusion criteria and patients included in the study were reflective of the population that will be utilizing this medication. Larger, multicenter studies on this topic should be conducted in order to confirm these results.

There were also strengths to this study, such as the statistically and clinically significant results that were found among the two groups. This reaffirms that the criteria from the guidelines are in place for a reason, and this reason is to keep patients safe from life threatening adverse reactions from dofetilide. These results can be used to ensure that physicians are prescribing this medication appropriately and considering other options when the use of dofetilide is not appropriate. Other strengths include a low risk of bias or confounding altering the results. This further strengthens the internal validity of this study. Another strength of this study is that it was adequately powered; at least 30 patients were needed in each group to perform the statistically analysis.

Dofetilide is an effective medication for converting patients into normal sinus rhythm, and it is considered a first line option for antiarrhythmic therapy according to the guidelines.[1] However, the possibility of cardiac arrhythmias and cardiac arrest is a real risk associated with its use, and this risk should not be taken lightly or overlooked by practioners. The criteria needed to be met in order to initiate this medication should be closely monitored by providers. Having a multidisciplinary team evaluating options for antiarrhythmic therapy can assist in making sure the patient is receiving the most appropriate, safest, and most effective medications for cardiac arrhythmic disorders. Pharmacists who are experts in cardiac medications can offer assistance and guidance for providers who are considering using dofetilide for their patients. Having multiple healthcare professionals involved in this process and more closely following the guidelines and protocols that are available can improve patient safety and lead to better outcomes for these patients and institutions.

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