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Dronedarone for Atrial Fibrillation Prophylaxis in Patients Undergoing Open Heart Surgical Interventions: A Case Series

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Abstract

Atrial fibrillation (a-fib) is one of the most frequently encountered and studied arrhythmias in medicine. The presence of a-fib in the post-operative period of coronary artery bypass graft (CABG) surgery is of particular concern for clinicians as this presents risks of post-operative stroke, hospital readmission, or anticoagulation dilemmas depending on the patient's comorbidities. In this case study, we present 5 patients who were treated with dronedarone prior to undergoing open heart procedures. We subsequently followed each patient's clinical course paying close attention for any evidence of post-operative a-fib.

Keywords: Atrial fibrillation, Dronedarone, Coronary artery bypass graft, Postoperative arrhythmia

1. Introduction

Atrial fibrillation (a-fib) is the most common arrhythmic complication from coronary artery bypass graft (CABG) surgery accounting for approximately 15–40% of all complications of this surgery.1 In aortic valve replacement surgeries, this number is larger ranging from 37 to 50% incidence in the early post-operative period.2 Typically, the peak incidence for post-operative atrial fibrillation (POAF) is on postoperative day 2; making a-fib prophylaxis an important part of patients perioperative clinical care.2 Current management in the perioperative period of CABG entails pre- and postoperative treatment with amiodarone to prophylaxis against atrial fibrillation.3 In a 2006 meta-analysis, this was demonstrated to both reduce length of stay and reduce postoperative stroke incidence.2 The pathophysiology of POAF is multifactorial and somewhat theoretical including inflammation around the atrium with possible remodeling of the atrial electrical conduction system.4 Overall, this topic is of importance as atrial fibrillation confers a long-term mortality risk, impacts in-hospital stroke burden, and can significantly change a patient's quality of life. Moreover, it correlates with an increased utilization of hospital resources and subsequent increase in cost for the health care system.5 Amiodarone is a commonly prescribed medication but it does come with the risk of several side effects which prevents its usage across all patients for atrial fibrillation prevention post-cardiac surgery.3,6 While the efficaciousness of amiodarone has been demonstrated in multiple trials such as the ARCH trial and PAPABEAR trial, additional anti-arrhythmic medications are available and require further investigation. One medication that is available as a potentially safer alternative is dronedarone, which was studied in several trials including the PALLAS trial, ATHENA...
trial, and DIONYSOS trial for POAF prophylaxis.7 The primary intent of this case series is to extrapolate from the literature regarding the use and pharmacology of dronedarone while analyzing its effect in prevention of atrial fibrillation in the patients we studied who underwent an open-heart surgical intervention.

2. Methods

This observational case series was conducted among patients admitted to our hospital who after undergoing cardiac interventions, were found to have indications for open heart surgery, primarily coronary artery bypass grafting or valve repair. A retrospective chart review was performed on 6 patients who were deemed to have clinical indications for open heart surgery and met inclusion criteria for dronedarone use. The inclusion criteria for patients in this study were no previous history of atrial fibrillation (permanent or paroxysmal) or use of anti-arrhythmic drugs, no history of heart failure, and consent for the clinically indicated open heart surgical procedure. One patient was excluded as they did not undergo open heart surgery. Each patient was prescribed dronedarone 400 milligram (mg) per oral (po) twice daily (bid) from the cardiologist upon consenting for the open heart surgical intervention. Patients were subsequently taken for the surgical procedure and telemetry data and electrocardiograms (EKG) in the postoperative period were reviewed for evidence of atrial fibrillation.

2.1. Patient case 1

72 year old male with a history of type 2 diabetes mellitus (T2DM), coronary artery disease (CAD) status post percutaneous coronary intervention (PCI) with 3 stents, hypertension (HTN), hyperlipidemia (HLD) presented with complaints of 2 week history of chest pain worse with exertion, associated with shortness of breath and diaphoresis. His point of care (POC) troponin was 0.68 ng/mL and lab troponin was 1.19 ng/mL. Admission EKG demonstrated normal sinus rhythm (NSR) with left bundle branch block (Fig. 1a). He was treated as non-st-elevation myocardial infarction (NSTEMI) and taken for left heart catheterization (LHC) on hospital day 2. LHC revealed triple vessel disease and the patient was referred to cardiothoracic surgery for CABG and dronedarone 400 mg po bid was started. CABG was performed on hospital day 5. EKG on hospital day 7 demonstrated atrial fibrillation with rapid ventricular response (Fig. 1b). The patient subsequently underwent transesophageal echocardiogram guided cardioversion on hospital day 7. This was shown to be successful.
2.2. *Patient case 2*

77-year-old male with a past medical history of CAD status post stent to left anterior descending artery (LAD), HTN, sick sinus syndrome status post pacemaker, T2DM who presented for elective left heart catheterization. EKG on admission demonstrated sinus bradycardia, right bundle branch, and t wave abnormalities (Fig. 2a). On admission, his POC troponin was 0.01 ng/mL. Left heart catheterization demonstrated left main artery disease and in stent restenosis of the stent in the LAD and patient was scheduled for CABG. Two days prior to the procedure, the patient was started on dronedarone 400 mg po bid. On pump CABG was performed with grafts created from left internal mammary artery (LIMA) to (LAD) and saphenous venous graft (SVG) to first obtuse marginal (OM1) artery. There were no intraoperative or postoperative complications. Post-operative ejection fraction (EF) was 55%. Postoperative EKG demonstrated NSR and an incomplete right bundle branch block (Fig. 2b). The patient was discharged on dronedarone on postoperative day (POD) 4. The patient remained in normal sinus rhythm throughout his postoperative hospital course.

2.3. *Patient case 3*

51-year-old male with past medical history of HTN, HLD, meniere’s disease and T2DM who presented with 8/10 chest pain (0 being no pain, 10 being the worst pain of their life) associated with shoulder pain and diaphoresis. EKG demonstrated NSR, right bundle branch block pattern (Fig. 3a). Troponin was 0.245 ng/mL on admission. Patient was diagnosed with NSTEMI and cardiology was consulted for cardiac catheterization where it was discovered the patient had 90% occlusion of the left main artery, 90% occlusion of the ostial branch of the LAD, and 90% occlusion of the left circumflex. Echocardiogram demonstrated ejection fraction of 55%. Patient was subsequently referred to cardiothoracic surgery for CABG and was started on dronedarone 400 mg bid on hospital day 1. On pump double vessel CABG was completed on hospital day 3: LIMA to LAD and SVG to OM1. Post-operative course was uneventful. Dronedarone was resumed post-operatively until discharge on hospital day 8. EKG from hospital day 6 demonstrated: NSR, with right bundle branch pattern (Fig. 3b). He was discharged uneventfully.

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Fig. 2. a Pre - Operative EKG for patient 2: Atrial paced rhythm, Right bundle branch block, QTc 468, Ventricular rate 60 BPM, QRS 138 ms. Post - Operative EKG for patient 2 notable for Normal sinus rhythm, incomplete Right bundle branch block, QTc 482 ms, Ventricular rate 68 BPM, QRS 118 ms.
2.4. Patient case 4

72-year-old male with past medical history of severe multi-vessel CAD, carotid artery disease, HTN, T2DM, HLD, chronic kidney disease (CKD) Stage 3 presented to our facility with band like substernal chest pain that radiated to the jaw which was relieved with nitroglycerin. Admission EKG demonstrated NSR (Fig. 4a). He underwent left heart catheterization on the day of admission and found to have multi vessel disease with in-stent restenosis. Patient was medically managed with heparin drip, antihypertensive medications as well as dronedarone 400 mg po bid which was started 2 days prior to CABG. The patient received quadruple bypass on hospital day 3: LIMA to LAD, SVG to OM1, SVG to proximal descending artery (PDA), SVG to 1st diagonal. Post-operative EF was 40–45%. Post-Operative EKG showed sinus rhythm with 1st degree block (Fig. 4b). Patient, however, did not tolerate dronedarone, citing gastrointestinal side effects. He was switched to amiodarone and discharged uneventfully on hospital day 8.

2.5. Patient case 5

66 year old male with past medical history of hypothyroidism and lymphedema presented for shortness of breath and worsening lower extremity peripheral edema. EKG on hospital admission demonstrated NSR and left ventricular hypertrophy (Fig. 5a). Echocardiogram on hospital day 1 demonstrated vegetation on the aortic valve (AV) but had poor acoustic quality so transesophageal echo was completed on hospital day 3; this demonstrated EF 55%, irregular solid mobile vegetation on non-coronary cusp of AV, and severe regurgitation, valve area of 1.67 cm². Cardiac catheterization was completed which demonstrated no severe obstructive CAD however confirmed severe aortic valve regurgitation. He was deemed a surgical candidate for aortic valve replacement. Patient was started on dronedarone 400 mg po bid on day 5. Open heart surgery for valve repair took place on day 5 with placement of a 23 mm prosthetic tissue valve. Recovery from cardiac surgery was uneventful. Post-operative EKG showed sinus tachycardia (Fig. 5b). The patient’s hospital course, however, was complicated with heparin induced thrombocytopenia and bacteremia resulting from the endocarditis. Dronedarone was continued until discharge on day 34. Sinus rhythm was maintained throughout this patient’s hospital course.

3. Discussion

The primary goal of this case study is to illustrate the potential utility of perioperative dronedarone in
the prevention of new onset atrial fibrillation after open heart surgery in the hospital setting. The literature has proven that new onset atrial fibrillation after CABG procedures is an independent predictor of long-term risk for stroke and mortality. Thus, providing an effective modality for atrial fibrillation prophylaxis is an important consideration for these patients, while limiting potential side effects and re-hospitalizations.

Amiodarone is a commonly utilized antiarhythmic for atrial fibrillation prophylaxis. In the ARCH TRIAL, it was demonstrated that amiodarone
reduced postoperative atrial fibrillation from 47% in the placebo arm to 35% in the treatment arm.\textsuperscript{6} It’s use has been widespread in the prophylactic treatment of atrial fibrillation in both CABG procedures and valvular interventions. However, one of the large constraints with amiodarone is the concern of numerous side effects. These include: QTc interval prolongation, hypotension, bradycardia, pulmonary toxicity, hepatotoxicity, and thyroid derangements.\textsuperscript{7}

Dronedarone, a benzo furan derivative comparable to amiodarone, offers a viable alternative. The designers of the medication sought to improve amiodarone by creating a de-iodinated variant with the hopes of reducing the toxicity of the medication. Subsequently, dronedarone is noted to have improved pharmacokinetics with a shorter half-life and reduced accumulation in tissues. These attributes lead to a lower adverse effect profile and effective maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation.\textsuperscript{9} While many antiarrhythmic medications including sotalol and dofetilide often require hospitalization to monitor QTc and development of Torsades de Pointes, dronedarone can safely be started outpatient as the pro-arrhythmic risks are relatively low. Moreover, patient populations with coronary artery disease could start on dronedarone as it was found to be safe and effective in the ATHENA trial. Given the improved side effect profile when compared to amiodarone and our intention to use as a prophylactic agent for atrial fibrillation, we think that dronedarone is a safer alternative with a shorter half-life as to prevent complications and re-hospitalization for our patients who underwent open heart surgical interventions.

In the PALLAS study, dronedarone was used for patients with known permanent atrial fibrillation for at least 6 months prior to being enrolled and was stopped early due observance of primary endpoints including stroke, myocardial infarction or death from cardiovascular causes.\textsuperscript{10} However, our case series assessed dronedarone use in patient with no known history of atrial fibrillation in the past, permanent or paroxysmal. We used a short course of dronedarone (2–3 days pre-operative and 2–3 days post operative from open heart surgical intervention) in an effort to reduce the known complications and associated mortality from post operative atrial fibrillation. The DIONYSOS study was a head to head comparison of dronedarone vs amiodarone that also had an inclusion criteria of known history of atrial fibrillation and assessed efficacy of each medication with a primary end point of atrial fibrillation recurrence.\textsuperscript{7} Again, our case study included a sample of patients without history of atrial fibrillation and our objective was to observe dronedarone use for prevention of new onset atrial fibrillation among those who underwent open heart surgical intervention.

The aforementioned ATHENA study, a double blinded prospective clinical trial, assessed dronedarone 400 mg po bid in patients with paroxysmal or persistent atrial fibrillation or atrial flutter. Compared to standard therapy, dronedarone demonstrated relative risk reduction in first hospitalization of 24%. Dronedarone reduced all-cause mortality by 16%, cardiovascular related mortality by 29%, stroke mortality by 26%, and overall length of stay by 1.26 days/patient/year.\textsuperscript{11} Next, the Euridis and the Adonis trials studied by Singh et al. evaluated the use of dronedarone in atrial fibrillation and atrial flutter.\textsuperscript{12} It was found that dronedarone significantly reduced the risk of atrial fibrillation recurrence after cardioversion compared to placebo. The Euridis trial demonstrated a first recurrence of atrial fibrillation reduction of 22% and the EURIDIS demonstrated at 27.5% reduction. Post procedural atrial fibrillation prophylaxis data, however, is limited. Specifically, on pump/off pump CABG as well as valvular procedures.

In this small observational case series, we sought to demonstrate dronedarone as being an effective agent in the prevention of post-cardiac surgery new onset atrial fibrillation. Three out of the five cases in which dronedarone was utilized demonstrated no atrial fibrillation after postoperative follow-up in the inpatient setting. Patient case 4 demonstrated intolerance to the medication citing gastrointestinal side effects which is fairly common for this medication. Thus, its ability to maintain sinus rhythm in that patient was unable to be truly characterized. As mentioned before, typically the highest incidence of arrhythmia is on day 2 post operatively but atrial fibrillation incidence typically remains high in the acute postoperative period. We sought to demonstrate the potential utility of dronedarone in hospital for the perioperative period for atrial fibrillation prophylaxis for multiple cardiac surgical indications such as CABG, surgical aortic valve repair, etc.

Of course, like any medication, dronedarone is not without its side effects. Most commonly these patients will experience diarrhea, nausea (commonly grouped as gastrointestinal intolerance), bradycardia, or cutaneous rash. Most commonly patients, such as the one in case 4, will not tolerate dronedarone due to gastrointestinal side effects. This was also observed in the DAFNE trial. Prior to use, absolute contraindications to the medication must be considered. Dronedarone is contraindicated in class II/III NYHA heart failure especially in those with recent decompensation. Another absolute contraindication are patients...
with chronic atrial fibrillation. Thus, for the purposes of this study, patients with prior history of atrial fibrillation were excluded from the study. Other contraindications clinicians should be cognizant of are bradycardia especially those with sick sinus syndrome or heart block, a QTc of 500 milliseconds, patients with severe hepatic impairment, pregnant women, and patients on medications such as antifungal or macrolides.

4. Conclusion

Dronedarone offers a potentially viable solution for atrial fibrillation prophylaxis post-CABG and post-valvular intervention. Given the trial data surrounding its use and the favorable side effect profile in comparison to amiodarone, we hope to shed light on its potential application for prophylaxis against postoperative atrial fibrillation. Our study demonstrated effective maintenance of normal sinus rhythm in the immediate postoperative period following open heart surgical intervention. However, more trial data is needed for the indication of atrial fibrillation prophylaxis in the hospital and likely those needing longer follow up periods.

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Conflict of interest

There are no conflicts of interest for this publication.

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