Research & Reviews: Journal of Hospital and Clinical Pharmacy

Dronedarone-induced Pulmonary Toxicity - A Case Report and Literature Review

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Case Report

Received date: 16/03/2016
Accepted date: 06/04/2016
Published date: 20/04/2016

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Keywords: Pulmonary toxicity, Case report, Literature review.

ABSTRACT

Dronedarone is an amiodarone analog often used to treat atrial fibrillation as it is typically thought to have a more favorable safety profile than amiodarone including less major organ toxicities. Although rare, there are published case reports and the presented case that describe the association of pulmonary toxicity and dronedarone which should prompt clinicians to heed the warnings of the Federal Drug Administration and monitor for side effects of dyspnea in patients on this therapy. The authors present a case of a 69-year-old male with atrial fibrillation, congestive heart failure, and chronic obstructive pulmonary disease with worsening dyspnea that was admitted for an elective bronchoscopy. His current medications included dronedarone for atrial fibrillation. The timeline of drug initiation, rapid patient improvement upon drug discontinuation and steroid therapy, and unique radiological imaging are consistent with dronedarone induced pulmonary toxicity.

INTRODUCTION

Atrial fibrillation (AF) prevalence is estimated in the United States at 2.7 million to 6.1 million in 2010 with 45% male of those patients [mean age: 66.8 years (male) vs.74.6 years (female)]; by 2050 this number is expected to increase to 5.6 million to 12 million [1]. Treatment of AF includes the use of agents for either rate or rhythm control. The risk of life-threatening side effects associated with long-term therapy with available agents has sparked pharmacological development [2]. Dronedarone hydrochloride (Multaq), one of the newest anti-arrhythmic agents approved, is an analog of amiodarone, but lacks the iodine moiety and methane-sulfonyl group resulting in fewer side effects, decreased lipophilicity, and a shorter half-life than amiodarone [2-6]. Dronedarone, although its exact mechanism of action is unclear, is typically regarded as a class III anti-arrhythmic agent but exhibits all four Vaughn-Williams antiarrhythmic classes and has similar multichannel blocking properties as amiodarone [2].

Based upon a large randomized controlled trial, the class III anti-arrhythmic agent dronedarone was approved for the treatment of AF and atrial flutter in March 2009 by the Food and Drug Administration (FDA) [7]. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society Guideline for the management of patients with AF recommends dronedarone to be used for rhythm control in patients with persistent or paroxysmal AF [8]. When compared with amiodarone, dronedarone is less effective at preventing AF recurrence but has a more favorable safety profile [9,10].

Dronedarone has significant drug interaction due to extensive first pass metabolism by cytochrome P450 (CYP) 3A4 enzyme as well as inhibition of CYP2D6 and P-glycoprotein resulting in a higher risk of increased other concomitant drug levels and subsequent adverse reactions when given with such drugs as digoxin, statins, rivaroxaban, dabigatran, beta-blockers, and non-dihydropyridine calcium channel blockers [4]. In addition to being contraindicated in patients with heart failure and permanent AF [11], dronedarone has been associated with certain organ toxicities such as pulmonary toxicity as seen by post-market case

reports [12-14]. The FDA warns that cases of interstitial lung disease including pneumonitis and pulmonary fibrosis have been reported with the use of dronedarone [15]. According to the FDA, patients with the onset of dyspnea or nonproductive cough while on dronedarone should be evaluated for pulmonary toxicity [15]. The purpose of this case report is to describe an elderly man with AF admitted for increasing dyspnea secondary to pulmonary toxicity related to dronedarone.

Case Report

During hospitalization for endarterectomy, a 69-year-old white male was developed new AF with rapid ventricular response. At that time, amiodarone was avoided due to history of lung disease, and dronedarone was initiated for rhythm control. Less than 6 months later, the patient presented to the emergency room for significant shortness of breath. However, he didn't have purulent sputum production. Chest X-ray revealed underlying emphysema resulting in an elective bronchoscopy procedure. He had an extensive past medical history significant for AF, chronic obstructive pulmonary disease (COPD), emphysema, heart failure with preserved ejection fraction (EF 50-55%), coronary and peripheral artery disease, and hypertension. He was a former smoker and used alcohol as well as chewing tobacco daily. Patient weighed 108.1 kg and was 172.7 cm tall with a body mass index of 36.2 kg/m^2. For non-valvular AF the patient had been taking dronedarone 400 mg by mouth twice daily, verapamil 240 mg by mouth daily and rivaroxaban 20 mg by mouth daily. He also had been taking fluticasone/salmeterol 250 mcg-50 mcg 1 puff inhaled 2 times a day, tiotropium inhalation 18 mcg inhalaed daily, albuterol 90 mcg/inh 2 puffs inhale 4 times a day as needed, potassium chloride 10 meq by mouth 2 times daily, alprazolam 0.25 mg by mouth at bedtime, atorvastatin 20 mg by mouth daily, methocarbamol 500 mg by mouth 2 times daily, prazosin 2 mg by mouth 2 times daily, pramipexole 0.25 mg by mouth at bedtime, tramadol 50 mg by mouth 3 times per day as needed for pain, omeprazole 20 mg by mouth daily for various other co-morbid conditions including oxygen at night. Four days prior to bronchoscopy, rivaroxaban was discontinued.

Upon review of systems and physical exam, the patient had complaints of shortness of breath with exertion, swelling of the hands and feet, and difficulty breathing while lying down. Other concerns included easy fatigability, wheezing, back pain, and weight gain. After elective bronchoscopy, he was admitted to the intensive care unit secondary to respiratory distress and respiratory acidosis despite supplemental oxygen ($PH/PCO_2/PO_2/HCO_3$: 7.14/78/63/27) and mechanical ventilation was initiated. A chest X-ray revealed mild central pulmonary venous congestion and opacification of the right middle lobe and right lung base. Bronchoalveolar lavage fluid analysis revealed slightly cloudy light red fluid, red blood cell count of 3378/uL, white blood cell (WBC) count of 180/uL, neutrophils 12%, and lymphocytes 14%. Complete blood count with differential showed WBC 10,000/uL, neutrophils 93.2%, lymphocytes 4.1%, monocytes 2.7%, esosinophils 0% and basophils 0%.

Dronedarone was discontinued upon admission due to ongoing respiratory distress. In addition to the initiation of home medications excluding rivaroxaban and dronedarone, the patient was initially prescribed methylprednisolone 40 mg IV three times a day as well as sedation, deep vein thrombosis prophylaxis and maintenance fluids.

On the evening of day 2, the patient's respiratory status and arterial blood gase had improved significantly ($PH/PCO_2/PO_2/HCO_3$: 7.36/41/126/23) and he was subsequently extubated and maintained with >90% SpO_2 on aerosol mask and then on 6 L nasal cannula. Chest X-ray showed hyperinflation with bibasilar consolidation worse on the right and new left pleural effusion. Respiratory culture grew normal respiratory flora. Upon lung washing, *Candida albicans* was isolated but was negative for calcofluor and only normal flora was seen on bronchoalveolar lavage quantitative test on day 2.

He continued to demonstrate significant respiratory improvement over the next few days and was transferred from the intensive care unit to the telemetry floor. Lower extremity edema associated with acute decompensated heart failure became evident on day 4 resulting in initiation of diuresis with one dose of intravenous furosemide 40 mg. CT scan of the chest with contrast revealed bilateral pulmonary nodules as well as patchy foci of airspace opacification within both lower lobes. In the next two days, diuresis with furosemide and methylprednisolone therapy were continued for persisting edema and shortness of breath although oxygen requirements were lower (4 L nasal cannula with SpO_2 >90%). Methylprednisolone 40 mg IV three times daily was continued until day 8 when prednisone 30 mg by mouth daily was initiated and continued at discharge with tapering doses. Due to the patient's paroxysmal AF and episodes of rapid ventricular response during hospital stay, a cardiologist was consulted and the patient was managed with diltiazem and sotalol. Previous oral anticoagulant (rivaroxaban) was changed to warfarin for stroke prevention due to hemoptysis since bronchoscopy, even though rivaroxaban was discontinued 4 days before the procedure. Chest X-ray revealed improving right lung base infiltrate on day 7 and on day 8 showed a normal exam (The lungs are clear. There is no pleural abnormality). Before discharge on day 9, the patient was noted to have been doing well on 2 L nasal cannula and was even able to take a shower without difficulty. Before admission he had short of breath at less than 10 feet of exertion.

With the exception of rivaroxaban and dronedarone, the patient was discharged on previous outpatient medications as well as sotalol 40 mg by mouth once daily for AF, prednisone 30 mg by mouth once daily with tapering doses, and warfarin 5 mg by mouth once daily for AF stroke prevention. Patient was also discharged on oxygen at 2 L nasal cannula. In 3-month follow-up visit, chest x-ray revealed clear lungs.

DISCUSSION

In many randomized controlled trials investigating dronedarone, major organ toxicities were either not found or their

occurrences were not significant [10,11,16-20]. The adverse effects of dronedarone seen in published studies are summarized in **Table 1.** The most common adverse reactions with dronedarone include QT prolongation, increased serum creatinine, bradycardia, diarrhea, nausea, and abdominal pain [9]. Rare reactions such as acute hepatic failure, interstitial pulmonary disease, pneumonitis, and pulmonary fibrosis have been seen in post-market case reports [15].

Table 1. Adverse reactions seen during the investigation of dronedarone.

Study	Treatment	Duration	Adverse Effects
DAFNE (n=270) [18]	400 mg PO BID and 800 mg BID vs. placebo	6 months	• Gastrointestinal (GI) side effects and QT prolongation (more in 800 mg BID)
EURIDIS/ADONIS (n=1237) [19]	400 mg PO BID vs. placebo	12 months	• Adverse event rate similar, slight increase in serum creatinine • No Torsades de Pointes (TDP) tachycardia or organ toxicity,
ERATO (n=174) [20]	400 mg PO BID vs. placebo	6 months	• No significant differences in discontinuation rates, or serious or more frequent adverse events including organ toxicity (pulmonary symptoms, interstitial lung disease, or thyroid dysfunction)
ANROMEDA (n=627)a [11]	400 mg PO BID vs. placebo	Median follow-up 2 months, all followed for 6 months after treatment cessation	• Increased creatinine concentration
ATHENA (n=4628) [16]	400 mg PO BID vs. placebo	Mean follow-up 21 +/- 5 months, maximum 2.5 years	• More adverse events: GI, bradycardia, QT-prolongation, rash, and increase in serum creatinine vs. placebo • No differences in organ toxicity • One single case of TDP tachycardia
DIONYSOS (n=504) [10]	400 mg PO BID vs. amiodarone 600 mg loading dose then 200 mg/day	7 months	• More GI side effects • Fewer bradycardia, and thyroid, neurological, skin and ophthalmologic events • Analysis of main safety endpoint (MSE) showed no statistically significant difference • Pre-specified endpoint on severe adverse events, excluding GI side effects, revealed significant difference in favor of dronedarone
PALLAS (n=3236)b [17]	400 mg PO BID vs. placebo in permanent AF	Median follow up of 3.5 months	• Significant difference in adverse events • Diarrhea, nausea and vomiting, asthenic conditions, dizziness, dyspnea, bradycardia, increase liver function tests, and QT prolongation

Note: [a]Excess mortality seen due to worsening heart failure, stopped prematurely after 7 months
[b]Stopped early due to safety concerns

Dronedarone is an analog of amiodarone which is known to cause pulmonary toxicity. Amiodarone-induced lung toxicity is defined in studies as the development of cough, fever, dyspnea and/or pleuritic chest pain with new radiographic findings such as alveolar or ground glass opacities when differential diagnoses such as infections, malignancy, congestive heart failure, and pulmonary embolism have been explicitly ruled-out [21,22]. In an experimental study comparing the structure-activity relationship of amiodarone, its metabolites, and analogs, Quaglino et al. found that the nitrogen of the diethylaminoethoxy group seen in amiodarone's structure correlates with toxicity toward alveolar macrophages [23]. Notably, the study determined that dronedarone, which contains the diethylaminoethoxy group, resulted in more alveolar macrophage toxicity than amiodarone [23]. While required during amiodarone therapy, monitoring for thyroid, liver, and pulmonary toxicity is not required for patients taking dronedarone at this time; however, experimental studies and recent case reports describe the risk of pulmonary toxicities with the use of dronedarone [12-14]. Recent changes to FDA labeling and the drug package insert also indicate that there is a risk of pulmonary toxicity with dronedarone [15,16]. Published case reports with dronedarone pulmonary toxicities are summarized in **Table 2** [12-14].

Table 2. Case reports involving dronedarone associated pulmonary toxicity.

Case	Age (years), Gender	Pertinent PMH	Dronedarone Therapy (duration)	Clinical Presentation	Radiological Findings	Outcomes
Hernandez et al. [12]	73, M	• Arterial HTN • Obstructive sleep apnea • Paroxysmal AF	• Previous amiodarone therapy for 26 months • Dronedarone recently discontinued after 70 days of treatment	• Dyspnea • Nonproductive cough • Hypoxemia	CT: Septal thickness, parenchymal diffuse opacities	• Drug discontinuation • Patient improved with no specific treatment

Siu et al. [13]	72, F	• Paroxysmal AF • No other PMH mentioned	• Previous amiodarone for 14 months • Dronedarone, for 9 months	Progressive dyspnea for 3 weeks	• Chest radiography: bilateral diffuse pulmonary infiltrates • CT:diffuse ground glass opacities, BOOP	• MVRF • Broad spectrum antibiotics failed • Diagnosed amiodarone-induced toxic lung effects • Patient passed away
Siu et al. [13]	82, M	• HTN • Diabetes • New onset AF	• Previous amiodarone for 10 days • Dronedarone for 4 days	• New onset AF • Dyspnea two days after discontinuation of dronedarone	Chest radiography/ CT: diffuse ground glass opacities	• Dronedarone discontinuation • MVRF • Broad spectrum antibiotics failed • Methylprednisolone given and improved
Stack et al. [14]	68, W	• Paroxysmal AF • CAD • Raynaud phenomenon	Dronedarone for 6 months	• Dyspnea and dry cough for 5 months • Hypoxia • Pulmonary rales and rhonchi	Chest CT: diffuse ground glass pacification bilaterally	• Dronedarone discontinuation • Empiric antibiotics failed • Corticosteroids given and improved

Note: HTN: hypertension, AF: atrial fibrillation, CT: computed tomography, PMH: past medical history, BOOP: bronchiolitis obliterans with organizing pneumonia, MVRF: mechanical ventilation-required respiratory failure, CAD: Coronary Artery Disease, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, PVD: peripheral vascular disease, MV: mechanical ventilation

In the three case reports from 2012, all patients had been taking amiodarone prior to switching to dronedarone [12-14]. The duration of therapy differed in these patients as one patient discontinued dronedarone after 4 days of therapy due to new onset of heart failure while another had been taking dronedarone for 9 months before hospitalization [12,13]. In contrast, the patient described in Stack et al. as well as our described patient did not receive amiodarone prior to dronedarone therapy [14]. Both of these patients had been taking dronedarone for about six months prior to hospitalization [14]. All five patients had increased dyspnea after dronedarone therapy (duration: 4 days – 9 months) and radiological imaging revealed diffused opacities as well as varying other abnormalities such as infiltrates and nodules [12-14]. After discontinuation of dronedarone, one of the patients improved without specific treatment while three of the patients including our described patient improved with pulse methylprednisolone therapy [12-14]. One of the patients described in Siu et al. died despite treatments [13].

According to the Naranjo Adverse Drug Reaction Probability Scale (score of 7), it is probable that the described 69-year-old case patient's pulmonary symptoms were related to dronedarone **(Table 3)** [24]. He had no other medications that would have individually contributed to his respiratory symptoms. The diagnosis of dronedarone-induced interstitial lung disease should be suspected based upon the patient's increased dyspnea, consistent radiological findings, and the exclusion of other likely causes, such as pneumonia, malignancy, pulmonary embolism, a COPD exacerbation or acute decompensated heart failure.

Table 3. Naranjo adverse drug reaction probability scale.

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was re- administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0

10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total score				7

The patient's bronchoalveolar lavage results, including elevated neutrophil count ≥ 5%, suggested a possible association with diffuse lung diseases including idiopathic interstitial pneumonitis and/or drug-induced pneumonitis but did not indicate infection, drug allergy, or malignancy [25]. The radiological findings of opacifications, bibasilar consolidation, pleural effusion, pulmonary nodules, and foci of airspace opacification are consistent with published data on interstitial lung disease (ILD) and amiodarone-induced pulmonary toxicity and may suggest drug-induced ILD occurred in this case [26,27].

The patient was taking both dronedarone and verapamil at home, both of which are primarily metabolized by and are minor inhibitors of the CYP3A4 enzyme which results in a major drug interaction necessitating therapy modification [4,28]. Dronedarone prescribing information states that dronedarone exposure was increased 1.4 to 1.7 fold with concurrent verapamil secondarily to the inhibition of the metabolism of dronedarone via CYP3A4 [4,28]. Higher maintenance and cumulative doses of amiodarone are independent risk factors for pulmonary toxicity and it is likely that this relationship can be extrapolated for dronedarone pulmonary toxicity as well [21]. Although an important drug interaction to note in this case that may have increased the patient's risk for adverse effects, there are no well-controlled studies or case studies regarding this interaction and the combination results in only a moderate inhibition of metabolism and is unlikely the sole or main contributor to the patient's pulmonary toxicity.

Considering differential diagnoses regarding the patient's symptoms, the patient did not present with fever or leukocytosis and infection, although initially treated, was ruled out. Deep vein thrombosis and pulmonary embolism were also not suspected based on radiological imaging. Other alternative causes for the patient's respiratory symptoms include either a COPD exacerbation or acute decompensated heart failure. The patient was admitted with 4 L nasal cannula and was discharged on 2 L nasal cannula suggesting that upon admission dronedarone contributed to the patient's respiratory decline as exacerbations of his chronic medical conditions likely wouldn't have resulted in a lower oxygen requirement upon discharge. Extremity edema and the persisting shortness of breath during the patient's stay were relieved by significant diuresis with furosemide suggesting acute decompensated heart failure may have contributed to the patient's symptoms and physical exam complaints but acute decompensated heart failure is unlikely the reason for the initial respiratory distress since symptoms improved although therapy for fluid overload was not initiated until day 4. Interestingly, in the recent 2012 PALLAS trial looking at dronedarone treatment in high-risk permanent AF patients, there were a significant increase in breathing abnormalities noted which included a large percentage of elderly heart failure patients with AF [17]. Pulse methylprednisolone therapy is currently considered the standard therapy for interstitial lung diseases including amiodarone-induced pulmonary toxicity [29]. Although controlled studies are lacking, the successful use of corticosteroids support the benefits of its use in pulmonary toxicity and likely contributed to the patient's recovery from dronedarone-induced pulmonary toxicity.

This patient was successfully discharged with a final diagnosis of diffuse ILD secondary to dronedarone. Based upon the patient's worsening respiratory symptoms after drug initiation, response to treatment and symptomatic improvement prior to discharge, dronedarone can be implicated as the probable culprit responsible for the patient's respiratory decline.

CONCLUSION

The amiodarone analog dronedarone has been popularized as having a shorter half-life and less adverse effects than amiodarone. Organ toxicities such as pulmonary toxicity were presumed to be absent or particularly insignificant upon results of the early safety and efficacy trials investigating dronedarone; however, the presented case described probable association of pulmonary toxicity and dronedarone which should prompt clinicians to monitor for side effects of dyspnea in patients on this therapy.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest to disclose.

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