GLOBAL CARDIOLOGY SCIENCE & PRACTICE
A Qatar Foundation Academic Journal

OPEN ACCESS

Lessons from the trials

Dronedarone-digoxin interaction in PALLAS: A foxglove connection?

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ABSTRACT

In the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) study, dronedarone use was associated with an excess risk of stroke, cardiovascular death and hospitalizations. However, an increased level in the serum digoxin level was observed in the dronedarone arm, as it is a potent inhibitor of the P-glycoprotein transport system. The PALLAS subanalysis suggests that digoxin-dronedarone interaction was responsible for the higher arrhythmic death rate observed in the trial. These data are consistent with several other studies that demonstrate the potential hazard of the use of digoxin in heart failure and/or atrial fibrillation. One must consider other safer alternatives before prescribing digoxin in atrial fibrillation patients.

http://dx.doi.org/10.5339/gcsp.2015.4

Submitted: 02 January 2014
Accepted: 03 February 2015

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Cite this article as: ElMaghawry M, Farouk M. Dronedarone-digoxin interaction in PALLAS: A foxglove connection? *Global Cardiology Science and Practice* 2015:4 http://dx.doi.org/10.5339/gcsp.2015.4

INTRODUCTION

Antiarrhythmic drug therapy remains the cornerstone for the management of atrial fibrillation (AF). Despite being not FDA approved for the use in atrial fibrillation, amiodarone is the most commonly used medication to maintain sinus rhythm in patients with AF. Dronedarone is the first of a group of drugs that have been designed to resemble amiodarone with fewer non-cardiovascular side effects. It is similar in structure to amiodarone with the addition of a methylsufonamide group and absence of iodine moieties (Figure 1).[1] In the trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA), dronedarone use in patients with non-permanent AF was associated with significant reduction in the rate of composite end point of death from cardiovascular causes and hospitalization due to cardiovascular events.[2] The positive results of ATHENA incited investigators to further test the effect of dronedarone on permanent AF patients. In the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), dronedarone use was associated with an excess risk of stroke, cardiovascular death and hospitalizations.[3] However, an increased level in the serum digoxin level was observed in the dronedarone arm. A recent analysis, published in Circulation Arrhythmia and Electrophysiology Journal examined whether the dronedarone–digoxin interaction might explain these adverse outcomes.[4]

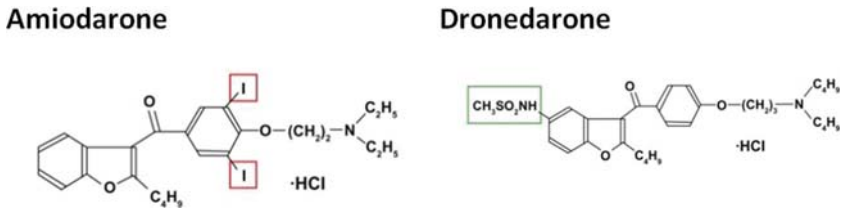

Figure 1. Dronedarone molecular structure in comparison to amiodarone. Note there are no iodine moieties in dronedarone.

PALLAS DESIGN AND OUTCOMES

PALLAS was designed to determine if dronedarone would reduce major vascular events in patients with permanent AF. Permanent AF was defined as ECG documentation of AF or flutter within 14 days of randomization and also ≥6 months before, with no evidence of sinus rhythm intervening and with no plans to restore sinus rhythm. Patients had to be ≥65 years with ≥1 risk factor for cardiovascular events. Eligible patients were randomized double-blind to receive dronedarone 400 mg twice daily or matching placebo. The first co-primary outcome was a composite of stroke, myocardial infarction, systemic embolism, or cardiovascular death. The second co-primary outcome was unplanned cardiovascular hospitalization or death. Other outcomes were death from cardiovascular causes, death from arrhythmia, hospitalization for heart failure or heart failure episode without hospitalization, and death from any cause.

After the enrollment of 3236 patients, the study was stopped for safety reasons. The first co-primary outcome occurred in 43 patients receiving dronedarone and 19 receiving placebo (hazard ratio, 2.29; 95% confidence interval [CI], 1.34 to 3.94; P = 0.002). There were 21 deaths from cardiovascular causes in the dronedarone group and 10 in the placebo group (hazard ratio, 2.11; 95% CI, 1.00 to 4.49; P = 0.046), including death from arrhythmia in 13 patients and 4 patients, respectively (hazard ratio, 3.26; 95% CI, 1.06 to 10.00; P = 0.03). Stroke occurred in 23 patients in the dronedarone group and 10 in the placebo group (hazard ratio, 2.32; 95% CI, 1.11 to 4.88; P = 0.02). Hospitalization for heart failure occurred in 43 patients in the dronedarone group and 24 in the placebo group (hazard ratio, 1.81; 95% CI, 1.10 to 2.99; P = 0.02).

INTERACTION BETWEEN DIGOXIN AND DRONEDARONE IN THE PALLAS TRIAL

Subgroup analysis was performed to compare outcomes of patients on digoxin at baseline or not. Of 3236 patients: 1619 were randomized to dronedarone and 1617 to placebo, of whom 544 (33.6%) and 526 (32.5%) were receiving digoxin, respectively. Median digoxin serum concentration on day 7 was 1.1 ng/mL on dronedarone and 0.7 ng/mL on placebo (P < 0.001). Among patients on digoxin, there were 15 (8.6%/year) cardiovascular deaths on dronedarone and 2 (1.2%/year) on placebo (adjusted

hazard ratio, 7.31; 95% confidence interval, 1.66–32.20; P = 0.009). Among patients not on digoxin, there were 6 cardiovascular deaths on dronedarone (1.7%/year) and 8 on placebo (2.2%/year; adjusted hazard ratio, 0.67; 95% confidence interval, 0.23–1.95; P = 0.46; interaction P value 0.01). In patients on digoxin, there were 11 arrhythmic deaths on dronedarone and none on placebo; and in patients not on digoxin, there were 2 arrhythmic deaths on dronedarone and 4 on placebo (P value for interaction 0.002). There was no interaction between baseline digoxin use and the adverse effect of dronedarone on heart failure events.

CRITIQUE

Dronedarone trials in AF

Other than the PALLAS, five major trials studied the use of dronedarone in AF: EURIDIS, ADONIS, ANDROMEDA, ATHENA and DIONYSIS; all of which are named after Greek mythology characters. In the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS), rate of recurrent AF was significantly lower with dronedarone (67%) versus placebo (77%). Similar results were observed in the American-Australian-African (ADONIS) trial, with 61% rate of AF recurrence in the dronedarone arm versus 75% with placebo.[5] However, the Antiarrhythmic Trial of Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) showed doubling of death rate in the dronedarone group, predominantly due to cardiovascular causes.[6] Therefore, Dronedarone is contraindicated in patients with decompensated congestive heart failure. In the ATHENA, conducted on healthier patients with paroxysmal AF, dronedarone showed significant reduction in the rate of composite end point of death from cardiovascular causes and hospitalization due to cardiovascular events. The DIONYSIS study compared the efficacy and safety of dronedarone versus amiodarone for the maintenance of sinus rhythm in patients with persistent AF. Rate of recurrent AF was 63% with dronedarone in contrast to 42% with amiodarone. However, dronedarone showed significantly lower adverse effects compared to amiodarone.[7]

Digoxin use in cardiovascular medicine

Digitalis is a genus of about 20 species of herbaceous perennials, shrubs, and biennials that are commonly called foxgloves. The use of digitalis extract containing cardiac glycosides was first described in the English-speaking medical literature by William Withering, in 1785 (Figure 2). Interestingly, Withering (1741–1799) first learned the use of digitalis in treating dropsy, i.e. congestive heart failure, from an old woman who practiced as a folk herbalist in Shropshire.[8]

Despite this long history, clinical use of digoxin in cardiovascular medicine has always been a subject of controversy, mainly because of its narrow therapeutic window and its potential contribution to life-threatening ventricular tachyarrhythmias and severe bradyarrhythmias. Randomized clinical trials published in the early 1990's, such as RADIANCE and PROVED, have shown clinical benefits of digoxin in patients with congestive heart failure without AF.[9,10] However, the largest of these studies, the Digitalis Investigation Group (DIG) trial, published in 1997, found that digoxin had a neutral effect on mortality and modestly reduced hospitalizations because of worsening heart failure.[11] Noteworthy, all of these trials were conducted prior to the contemporary use of beta blockers in heart failure. Furthermore, these results were only observed in the setting of strict monitoring of serum digoxin concentrations. In fact, subsequent large-scale observational studies reported that digoxin therapy was associated with increased cardiovascular mortality. For instance, a recent study evaluating the effectiveness and safety of digoxin in a contemporary cohort of patients with incident systolic heart failure showed that the use of digoxin was independently associated with increased total mortality.[12]

Concerning the use of digoxin for rate control in AF, there have also been reports on increased mortality. In the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, digoxin was associated with a significant increase in all-cause mortality in patients with AF after correcting for clinical characteristics and comorbidities, regardless of gender or of the presence or absence of heart failure.[13]

Role of P-glycoprotein in digoxin toxicity

Dronedarone increases digoxin plasma concentration by a pharmacokinetic interaction as it is potent inhibitor of the P-glycoprotein transport system. P-glycoprotein mediates the export of drugs from cells

Figure 2. ***Digitalis purpura*** **(commonly known as Foxglove).**

located in the small intestine, blood brain barrier, hepatocyte, and kidney proximal tubules, serving a protective function of the body against foreign substances. Digoxin has a narrow therapeutic index, and therefore can demonstrate large increase in concentration when co-administered with potent P-glycoprotein inhibitors. Other commonly used P-glycoprotein inhibitors include: azithromycin, ofloxacin, amiodarone, quinidine, verapamil, carvidolol, atorvastatin, orange and grapefruit juices.

LIMITATIONS TO THE CURRENT ANALYSIS

Because digoxin therapy was not randomized, it is possible that the present analysis is confounded by other variables. Patients on digoxin were older, had more heart failure symptoms, coronary artery disease, impaired ejection fraction, and received more diuretics. Digoxin use could have s been an indicator of subset of patients more prone to have side effects from dronedarone. As mentioned earlier, dronedarone was found to increase mortality in congestive heart failure patients as demonstrated in the ANDROMEDA trial. Indeed, in the dronedarone arm of the PALLAS trial, about 19.4% of the patients had heart failure with NYHA class III and as many as 45.8% had an ejection fraction of less than 40%. The analysis did not correct the arrhythmic- nor non arrhythmic- deaths, to such important confounders. Furthermore, the data concerning the use of aldosterone antagonists in both arms are lacking. The use of aldosterone antagonists and potassium losing diuretics could also confound the results due to possible electrolyte disturbance that leads to arrhythmic deaths.

On the other hand, there was no observed interaction related to combined use of digoxin and dronedarone and increased rates of heart failure. The specificity of the observed interaction for arrhythmic mortality, together with the known potential for digoxin toxicity to cause lethal brady- and tachyarrhythmias, strongly suggests that the observed interaction is indeed directly related to increased digoxin levels via P glycoprotein inhibition.

More importantly, the current analysis does not explain the increased risk of heart failure seen with dronedarone in PALLAS. The increased risk of heart failure observed in both the DIONYSIS and PALLAS necessitates further studies to assess the mechanism through which dronedarone worsens heart failure and to further identify the at-risk subgroups.

WHAT HAVE WE LEARNT?

The PALLAS data suggest that digoxin-dronedarone interaction was responsible for the higher arrhythmic death rate observed in the trial. These data are consistent with several other studies that demonstrate the potential hazard of the use of digoxin in heart failure and/or atrial fibrillation. One must consider other safer and more efficient alternatives, such as beta blockers, before prescribing digoxin in AF patients for rate control. Furthermore, prudent patient-evaluation is essential when considering the use of dronedarone. The less-than-rigorous monitoring of serum levels of digoxin can lead to dangerous sequalae in clinical practice. In fact, this lesson dates back to 230 years ago:

> "The Foxglove when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death"

William Withering, An Account of the Foxglove and some of its medical uses: with practical remarks on Dropsy and other diseases. 1785.

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