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Proarrhythmic Potential of Dronedarone: Emerging Evidence from Spontaneous Adverse Event Reporting

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Abstract

Context—Dronedarone has not been previously associated with a major risk for ventricular arrhythmia, but increased fatal arrhythmias among patients with permanent atrial fibrillation in a recent randomized trial. The mechanism of this adverse safety signal leading to trial discontinuation is unknown.

Study Objective—To characterize cardiac events, including torsade de pointes, associated with dronedarone and its structural analogue, amiodarone, outside of the clinical trial setting.

Design—Publicly available extracts from the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) system were screened for events occurring from 7/1/2009, the time of dronedarone approval, through 6/30/2011.

Data extraction—Cardiac events were defined as serious if they involved death, disability, hospitalization, required intervention, or were life-threatening. Active ingredients were identified using the Drugs@FDA Database, and the Medical Dictionary for Regulatory Activities (MedDRA) was used to aggregate related adverse events. To avoid redundant counting, all statistics were generated in reference to unique case identifiers.

Results—Dronedarone was associated with more adverse cardiovascular event reports than amiodarone (810 vs. 493) during the evaluation period. Dronedarone was the leading reported culprit for torsade de pointes in the US (37 cases) followed by amiodarone (29 cases). Dronedarone was also associated with more cases of ventricular arrhythmias and cardiac arrest than amiodarone (138 vs. 113) as well as heart failure events (179 vs. 126).

Limitations—AERS data is subject to reporting biases and cannot generate actual incidence rates.

Conclusion—Dronedarone is associated with reports of ventricular arrhythmia and torsade de pointes in clinical practice. Whether this observation accounts for the increased risk of fatal arrhythmia observed in a recent prospective trial requires further investigation.

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Background

Dronedarone is a novel antiarrhythmic agent approved for the prevention of cardiac hospitalization among patients with intermittent atrial fibrillation and atrial flutter (1). The drug is a non-iodinated, shorter acting derivative of amiodarone. It shares similar cardiac ion channel activity including beta-adrenergic, calcium, sodium, and delayed rectifier potassium ion (I_{Kr}) channel blockade (2). The apparent lack of organ toxicity involving skin, thyroid and lung tissue positioned dronedarone as a very attractive candidate to supplant amiodarone as first line therapy for rhythm disorders.

In the ATHENA trial dronedarone reduced the risk of cardiovascular hospitalization among patients with intermittent atrial fibrillation (3) and was the basis for FDA public deliberations (4) and ultimately drugapproval (5). Only one case of torsade de pointes was reported in the ATHENA population, though this group had a relatively low prevalence of structural heart disease. Dronedarone carries a boxed warning label for patients with advanced heart failure given a higher mortality rate observed in a prior study of recently decompensated heart failure patients (6); however, current product labeling does not recommend routine QT-interval screening despite dronedarone's I_{Kr} -blocking properties.

Subsequent to approval, the PALLAS study compared dronedarone to placebo in patients with permanent atrial fibrillation and found a significant increase in cardiovascular mortality in the dronedarone-treated group (7). This study population was notable for a greater burden of structural heart disease compared with patients in the ATHENA trial. Arrhythmia-related events in PALLAS appeared to account for the majority of cardiac deaths, but arrhythmia characterization was not determined. Given a greater propensity for arrhythmia among patients with structural heart disease, we hypothesized that dronedarone may predispose susceptible patients to torsade de pointes.

METHODS

Data Source and Extraction

Data files were downloaded from the FDA Center for Drug Evaluation and Research Office of Surveillance containing deidentified records of all adverse event reports occurring between July 1 2009 (dronedarone marketing approval date) and June 30 2011 (8). Files were imported directly into a MySQL Server instance (MySQL Server 5.5.18, Oracle Corporation, Redwood Shores, CA). Redundant reports were identified and only the most recently version of the report was retained, in accordance with AERS documentation. Since multiple reports of the same adverse drug event may appear in the AERS database, all statistics were generated in reference to unique case identifiers rather than reports to avoid redundant recounting.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0 (Northrop Grumman) serves as a controlled terminology in AERS to describe all adverse drug events and includes levels of aggregation of related adverse events. These levels are named 'System Organ Classes', 'High Level Group Terms', 'High Level Terms', 'Preferred Terms' and 'Low Level Terms' in order of increasing specificity. Drug names were validated using the Drugs@FDA database using string matching. Unvalidated drug names > 2 characters long were matched to Drugs@FDA entries using complete, then partial string matching to both trade names and active ingredients was performed. Unvalidated drug names with a length < 3 characters were not matched.

We analyzed both High Level Terms and selected Preferred Terms in order to evaluate all adverse cardiac events associated with approved drugs in the US during the study period.

We then tabulated cardiovascular events between dronedarone and amiodarone given the chemical similarity between these antiarrhythmic agents. High-level categories of adverse cardiac events included: supraventricular tachycardia, heart failure, rate and rhythm disorders, and ventricular arrhythmia/cardiac arrest. Reporting rates for torsade de pointes, stratified by gender among selected additional I_{K_r} -blocking drugs was also performed to gauge relative frequency.

RESULTS

The total number of reported adverse events associated with dronedarone and amiodarone during the observation period was similar (1737 and 1830 respectively). However, cardiovascular events categorized using the MedDRA hierarchy of High Level Terms were more commonly associated with dronedarone than amiodarone (810 vs. 493) during the observation period (Table 1). With regard to arrhythmia reports, dronedarone was associated with more cases of ventricular arrhythmias/cardiac arrest than amiodarone (138 vs. 113).

When assessing Preferred Terms, dronedarone was the leading reported culprit for torsade de pointes in the US (37 cases) followed by amiodarone (29 cases). In addition, there was a greater number of reported heart failure events associated with dronedarone therapy compared with amiodarone (179 vs. 126). Torsade de pointes events attributed to other I_{K_r} -blockers including sotalol, dofetilide, haloperidol, and moxifloxacin were less common during the observation period (Table 2). Torsade de pointes arrhythmia events were also more commonly observed among females.

Discussion

Given the approximately 10-fold larger prescriptive volume for amiodarone (9), these data raise concern that dronedarone has a potentially disproportionate risk for ventricular arrhythmia and cardiac arrest. In particular, dronedarone is currently the most commonly reported drug associated with torsade de pointes since its marketing authorization in the US. Dronedarone-associated torsade de pointes reported events exceed amiodarone as well as other common I_{K_r} -blocking drugs. This could theoretically account for the fatal arrhythmia signal observed in the PALLAS trial. Although adverse events are more likely to be reported after the launch of newer compounds, the so-called Weber effect, (10) this does not diminish concern regarding the safety of dronedarone, since only a fraction of adverse events in clinical practice are actually reported to the AERS system (11). Therefore, from the perspective of public safety, the major limitation of spontaneous pharmacovigilance systems is under-reporting bias, particularly as it relates to rare adverse drug reactions such as torsade de pointes (12).

It is surprising that the number of reported ventricular arrhythmia/cardiac arrest cases associated with dronedarone in AERS was comparable to the number of heart failure reports. Heart failure is a well-known complication of dronedarone, which resulted in a boxed warning label proscribing its use in this population. However, beyond limiting its usage when the rate corrected QT [QTc]-interval exceeds 500 ms, there is no such warning with regard to actual arrhythmia risk in dronedarone product labeling. This suggests that ventricular arrhythmia may be an under-appreciated toxicity of dronedarone, as the number of arrhythmia cases reported is probably artificially low, while a positive reporting bias for heart failure predominates. The frequency of reports of worsening heart failure is concerning in and of itself, since administrative claims data suggest that practitioners are appropriately avoiding its use in patients with recently decompensated heart failure (13).

The discordant findings between the ATHENA trial and the increased mortality rate observed in both ANDROMEDA and PALLAS remains a subject of uncertainty. A number of potential explanations should be considered. First, the utilization of an antiarrhythmic agent, such as dronedarone, in patients with permanent atrial fibrillation in PALLAS is clinically counterintuitive. Antiarrhythmic drugs are generally reserved for maintenance of sinus rhythm among those with non-permanent or intermittent atrial fibrillation. In PALLAS, only 3.7% of patients receiving dronedarone were in sinus rhythm at 4-month follow-up. It is therefore possible that patients were exposed to proarrhythmic risk without receiving the potential benefits from restoration of sinus rhythm. This is particularly relevant among patients with permanent atrial fibrillation who have an inherently greater arrhythmia propensity given a higher burden of underlying structural heart disease. Another possibility is that despite a sample size of 4,628 patients, ATHENA was underpowered to detect an increase in the rate of rare events such as ventricular arrhythmia associated with dronedarone. In contrast, contemporary atrial fibrillation studies have been performed with sample sizes exceeding 18,000 patients (14,15). The reason for the large sample sizes in these recent trials reflects the fact that the primary endpoint event rate (stroke or systemic embolism) was relatively low. Even rarer safety events such as torsade de pointes, are therefore unlikely to be reliably ascertained pre-approval, making post-marketing surveillance a useful tool for detection of these safety events.

We acknowledge a number of important limitations to this study. The specificity of a diagnosis of torsades de pointes in the FDA MedWatch database is uncertain since no independent electrocardiographic adjudication of reports is possible. However, we observed an expected increased frequency of arrhythmia events among women lending credibility to the accuracy of the data. Since dronedarone was undergoing clinical trials during the study period, and amiodarone may not have been to the same degree, there is an inherent bias favoring reporting for dronedarone. Because a true denominator is not available and all events are self-reported, incidence rates cannot be calculated. Most importantly, the association between dronedarone and ventricular arrhythmias is concerning, yet a causal association cannot be established with observational data.

An accurate safety profile regarding rare arrhythmic events is not always apparent at the time of FDA approval of a new drug. Given the commonly reported ventricular arrhythmia events associated with dronedarone in the AERS database, it remains plausible that differing ion-channel blockade with dronedarone compared with its parent compound, amiodarone makes it more proarrhythmic. Like all Class III antiarrhythmic drugs, dronedarone and amiodarone prolong the QT-interval (16) via I_{K_r} -blockade, yet in animal models dronedarone appears to consistently trigger early after-depolarizations leading to torsade de pointes (17). Moreover, in this study, amiodarone reduced transmural dispersion of repolarization an additional parameter favoring amiodarone in terms of lower predicted arrhythmia risk. Since torsade de pointes often results from a convergence of clinical factors, the arrhythmia risk with dronedarone is expected to be magnified outside the confines of the clinical trial setting where coadministration of other QT-prolonging medications and metabolic inhibitors of dronedarone are commonplace.

The inherent limitations of these data notwithstanding, we suggest that dronedarone therapy be limited to low risk patients with intermittent atrial fibrillation, who are restored to sinus rhythm at or around the time of drug initiation. Beyond routine electrocardiographic screening for the presence of permanent atrial fibrillation during the maintenance phase of therapy -an obvious reason for drug discontinuation based on PALLAS-we suggest that careful attention to the QT-interval during this maintenance phase is warranted. Whether focused QTc-interval screening prior to initiation and during induction (as required for other potent I_{K_r} -blocking drugs) should be added to product labeling requires further study.

Regardless, patients with any structural heart disease, particularly those with heart failure or ventricular systolic dysfunction, should not receive dronedarone. This relegates dronedarone to a second or third line status for the maintenance of sinus rhythm solely in low-risk patients with symptomatic atrial fibrillation (18).

Conclusion

Despite the initial promise of reduced toxicity with dronedarone, its predecessor (amiodarone) remains the preferred antiarrhythmic agent from the perspective of minimal proarrhythmic potential (19,20), presumably due to a reduction in transmural dispersion of cardiac repolarization (21). Future studies of dronedarone in combination with the sodium channel blocker ranolazine suggest that combination therapy has the potential to enhance the safety and efficacy of this agent (22). Specifically, a combination of low dose dronedarone (150 to 225 mg) plus 750 mg of ranolazine will be prospectively evaluated in the HARMONY trial.

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Table 1

Adverse Drug Events Associated With Dronedarone and Amiodarone *

Cardiac Events	Dronedarone	Amiodarone
Supraventricular arrhythmia	431	146
Heart failure	179	126
Cardiac failure	90	66
Congestive cardiac failure	80	37
Rate and rhythm disorders	149	128
Bradycardia or bradyarrhythmia	61	71
Tachycardia or tachyarrhythmia	33	21
Ventricular arrhythmias and cardiac arrest	138	113
Ventricular tachycardia	56	30
Cardiac arrest	38	34
Torsade de pointes	37	29
Ventricular fibrillation	24	18

* Number of events from July 1 2009 through June 30 2011; High Level and selected Preferred Terms.

Table 2

Reports of Torsade de Pointes among Potassium Channel Blocking Agents

	Total Events	Male	Female
Dronedaron	37	13	23 *
Amiodarone	29	14	15
Sotalol	4	1	2 *
Dofetilide	12	5	7
Moxifloxacin	10	2	6 **
Haloperidol	6	5	1

* Number of events: Gender unspecified in 1 case;

** Gender unspecified in 2 cases