Dronedarone-associated acute renal failure: evidence coming from the Italian spontaneous ADR reporting database

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dronedarone partially inhibits the tubular transport of creatinine, with a slight increase in creatinine concentrations leading to a limited rise in serum creatinine not correlated with a decline in renal function.
- In the PALLAS study, adverse drug reactions (ADRs) related to renal function, including serious renal failure, were more frequently reported in the dronedarone group compared with the placebo group.
- Four cases of acute kidney failure were collected in the Medwatch filing since the date on which the Food and Drug Administration approved the drug (August 2009).

WHAT THIS STUDY ADDS

- Our study describes four cases of acute renal failure (ARF), two cases of renal failure (RF) and three of increase of serum creatinine from dronedarone collected in the Italian spontaneous reporting system. These findings may contribute to define better the risk–benefit profile of the drug. Communication of this evidence to physicians and patients is important to mitigate the risk for ARF in patients treated with dronedarone.

AIM

To describe cases of acute renal failure (ARF) and of renal failure (RF) from dronedarone retrieved in the general population during post-marketing surveillance through the Italian spontaneous ADR reporting database.

METHODS

A case by case analysis was performed. Reports codified with the System Organ Class (SOC) term 'urinary system disorders' of the ADR terminology of the World Health Organization associated with dronedarone treatment were selected.

RESULTS

Out of 124 069 ADR reports, in 55 of them dronedarone was listed as the suspected drug. Among these reports, we identified four cases of ARF, two of RF and three cases of increase of blood creatinine submitted by physicians between October 2010 and December 2011. The patient age was from 61 to 84 years and most cases occurred within the first 13 days of initiation of dronedarone therapy (range 6 days – 2 months). Only one patient received a co-suspected drug labelled for causing ARF. In all reports but one, positive dechallenge was reported.

CONCLUSIONS

Clinicians should be made aware of the risk of ARF/RF associated with dronedarone and of the need to screen patients appropriately for ARF/RF risk factors before starting dronedarone therapy.

Introduction

Dronedarone is a multichannel blocker derivative of amiodarone. It has had the iodine groups removed and a methane sulfonyl group added to decrease lipophilicity, in order to reduce tissue accumulation and minimize adverse effects.

This new drug was approved in 2009 by the European Commission after the positive opinion of the CHMP, which assessed dronedarone as a less efficacious but possibly safer anti-arrhythmic drug than amiodarone [1]. The latter, in fact, has been shown to be effective in the management of atrial fibrillation (AF), but has also been associated with extra-cardiac toxicity, including effects on the thyroid and on the lung [2].

On the contrary, dronedarone did not seem to prolong significantly the QT_c interval and no significant pulmonary, hepatic, ocular or neurologic toxic effects have been observed in the pivotal clinical trials [3–7].

However, already during the clinical development of the dronedarone, some unfavourable safety issues were raised.

In the ANDROMEDA study, the drug doubled the death rate compared with placebo in patients with severe heart failure and left ventricular systolic dysfunction [7]. After about 1 year from the marketing authorization, two life-threatening cases of liver failure requiring liver transplantation were reported [8]. As a consequence, the Summary of Product Characteristic (SPC) was updated in order to ensure that patients' liver function is tested before initiation of treatment, closely monitored during treatment and discontinued if signs of potential liver damage appear.

In July 2011, the PALLAS study [9] was prematurely terminated because of an increased rate of heart failure, stroke and death from cardiovascular causes in the dronedarone group compared with placebo in patients with permanent AF and at risk for major cardiovascular events. Its use was therefore restricted to maintenance of sinus rhythm in patients with paroxysmal and persistent AF, and was contraindicated for patients with permanent AF and patients with current or previous episodes of heart failure or left ventricular systolic dysfunction.

In addition, reports of possible lung toxicity [10] have led to warnings and additional risk minimization measures to monitor and prevent the occurrence of pulmonary events.

In the matter of renal disorders, the SPC approved by the European Medicine Agency (EMA) states that an increase in plasma creatinine has been observed with dronedarone in healthy subjects and in patients. Consequently, it recommends that plasma creatinine values are measured prior to and 7 days after initiation of the drug, re-measuring values if further increased creatininaemia is observed. More importantly, it states that increased concentrations of creatinine are not necessarily indicative of a deterioration in renal function, and the evolution to renal

failure is not expected. In the FDA approved SPC, the serum creatinine increase is indicated with an incidence of 51% vs. 21% of placebo [11].

A study conducted in healthy subjects showed that dronedarone, similar to amiodarone, partially inhibited the tubular transport of creatinine, with a slight increase (10%–20%) in creatinine concentrations [12], suggesting that it causes a specific partial inhibition of tubular organic cation transporters leading to a limited increase in serum creatinine not correlated with a decline in renal function [13].

Results from the PALLAS study, instead, highlighted that ADRs related to renal function, including serious renal failure, were more frequently reported in the dronedarone group compared with the placebo group.

According to the Institute for Safe Medication Practices report available in November 2010, four cases of acute kidney failure were also collected in the Medwatch filing since the date on which the Food and Drug Administration approved the drug (August 2009) [14].

The procedure initiated in January 2011 and lasting until December 2011 from the European Commission in view of the above safety concerns concluded that it would be appropriate to provide further information to prescribers on what degree of elevation of serum creatinine may be expected, and time points at which the tests should be performed in order to allow distinction between cases of elevated serum creatinine due to inhibition of tubular creatinine secretion (where a plateau would be reached) and cases of 'true' renal failure (where serum creatinine would continue to increase) [15].

To our knowledge, no published studies have described reports of acute renal failure (ARF) or renal failure (RF) coming from a spontaneous reporting system.

The aim of our study was to describe cases of ARF/RF from dronedarone identified in the general population during post-marketing surveillance through the Italian spontaneous ADR reporting database.

Methods

The Italian Medicines Agency (AIFA) runs a pharmacovigilance database where all suspected adverse reactions from drugs and from vaccines since January 1988 are stored. Health care professionals are required to report those ADRs considered serious or unexpected. However, any adverse reaction (even mild and/or expected) from vaccines and from new drugs belonging to a list periodically up-dated should be reported to the system. The quality of the data collected is ensured because each report is verified both by the respective regional pharmacovigilance centre and also by AIFA.

For our purpose, spontaneous ADR reports collected in the database up to 31 December 2011 have been considered, regardless of their causality and seriousness. To provide evidence concerning the possible causal

Table 1

Demographic and clinical characteristics of the cases

Case number [Reporter]/ (Reporting date)	Age (years)/gender (and previous clinical conditions)	ADR(s) (MedDRA)	Suspected drugs	Concomitant drugs	Dechallenge (days to recovery after dechallenge)	Clinic and laboratory analysis	Causality assessment (Naranjo scale)
1 [Hospital doctor]/ (04/10/2010)	76/F (diabetes mellitus, arterial hypertension, hypothyroidism, myocardial infarction)	Renal failure	Fenofibrate 200 mg day ⁻¹ (since 8 days) Dronedarone 800 mg day ⁻¹ (since 6 days)	Atenolol, digoxin, aliskiren, glibenclamide/metformin, enoxaparin, furosemide, furosemide/spironolactone, sodium levothyroxine	Yes (13)	At the day of the ADR occurrence: blood urea, BC (176 mg dl ⁻¹) and 4.68 mg dl ⁻¹ , respectively, and cystatin C increased (2.36 mg l ⁻¹)	Possible
2 [Hospital doctor]/ (09/12/2010)	76/F	Asthenia, nausea, acute renal failure, tremor, vomiting	Dronedarone 400 mg day ⁻¹ (since 6 days)	Digoxin	Yes (n/a)	✓	Probable
3 [Hospital doctor]/ (04/02/2011)	79/M (septic shock, pulmonary fibrosis and hypothyroidism during treatment with amiodarone hydrochloride)	Secondary anaemia, acute renal failure	Dronedarone 800 mg day ⁻¹ (since 8 days)	Enalapril, allopurinol, potassium chloride, spironolactone, furosemide, salmeterol/fluticasone propionate, levothyroxine sodium, warfarin sodium, clonidine, tiotropium bromide monohydrate, oxygen	Yes (n/a)	At the day of the ADR occurrence: blood potassium (5.6mEq l ⁻¹) and BC increased (4.5 mg dl ⁻¹). Red blood cell count (3.1 U) and haemoglobin (8.7 g dl ⁻¹) decreased. BUN increased (227 mg dl ⁻¹)	Possible
4 [Hospital doctor]/ (14/03/2011)	61/F	Bradycardia, acute renal failure, acute renal tubular necrosis	Dronedarone 800 mg day ⁻¹ (since 13 days)	Pantoprazole, indobufen, beclomethasone dipropionate/formoterol fumarate dihydrate, tiotropium bromide monohydrate, atorvastatin, levosulpiride	Yes (patient did not yet recover at time of ADR reporting)	At the day of the ADR occurrence: BC increased (14 mg dl ⁻¹). After ADR start: blood potassium (9.6 mEq l ⁻¹)	Probable
5 [Outpatient specialist]/ (06/04/2011)	84/M (dysthyroidism during treatment with amiodarone, post-infarction ischaemic heart disease, nodule in right lung, bilateral adenoma NOS)	BC increased	Dronedarone 800 mg day ⁻¹ (since 2 months)	Bisoprolol hemifumarate, felodipine, furosemide, thiamazole, lansoprazole, dutasteride, tamsulosin hydrochloride, simvastatin	Yes (8)	At the day of the ADR occurrence: BC (2.2 mg dl ⁻¹). BC (1.1 mg dl ⁻¹) nine days after	Possible
6 [Hospital doctor]/ (25/05/2011)	73/F	Renal failure	Dronedarone 400 mg day ⁻¹ (since 6 days)	✓	Yes (8)	BC (3.29 mg dl ⁻¹), BUN increased (175 mg dl ⁻¹)	Probable
7 [General Practitioner]/ (21/06/2011)	63/F	BC increased, fatigue	Dronedarone 800 mg day ⁻¹ (since 7 days)	Nebivolol, telmisartan/hydrochlorothiazide, mesalazine, pantoprazole	Yes (6)	At the day of the ADR occurrence: blood potassium decreased (3.2mEq l ⁻¹), blood sodium decreased (134mEq l ⁻¹). After ADR start date: BC increased (12/04/2011: 1.76 mg dl ⁻¹ , 15/04/2011: 1.06 mg dl ⁻¹) then decreased (26/04/2011: 0.89 mg dl ⁻¹)	Possible
8 [Outpatient specialist]/ (08/07/2011)	65/F (renal transplantation, in good condition)	Azotaemia and transaminases increased, hypercreatinemia	Dronedarone 800 mg day ⁻¹ (since 1 month)	Atorvastatin, mycophenolate mofetil, clonidine hydrochloride, clopidogrel/ASA, calcitriol, calcium carbonate,	✓	✓	Possible
9 [Hospital doctor]/ (07/10/2011)	73/M (dehydration, rectal resection, ileostomy, rectal adenocarcinoma)	Acute renal failure	Dronedarone 800 mg day ⁻¹ (since 1 month) Olmesartan medoxomil 2.5 mg day ⁻¹ , (since 4 months)	Esomeprazole magnesium trihydrate, enoxaparin sodium, levothyroxine sodium	Yes	Before the day of the ADR occurrence: BC increased (2 mg dl ⁻¹). At time of ADRs start date: pressure arterial decreased (92/52 mmHg), blood bicarbonate decreased (17.5 mmol l ⁻¹), blood potassium (5mmol l ⁻¹), blood urea increased (131 mg dl ⁻¹), BC increased (8 mg dl ⁻¹), heart rate decreased (40 beats min ⁻¹), normal renal ecography	Possible

BC, blood creatinine.

association between dronedarone and renal disorders, a case-by-case analysis was applied [16]. According to ADR Terminology of the World Health Organization (WHO-ART), cases codified with the SOC term 'urinary system disorders' (1300 code) associated with dronedarone treatment have been retrieved from the database.

Results

At 31 December 2011, after removal of possible duplicates and of reports from drugs and vaccines coming from the literature, the database contained a total number of 124 069 ADR reports. Dronedarone was listed as the suspected drug in 55 reports. Among these, we identified four cases of ARF, two of RF and three increases in blood creatinine (numbers 5, 7 and 8, see Table 1). All the nine reports were submitted by physicians between October 2010 and December 2011. In the case number 8, an increase in azotaemia and in serum transaminase was also reported. Six out of nine reports concerned females. The patient age was from 61 to 84 years and the ADRs were classified as serious in four cases (numbers 1, 3, 4 and 9).

The majority of cases occurred within the first 13 days of initiation of dronedarone therapy, with a range of 6 days to 2 months.

Except for one, all reports of renal failure, both acute and not, required hospitalization or resulted in prolonged hospitalization (5/6, 83%). In seven cases, the only suspected drug reported was dronedarone. In eight out of nine cases, concomitant drugs were reported but only in three of them, ARF was a labelled ADR [i.e. enalapril (case number 3), telmisartan plus hydrochlorothiazide (case number 7), clopidogrel plus aspirin (case number 8)].

In case number 9, the patient received a co-suspected drug (olmesartan) labelled for causing ARF.

In all reports except one positive dechallenge was reported.

In two cases (numbers 3 and 5), the patients had developed previously a dysthyroidism caused by amiodarone, whereas in two other cases (numbers 1 and 9) levothyroxine was a concomitant drug.

Discussion

The four cases of ARF, two of RF and three of increase of serum creatinine are not a negligible number when compared with the initial low use of this new drug in Italy (reimbursed in Italy since 29 July 2010, with a consumption in 2011 of 0.1 DDD/inhabitants day⁻¹ [17]). As several studies have shown, for each serious case reported more than 15 are not reported, due to the under-reporting (particularly in Italy) [18, 19]. So, we can suspect that more than one hundred cases of renal disorders could have occurred in this period in our country.

As for the possible mechanism of dronedarone-induced renal failure, perhaps its multichannel blocking activity could be considered, also in the light of the renal side effects of its related compound amiodarone (including renal insufficiency, acute renal failure and renal impairment), as mentioned in the SPC of amiodarone [20].

Our findings have some strengths and some weaknesses: (i) all cases but one had a positive dechallenge, often with creatinine values going back to normal after withdrawal of dronedarone; (ii) the reporters indicated dronedarone as the only suspected drug in all cases but two; and (iii) the nine reports were almost regularly time spaced from the launch of dronedarone without any burst occurring after the EMA safety communication. Therefore, a notoriety bias affecting our results may be ruled out.

On the other hand, patients were old men and women, with several concomitant illnesses, and it is possible that these conditions may have precipitated their renal failure. We think that these cases are an important signal to be evaluated, and that periodic controls of renal function, in patients treated with dronedarone, should be recommended to the physicians.

In conclusion, the safety profile of dronedarone is not completely known, and it has been questioned in recent systematic reviews and meta-analyses [21, 22, 22, 23]. Our findings add to the body of evidence concerning cardiovascular, hepatic and pulmonary risks and suggest the need to reconsider the risk/benefit ratio of this new antiarrhythmic drug.

Clinicians should be aware of the risk for dronedarone-associated ARF and the need to screen patients appropriately for ARF risk factors before starting dronedarone therapy.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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