Prescribing dronedarone for paroxysmal atrial fibrillation: how is it done across the UK and is it safe?

Eron Yones, Jennifer Mullan, Andrew Horwood, Nicola Connell, Sarah Odams, Jean Maloney, Andreas L Kyriacou, Jonathan Sahu, Justin M Lee, Nicholas F Kelland

Department of Cardiology,
Northern General Hospital,
Sheffield Teaching Hospitals
NHS Trust, South Yorkshire, UK

Correspondence to

Dr Eron Yones, Department
of Cardiology, Northern
General Hospital, Sheffield
Teaching Hospitals NHS Trust,
South Yorkshire S5 7AU, UK;
eronyones@gmail.com

Received 9 January 2017
Revised 21 March 2017
Accepted 3 April 2017
Published Online First
12 May 2017

ABSTRACT

Dronedarone, a useful treatment for paroxysmal atrial fibrillation, is often only prescribed in secondary care. To support a protocol shared between primary and secondary care, dronedarone use was audited in our centre and prescribing practices across UK secondary care centres were reviewed. From 2010 to 2015, a total of 181 patients were started on dronedarone. There were no deaths or serious adverse events. Median cessation time due to adverse effects was 52 days and 88% stopped dronedarone within 6 months. Of 17 local prescribing protocols across the UK, 12 involved shared care and 5 purely secondary care follow-up. In our review, dronedarone was safe and well tolerated. The use of shared care protocols is well established in other UK centres. The development of a local shared care protocol between primary and secondary care is feasible with existing systems in place to support its introduction.

INTRODUCTION

Dronedarone is relatively new class III antiarrhythmic drug used predominantly for the treatment of paroxysmal atrial fibrillation (pAF) in clinically stable patients. It is a multichannel blocker with a similar structure to amiodarone, though it lacks the iodine molecular moiety. Dronedarone is recommended by the National Institute for Health and Care Excellence for the treatment of pAF to maintain sinus rhythm where first-line treatments have failed or are contraindicated.¹ It is safe to use in patients with hypertension, diabetes, previous stroke or transient ischaemic attack and in the elderly.² Dronedarone is contraindicated for use in patients with left ventricular systolic dysfunction (LVSD), congestive cardiac failure, liver failure, permanent AF, atrioventricular block and pulmonary fibrosis secondary to amiodarone.

Under many local UK prescribing arrangements, dronedarone is classified as either red (treatment initiated and prescription continued by secondary care) or amber (initiated by secondary care but prescription continued by primary care). This is due to rare but serious adverse events, such as fulminant liver failure (with two previous cases requiring liver transplantation in the USA³ and prolongation of the QT interval). Common side effects include dizziness, abdominal discomfort/upset, pedal oedema, shortness of breath and nausea.²

Current UK national prescribing guidelines recommend baseline liver function, urea and electrolytes, ECG and echocardiography to be

performed before commencing treatment.¹ Renal and liver function should be monitored and an ECG repeated 6 monthly, to ensure that patients have not developed permanent AF.⁴

Due to its relative novelty, many non-specialist clinicians and prescribers do not have experience or familiarity with dronedarone, which in addition to its potential adverse event profile, may cause some reluctance in fostering responsibility for long-term prescribing. For this reason current dronedarone prescribing guidelines in a tertiary cardiology centre, Sheffield Teaching Hospitals (STH) in South Yorkshire, dictate that patients are started by a specialist clinician in the cardiology clinic and subsequent prescribing and follow-up is managed and monitored through a specialist nurse-led clinic.

The safety, tolerability and efficacy of dronedarone from 2010 to 2015 in this clinic were audited.

Prescribing practices in multiple secondary and tertiary care centres across the UK were then reviewed to determine whether alternative policies or protocols were practised elsewhere.

Based on the results of the clinical data obtained from the STH dronedarone clinic and practices observed in similar centres across the UK, we aimed to develop a safe shared care prescribing protocol in South Yorkshire.

METHODS

A detailed retrospective analysis of all patients who were prescribed dronedarone between 2010 and 2015 in STH was undertaken. Using local clinical software, medical records were analysed to determine the treatment start and stop dates, as well as the incidence of any contraindications, side effects or serious complications (including death) related to dronedarone.

Data were analysed using Kaplan-Meier survival function as survival from adverse events. Patients were censored at the date of their last clinic appointment if they remained on the drug, if they were lost to follow-up or if they stopped the drug for any reason (eg, ineffectiveness, ablation and developed a contraindication such as permanent AF).

Following this analysis, a number of UK secondary and tertiary care centres, which had published their dronedarone prescribing guidelines online, were identified using web searches. Using this information, it was determined whether a strict secondary care pathway was practised or whether a shared care protocol with primary care was in

To cite: Yones E, Mullan J, Horwood A, et al. *Eur J Hosp Pharm* 2019;**26**:220–222.

Figure 1 Kaplan-Meier survival plot showing patients with paroxysmal atrial fibrillation (AF) on dronedarone treatment free from adverse effects over 18 months. Patients were censored when the drug is stopped for development of permanent AF, ineffectiveness, AF ablation or developed another contraindication.

place. Where a shared care protocol was used, the minimum secondary care follow-up duration was established.

RESULTS

In our centre between 2010 and 2015, a total of 181 patients were started on dronedarone, 99.5% of these were for pAF. One patient was treated for postural orthostatic tachycardia syndrome.

The median duration of treatment was 251 days ($SD \pm 450$ days). Of 103 patients who remained on dronedarone after 6 months, the majority reported good subjective control of symptoms however some went on to develop permanent AF. Seventy-one patients remained on dronedarone for at least 12 months and 37 for at least 24 months. Of the patients who stopped taking dronedarone due to contraindications, the most common was the development of permanent AF.

There were no deaths attributable to dronedarone, nor were there any episodes of liver failure or dronedarone-induced QT prolongation. The total adverse effect rate was 18.9% and the median drop-out time due to an adverse effect was 52 days. The greatest rate of stopping treatment occurred in the initial months of treatment (figure 1): 88% of patients who stopped due to adverse effects did so within 6 months of starting treatment. The drop-out rate due to adverse effects declined from 7.73% per month in the first month, to 3.87% in months 1–3, 2.33% by months 3–6 and 0.33% by months 6–9. No patients stopped taking dronedarone due to adverse effects after being stable on it for 18 months. The most common adverse effects were gastrointestinal upset/discomfort, nausea, dizziness, pedal oedema, shortness of breath and headache.

Dronedarone prescribing protocols were obtained from 17 UK secondary and tertiary care centres. Of these, 3 had listed dronedarone as red in their formulary, with 14 listing it as amber. There were 12 centres with shared care protocols and 5 with purely secondary care follow-up. Of the 12 centres, which had a shared care protocol in place, the minimum mandatory follow-up time ranged from none to 1 year. Of the centres that had adopted a shared care protocol, all initial investigations were carried out in secondary care and a detailed written handover of care was communicated to the

general practitioner (GP), once the patient was stabilised on dronedarone and the minimum mandatory follow-up duration was met. None of the protocols mandated the GP to accept the responsibility for dronedarone prescribing and monitoring, and an option to refuse was maintained. All shared care protocols maintained an open re-referral policy, if any patient required further secondary care input.

DISCUSSION

The data presented demonstrated that dronedarone is largely a safe drug with no associated deaths or serious adverse events in a large number of patients >5 years in our clinic. Furthermore, the majority of patients who were stabilised on dronedarone (minimum 6 months treatment) reported positive subjective symptom control and tolerated the medication well. In the group who stopped due to adverse effects, the majority did so early with no lasting or long-term effects reported.

The online search showed that dronedarone is managed in partnership between primary and secondary care institutions in many areas across the UK, reinforcing our clinical safety data. Although the establishment of a shared care prescribing protocol is not yet validated, it is nonetheless widely practised.

On the basis of this data analysis and review of practice across the UK, we propose the development of a shared care prescribing protocol within South Yorkshire. We propose a mandatory minimum follow-up period of 6 months in secondary care in view of the data showing that 88% of people who stop taking dronedarone do so within 6 months, thereby providing the majority of patients with a safe stabilisation period of close hospital review. After 6 months, ongoing prescription and monitoring of dronedarone could be done in primary care. This has potential to save patients' time and effort through avoiding unnecessary hospital visits.

Other shared care protocols are well established locally. Amiodarone prescribing, despite having a significant and recognised adverse event profile, has been handed over to the community within 4 weeks of commencement in the cardiology clinic for many years. Patients are given an amiodarone 'passport' and educated on monitoring and adverse features needing urgent medical attention. A similar protocol for dronedarone based on this established model is feasible and would facilitate the analysis and audit of subsequent outcomes and safety.

This study is limited by being a single-centre study and data collection was entirely retrospective. Furthermore, no quantifiable quality of life data were collected at clinic appointments, which limited efficacy analysis.

The changes proposed by this report fall in line with the South Yorkshire NHS Foundation Trust's Sustainability and Transformation plans,⁵ specifically addressing the Care and Quality Gap and Funding and Efficiency Gap which are targeted for achievement by 2021.

Thus, this study supports the development of a local shared care protocol between secondary and primary care. Once established, we would recommend that this protocol should be reviewed and regularly audited.

Contributors EY: Wrote and edited manuscript, collection of data. JM: Edited manuscript, interpretation and creation of graphical data. AH, NC, SO, JM, AK, JS, JML and NFK: dronedarone initiation and follow-up clinic, edited manuscript. NFK: conceived the original idea for the project.

Competing interests NFK: consults for Pfizer and Bristol Myers Squibb and has received travel/educational grants from several device and pharmaceutical companies. AK, JS and JML have also had similar relationships with various device companies.

Provenance and peer review Not commissioned; externally peer reviewed.

© European Association of Hospital Pharmacists (unless otherwise stated in the text of the article) 2019. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 NICE. www.nice.org.uk/guidance/ta197/resources/dronedarone-for-nonpermanent-atrial-fibrillation-378146845 (accessed 07 Jan 2017)
- 2 NICE. www.nice.org.uk/guidance/ta197 (accessed 07 Jan 2017)
- 3 FDA Drug Safety Communication: Severe liver injury associated with the use of dronedarone (marketed as Multaq). https://www.fda.gov/Drugs/DrugSafety/ucm240011.htm#data_summary (accessed 07 Jan 2017).
- 4 Connolly SJ, Camm AJ, Halperin JL, *et al.* Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;365:2268–76.
- 5 Sustainability and transformation plans (STPs). <http://www.southwestyorkshire.nhs.uk/quality-innovation/sustainability-transformation-plans-stps/> (accessed 16 Mar 2017).