Thrombosis Research 135 (2015) 1070–1074

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Concomitant use of dronedarone with dabigatran in patients with atrial fibrillation in clinical practice ☆

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ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form 7 March 2015
Accepted 10 March 2015
Available online 19 March 2015

Keywords:
Dabigatran
Dronedarone
Atrial fibrillation
Concomitant treatment
Plasma concentration

ABSTRACT

Introduction: Dronedarone is a strong P-glycoprotein inhibitor with a potential to increase bioavailability of dabigatran. We sought to measure and report plasma concentrations of dabigatran in patients with atrial fibrillation (AF) on concomitant dronedarone treatment.
Materials and methods: A cohort of 33 patients (mean age 64 years, 16 men) concomitantly treated with dabigatran at a dose of 110 mg twice a day (bid) and dronedarone at a dose of 400 mg bid at the discretion of the patient's cardiologist were followed prospectively.
Results: Median trough plasma concentration of dabigatran at one week and one month after the concomitant treatment start was 102.0 (range 8-251) ng/ml and 84 (range 27-302) ng/ml respectively. Median treatment length was 13 (range 1-21) months. There was one major bleeding event (2,8% per patient-year) and no thrombotic events during a total of 35.5 patient-years.
Conclusions: Median trough plasma concentration of dabigatran in our study was observed to be similar to median trough plasma concentration of dabigatran at a dose of 150 mg bid without concomitant dronedarone in earlier studies with low reported rate of bleeding and thrombosis. Since concomitant treatment offers potential benefits to patients with AF, larger future trials that might refute the current contraindication are warranted.

Introduction

Dabigatran etexilate is a novel oral direct thrombin inhibitor approved as alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation (AF). Unlike warfarin, dabigatran is given at a fixed dose and does not require dietary restrictions or regular coagulation monitoring.

The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial compared the use of dabigatran with warfarin in patients with atrial fibrilation [1]. Dabigatran at a dose of 150 mg twice a day (bid) was associated with lower risk of stroke and systemic thromboembolism without an increase in the overall rate of major bleeding. Dabigatran at a dose of 110 mg bid was non-inferior in reducing stroke and systemic thromboembolism at a lower rate of major bleeding.

Dabigatran elimination occurs predominantly (80%) via renal route [2] and impaired renal function can result in drug accumulation. Dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein (P-gp) in the intestine [3]. About 48% of patients with atrial fibrillation that use vitamin K antagonists take drugs that affect Pg-p [4] and thus can potentially alter bioavailability of dabigatran.

Dronedarone is an antiarrhythmic drug for maintenance of sinus rhythm that was shown to reduce the incidence of death or hospitalisation due to cardiac events in patients with paroxysmal or persistent atrial fibrillation [5]. Dronedarone is a strong P-gp-inhibitor with a potential to increase bioavailability of dabigatran if given concomitantly. Although dronedarone and dabigatran are often indicated in the same patient population, no previous study has addressed the safety and clinical endpoints of the concomitant treatment in AF patients. Co-administration of these two drugs has only been prospectively studied in 16 healthy volunteers (age 18-45, 81.3% males) and the conclusion of the study was that the trough concentration of dabigatran was 1.7-fold higher when dabigatran 150 mg bid was co-administered with dronedarone than when dabigatran was administered alone [6,7]. Retrospective cohort studies using claim databases has not demonstrated any increased risk of major bleeding with concomitant use of dabigatran and dronedarone compared to dabigatran alone [7,8] and hence the clinical significance of this drug interaction remains uncertain. However, the European Medicines Agency (EMEA) has decided that concomitant use of dabigatran and dronedarone should be contraindicated

☆ This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.
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http://dx.doi.org/10.1016/j.thromres.2015.03.015
0049-3848/

based on pharmacokinetic data from the Sanofi-Aventis study on healthy volunteers, using the dose of dabigatran 150 mg bid [8].

In this study we sought to measure and report plasma concentrations of dabigatran at a lower dose of 110 mg bid on concominant dronedarone treatment from a real-life setting in patients with atrial fibrillation.

Materials and Methods

Patients treated concomitantly with dabigatran 110 mg bid and dronedarone 400 mg bid at the discretion of the patient's cardiologist at Skåne University Hospital were referred to the anticoagulation clinic during the period of January 2012 to July 2013 and prospectively followed up in the internet-based Swedish national quality registry AuriculA. The patients discussed the risks and benefits of the treatment with their cardiologists. Plasma levels of dabigatran were reported to the cardiologist, responsible for the treatment. The registry contains key patient characteristics, information on anticoagulation treatment, comorbidities and complications to atrial fibrillation as quality indicators [9].

Concomitant treatment with dabigtran and dronedarone was introduced as an alternative to warfarin and dronedarone by local consensus and guidelines at Skåne University Hospital before the present contraindication. Given the strong inhibition of Pg-p by dronedarone, hospital cardiologists and coagulation experts agreed on guidelines using the dabigatran 110 mg bid dose concomitantly with dronedarone and, as a safety measure, measuring dabigatran levels in these patients. Hence, measurement of dabigatran concentrations and review of the patients' hospital records was a part of a quality control and assurance program aiming to follow up the introduction of this new therapeutic strategy.

The study outcome was plasma trough concentration of dabigatran at one week and one month after the start of concomitant treatment. The analysis of dabigatran was performed at Department of Clinical Chemistry, Skåne University Hospital. Trough venous samples at steady state, between 08:00 and 08:30 in the morning before patients had taken their morning dabigatran dose, were collected at pre-specified time points at one week and one month after the initiation of the concomitant treatment, to assess patient compliance. The patients did not receive any specific instructions about the timing of dronedarone and dabigatran intake other than that they should take both medicines twice daily. Plasma concentrations of dabigatran were obtained using the diluted thrombin time calibrated with dabigatran standard (Hemoclot thrombin inhibitor assay, HYPHEN BioMed) [10] in accordance to recommendations from International Society of Thrombosis and Homeostasis [11]. The total imprecision calculated as coefficient of variation was 9.85% at 100 ng/ml and 4.59% at 400 ng/ml.

Rate of major bleeding (according to International Society of Homeostasis and Thrombosis (ISHT) definition) [12] and rate of ischemic stroke or systemic embolism during the time of concomitant treatment were calculated. A review of all hospital records of every patient was performed in May 2014 to assess concomitant medications and to assure that no comorbidities or treatment complications were missed. The list of *in vivo* P-gp inhibitors and inducers was obtained from Food and Drug Administration (FDA) Guidance for Industry Drug Interaction Studies [13] in order to assess the use of other drugs that can alter P-gp. CHA_2DS_2-VASc [14] and HAS-BLED [15] scores were calculated to estimate the risk of stroke and bleeding. Concomitant use of cardiovascular drugs and medications that can affect bleeding risk (antiplatelet agents, non-steroidal anti-inflammatory drugs, proton pump inhibitors and corticosteroids) was also assessed.

Since dabigatran is eliminated predominantly via kidneys, estimated glomerular filtration rate (eGFR) was calculated using the Lund-Malmö equation (derived and internally validated at the present University Hospital) [16]. Renal function was monitored at treatment initiation, after 3, 6 and 12 months and thereafter annually [17].

Using AuriculA in routine health care complies with the Declaration of Helsinki and the Ethics Committee at the Lund University has approved research using this registry.The assignment of the medical intervention was not at the discretion of the investigators. The investigators did not have any relationship with the treating cardiologists other than reporting dabigatran levels and were not involved in the medical care of the patients. The investigators were responsible for development of the follow-up program in January 2012 and theretrospective review of the patients' records in May 2014. This paper only reports observational data of current clinical practice. Patients were not subjected to any additional hazards by the above-described follow-up of their treatment and therefore informed consent was not obtained by the authors.

Statistical analysis was performed using SPSS (version 21.0, Armonk, NY: IBM Corp). Median (IQR 25-75%) plasma concentration of dabigatran and median treatment length were calculated.

Results

Study Population

All patients treated concomitantly with dabigatran and dronedarone are reported to AuriculA registry for follow–up and thus none of potentially eligible patients were missed. None was lost to follow-up. Baseline characteristics of the study population (n = 33) are presented in Table 1. The mean age of the patients was 64 years and 48.5% were men.

The mean CHA_2DS_2-VASC score was 2.3 ± 1.3, range 0-6. One patient with CHA_2DS_2-VASC score 0 was treated with dabigatran prior to elective electrocardioversion.

Table 1
Baseline characteristics.

	Our study	RELY study Dabigatran 150 mg bid [1]
Treated patients, (n)	33	6076
Age, mean (SD), years	64.0 (8.7)	71.5 (8.8)
Males, n (%)	16 (48.5)	3840 (63.2)
eGFR, mean (SD), ml/min/1.73 m^2	66.0 (11.2)	N/A
<50	3 (9)	1126 (18.9)*
50-79	29 (88)	2898 (48.6)*
>80	1 (3)	1945 (32.5)*
Medical history:		
Heart failure, n (%)	2 (6.1)	1934 (31.8)
Hypertension, n (%)	23 (69.7)	4795 (78.9)
Vascular disease, n (%)	6 (18.2)	N/A
Diabetes, n (%)	3 (9.1)	1402 (23.1)
Prior stroke or TIA, n (%)	4 (12.1)	1233 (20.3)
Prior systemic or peripheral arterial embolism, n (%)	2 (6.1)	N/A
Renal disease, n (%)	0 (0)	N/A
Abnormal liver function, n (%)	0 (0)	N/A
Prior intracranial bleeding, n (%)	0 (0)	N/A
Prior other bleeding, n (%)	1 (3.0)	N/A
Labile INR, n (%)	3 (9.1)	N/A
Alcohol abuse, n (%)	3 (9.1)	N/A
CHA_2DS_2-VASC score		
0-1, n (%)	9 (27.3)	1958 (32.2)
2, n (%)	11 (33.3)	2137 (35.2)
3-6, n (%)	13 (39.4)	1981 (32.6)
HAS BLED score		N/A
0-2, n (%)	29 (87.9)	
3-4, n (%)	4 (12.1)	
Concomitant medications at baseline:		
Other Pgp-inhibitors/inducers, n (%)	1 (3.0)	N/A
Proton pump inhibitors, n (%)	4 (12.1)	847 (13.9)
Antiplatelet agents, n (%)	0 (0)	2352 (38.7)
Non-steroidal anti-inflammatory drugs, n (%)	0 (0)	N/A
Angiotensin converting enzyme inhibitor or angiotensin II antagonists, n (%)	19 (57.6)	4053 (66.7)
Beta-blocking agents, n (%)	28 (84.8)	3872 (63.7)
Statins, n (%)	12 (36.4)	2667 (43.9)
Corticosteroids, n (%)	2 (6.1)	N/A

* according to the RELY substudy [18].