Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

International Diabetes Federation

Does type 2 diabetes affect the on-treatment levels of direct oral anticoagulants in patients with atrial fibrillation?

Matej Samoš *, *Tomáš Bolek*, *Lucia Stančiaková*, *Ingrid Škorňová*, *Jela Ivanková*, *František Kovář*, *Peter Galajda*, *Peter Kubisz*, *Ján Staško*, *Marián Mokáň*

Department of Internal Medicine I, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic
National Centre of Hemostasis and Thrombosis, Department of Hematology and Blood Transfusion, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovak Republic

ARTICLE INFO

Article history:
Received 5 July 2017
Received in revised form
28 October 2017
Accepted 20 November 2017
Available online 23 November 2017

Keywords:
Type 2 diabetes
Direct oral anticoagulants levels
Dabigatran
Rivaroxaban
Apixaban
Hemoclot® Thrombin Inhibitor Assay
Atrial fibrillation

ABSTRACT

Aims: Type 2 diabetes (T2D) is connected with several abnormalities in haemostasis; and with higher risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NV-AF). However, it is recently unknown whether T2D affects the activity of direct oral anticoagulants (DOACs). The aim of this study was to determine the impact of T2D on DOACs activity in patients with NV-AF.

Methods: This pilot prospective study enrolled totally 65 patients with NV-AF (20 dabigatran-treated, 110 mg/twice daily; 28 rivaroxaban-treated, 15 mg/daily; 17 apixaban-treated, 5 mg/twice daily). 25 patients had T2D (8 dabigatran-treated, 11 rivaroxaban-treated, and 6 apixaban-treated). DOAC activity was tested with Hemoclot® Thrombin Inhibitor assay in dabigatran-treated patients, and with factor Xa-calibrated anti-Xa chromogenic analysis in rivaroxaban- and apixaban-treated patients prior and two hours after drug administration.

Results: There were no significant differences in dabigatran baseline (62.1 ± 8.0 vs. 51.8 ± 38.9 ng/ml, p = .76) and 2-h-post-drug-administration (91.7 ± 57.2 vs. 72.2 ± 33.2 ng/ml, p = .48) activity comparing T2D and non-diabetic patients. Similarly, no significant differences were found in rivaroxaban baseline (35.9 ± 22.5 vs. 55.3 ± 45.1 ng/ml, p = .19) and 2-h-post-drug-administration (145.7 ± 74.1 vs. 202.6 ± 135.0 ng/ml, p = .22) anti-Xa activity. In addition, no significant differences were present in apixaban baseline (96.0 ± 54.5 vs. 63.9 ± 36.8 ng/ml, p = .24) and 2-h-post-drug-administration (151.0 ± 78.3 vs. 151.7 ± 59.1 ng/ml, p = .98) anti-Xa activity between T2D and non-diabetic patients.

Conclusions: This pilot study did not detect differences in DOACs activity according to T2D status in patients with NV-AF.

* Corresponding author at: Department of Internal Medicine I, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Kollarova 2, 036 59 Martin, Slovak Republic.
E-mail address: matej.samos@gmail.com (M. Samoš).
https://doi.org/10.1016/j.diabres.2017.11.024
0168-8227/

1. Introduction

Type 2 diabetes (T2D) is connected with higher risk of stroke and systemic embolism in patients with atrial fibrillation (AF). Therefore, T2D patients with AF more often require long-term anticoagulation. Recently, direct oral anticoagulants (DOACs) – direct thrombin inhibitor dabigatran [1], direct factor Xa inhibitors rivaroxaban [2] and apixaban [3] – had been introduced for prevention of stroke and systemic embolism in patients with non-valvular AF (NV-AF). These agents generally offer some advantages, such as consistent and predictable anticoagulation, oral administration with good patient compliance and a good safety profile. The pharmacokinetic and pharmacodynamic properties of these directly acting oral anticoagulants are displayed in Table 1.

T2D is connected with several abnormalities in hemostasis, including altered platelet function [4], endothelial dysfunction [5,6], abnormalities in coagulation and fibrinolysis [7]. Now, there is a discussion about a possible interaction between T2D and antithrombotic therapy [8–11]. T2D is already known to modulate cytochrome P450 activity in humans and in animal models [12–14], and the drug-cytochrome P450 interaction might affect oral factor Xa inhibitors plasma activity [15]. Moreover, T2D is associated with changes in expression of P-glycoprotein [16], and therefore might affect also dabigatran activity [17]. Up to date, there is no study examining the interaction between T2D and DOACs plasma activity. This study aimed to clarify the impact of T2D on DOACs plasma activity in patients with NV-AF.

2. Patients and methods

2.1. Study design and patients

A pilot prospective study with an observational design in patients with NV-AF on DOACs therapy was performed. This study enrolled totally 65 consecutive presentations of patients with NV-AF (20 dabigatran-treated, 110 mg/twice daily; 28 rivaroxaban-treated, 15 mg/daily; 17 apixaban-treated, 5 mg/twice daily) admitted to Department of Internal Medicine. All patients had been taking DOACs prior to their hospitalization, and continued with the DOAC therapy during hospitalization. The average length of taking DOACs prior to blood sampling was 160.6 days. No antiplatelet agents, other anticoagulants, or other medication which might possibly affect coagulation was administrated in studied patients. CHA2DS2-VASc score was calculated in all patients (presence of congestive heart failure or left ventricular ejection fraction $\leq$40% – 1 point; hypertension – 1 point; age $\geq$75 years – 2 points; diabetes – 1 point; stroke or transient ischemic attack or systemic embolism – 2 points; vascular disease – 1 point; age from 65 to 74 years – 1 point; female gender – 1 point). The medication compliance was verified by a healthcare professional, who supervised each DOAC administration during hospitalization. Patients with known and correctly diagnosed history of T2D had been assigned to T2D group. This group included 25 patients (8 dabigatran-treated, 11 rivaroxaban-treated, and 6 apixaban-treated). In all patients without previous history of T2D a standard oral glucose tolerance test (75 g of glucose was administrated in 100 ml of water and a venous blood sample was taken two hours after the glucose administration) was performed. Patients with blood glucose value >7.8 mmol/l two hours after the glucose administration had been excluded from the study. Therefore, only patients without previous history of T2D, and with blood glucose value <7.8 mmol/l shown in oral glucose tolerance test had been assigned to non-diabetic (ND) group. After the obtaining patient's inform content, blood samples were taken on the fifth day of in-patient stay using 3.8% citrate vacutainer blood collection tubes prior and two hours after the administration of DOACs doses (2-h-post-drug-administration sample). All dabigatran-treated patients were fasting before swallowing the drug; and all factor Xa inhibitors-treated patients had eaten breakfast prior swallowing the drug. The research was done according to ethical standards and was approved by the local ethical committee. All patients agreed with study participation and signed a written informed consent prior to blood sampling.

Table 1 – Pharmacokinetic and pharmacodynamic properties of studied direct oral anticoagulants.

	Dabigatran	Rivaroxaban	Apixaban
Target factor	Factor IIa	Factor Xa	Factor Xa
Clinical indication	NV-AF PE or DVT prophylaxis PE or DVT treatment	NV-AF PE or DVT prophylaxis PE or DVT treatment	NV-AF PE or DVT prophylaxis PE or DVT treatment
Prodrug	Yes (dabigatran etexilate)	No	No
Hepatic metabolism	Yes(glucuronidation)	Yes (CYP3A4, CYP2J2)	Yes (CYP3A4/5, CYP21A2, CYPSC8, CYP2C9/19, CYP2J2)
Renal clearance	75–80%	60 – 65%	25 – 30%
Protein bound	35%	95%	87%
Half-life	12–17 h	9–13 h	8–15 h
On-set of action	0.5–2 h	2–4 h	1–3 h
Laboratory test for monitoring	Diluted thrombin clotting time, ecarin clotting time	Anti-Xa activity	Anti-Xa activity

Abbreviations: DVT – deep venous thrombosis; PE – pulmonary embolism; NV-AF – non-valvular atrial fibrillation, CYP – cytochrome P450.