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Direct oral anticoagulant therapy and drug interactions in patients with atrial fibrillation

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ABSTRACT

Background. Drug-drug interactions (DDIs) are one potential cause of adverse drug events. Very little has been done to study the relationship between potential DDIs in patients (p) with atrial fibrillation (AF) on direct oral anticoagulants (DOACs). Many anticoagulants are eliminated by the kidneys, so they can accumulate if their dose is not adapted to the kidney function. DDI is one particular type of drug error that can result in adverse drug events (ADEs) in exposed patients and was the aim of this study.
Materials and Methods. A total of 50 patients with AF on DOACs (25 patients on dabigatran and 25 on rivaroxaban) with normal, mildly or moderately decreased (estimated GFR > 30 mlmin-11.73m2) renal function were included (age 69±7 years, 26M/24F, body mass index (BMI) 35.4±5.1 kg/m2, duration of hypertension 11±5 years, duration of AF 5±2 years, eGFR 58±23 mlmin-11.73m2 (was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula).
Results. The 12-month administration of DOACs caused a nonsignificant decrease of eGFR (declined from 58±23 mlmin-11.73m2 to 56±17 mlmin-11.73m2 (p=0.01). All patients have the right dose of DOACs according to eGFR. Patients with AF and DOACs on more than 3 different drugs (20%) such as statins, verapamil and amiodarone were more prone to AE.
Conclusion. DDIs are one of the most important problems in every day practice. Coadministration of statins with dabigatran worsens clinical outcomes and a similar interaction might be seen with verapamil and amiodarone. Patients need to be on the right drug/right dose given the kidney function they have, with special care on DDIs.

Key words: drug-drug interactions, direct oral anticoagulants, renal function

INTRODUCTION

Drug-drug interactions (DDIs) are one particular type of drug error that can result in ADEs in exposed patients (1). Drug interaction studies mainly report the frequency of potential DDIs in medical prescriptions without investigating the occurrence of adverse clinical outcomes. Very little has been done to study the relationship between potential DDIs in patients (p) with atrial fibrillation (AF) on direct oral anticoagulants (DOACs).
Stroke risk stratification for patients with AF is performed by calculating a CHA2DS2-VASc (congestive heart failure/left ventricular dysfunction, hypertension, ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65 to 74 years, sex female) score (2). Stroke is one serious consequence of AF and oral anticoagulant therapy with vitamin K antagonist (VKAs) and four non-VKAs (direct oral anticoagulants) have been found to be at least as effective as and safer than VKAs for stroke prevention in patients with non-valvular AF (2).
Direct oral anticoagulants (DOACs) are easier to administer than VKAs because they can be given in fixed doses without routine coagulation monitoring. The DOACs include dabigatran, which inhibits thrombin, and apixaban, rivaroxaban and edoxaban, which inhibit factor Xa (3). The impact of some drugs such as permeability [P] glycoprotein [P-gp] agents inhibitors with DOACs was of particular interest in our work.
We investigate drug-drug interactions with effects and safety of DOACs on renal function parameters in AF patients with estimated glomerular filtration rate (eGFR) >30 mlmin-11.73m2

MATERIALS AND METHODS

A total of 50 patients with AF on DOACs (25 patients on dabigatran and 25 on rivaroxaban) with normal, mildly or moderately decreased (estimated GFR > 30 mlmin-11.73m2) renal function were included and followed for 12 months during 2016. (age 69±7 years, 26M/24F, body mass index (BMI) 35.4±5.1 kg/m2, duration of hypertension 11±5 years, duration of AF 5±2 years, eGFR 58±23 mlmin-11.73m2 (was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula).
Dabigatran was started as a 150 mg twice daily dose and rivaroxaban 20 mg once daily in patients with eGFR ≥ 50 mlmin-11.73m2. In patients with eGFR <50 and > 30 mlmin-11.73m2 dabigatran was started as a 110 mg twice daily dose and rivaroxaban 15 mg once daily. Apixaban was started at 2.5mg twice daily only in patients with DDIs (5 pt). Estimated glomerular filtration (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula). The HAS-BLED bleeding score is used to determine the risk for bleeding in patients with AF: A score is calculated on the basis of the a) Hypertension (systolic blood pressure > 160 mm Hg), b) Abnormal re-

nal or liver function, c) Stroke, d) Bleeding (major bleeding history, anemia, or predisposition to bleeding), e) Labile INRs (unable to maintain a stable, therapeutic INR ≥ 60% of the time), f) Elderly (aged > 65 years), g) Drug use (ie, antiplatelet agents or NSAIDs) (1 point each). A score ≥ 3 suggests increased risk of experiencing bleeding complications (4). For all patients CHA2DS2VASc (congestive heart failure (C), hypertension (H), age>75 y (A), diabetes mellitus (D), stroke (S), vascular disease (VA), sex (S)) score was also calculated (5). Bleeding or worsening of renal function or DDIs were categorized as adverse event (AE). The study was approved by the local ethics committee and provided written informed consent to participate.

Statistical anaysis was carried out using the software program STATISTIKA 10, 2011 softwere. The frequency of AE in patients with AF on DOACs was compared using the Chi-square test. A value $p < 0.001$ was considered statistically significant.

RESULTS

This cross-sectional study was carried out in 50 patients during one year. There were no statistically differences between groups in renal function, age, sex, duration of hypertension and AF, HAS-BLED /CHA2DS-2VASc score and number of medications between groups on dabigatran and rivaroxaban.

The mean HAS-BLED score was 2.8 and a mean CHA2DS2VASc score of 3.0 for all patients. All AF patients have the right dose of DOACs according to eGFR (Table 1). The 12-month administration of DOACs caused a nonsignificant decrease of eGFR (declined from 58±23 mlmin-11.73m2 to 56±17 mlmin-11.73m2 (p= 0.01)).

Patients with AF and DOACs on more than 3 different drugs (20%) such as statins (atorvastatin, simvastatin), verapamil and amiodarone were more prone to AE ($p < 0.001$). Only 5 (10%) patients on 6 and more medications, older than 80 years of age have AE which required hospitalization: 3 patients were hospitalized because of mild gastrointestinal bleeding (2 on dabigatran and 1 on rivaroxaban because of gastrointestinal bleeding Forrest II-III), 2 because of bleeding into the skin/ joint (on dabigatran) with low APTV levels. During the hospitalization they were converted to apixaban 2.5mg twice daily (Table 1).

Among patients aged 65 to 90 the use of six or more medications or supplements of any type was 69%. Concurrent use of interacting medications has increased during 12 months by 1.5 in older adults, potentially a risk for major drug-drug interactions.

Table 1. Patients on DOACs

CKD (eGFR,mlmin-11.73m2)	**Dabigatran (N=25)**		**Rivaroxaban (N=25)**	
	150mg (N=20)	110 mg (N=5)		Number of medications
>80 (normal)	2x150mg (5)	0	20mg x1(5)	2-3
50-80 (mildly decreased)	2 x 150mg (15)	0	20mg x1 (15)	3-7
30-50 (moderately decreased)	0	2 x 110 mg (5)	15mg x1 (5)	6-8
Apixaban 2.5mg x2 (N=5)	3 pt on 2x150	1 pt on 2x110	1 pt on 20mg	>6

*CKD= chronic kidney disease, eGFR=estimated glomerular filtration rate, N=number of patients

DISCUSSION

Our findings suggest that the use of multiple medications among older adults is a growing public health problem. We should carefully consider the adverse effects of commonly used prescription medication combinations when treating older adults. DOACs are safe medications for AF patients but dabigatran has a few drug interactions involving permeability [P] glycoprotein [P-gp] agents. P-gp inducers such as rifampin and St. John's Wort reduce exposure to dabigatran, while P-gp inhibitors such as ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin can raise dabigatran serum concentrations (1).

We should be looking regularly at kidney function and at other modifiable risk factors that heighten stroke risk in AF patients, because 80% of patients self-treat pain with NSAID and antibiotics which double the risk of bleeding (6,7). Strategies to reduce bleeding include correcting modifiable characteristics (e.g. alcohol use, hypertension, drug and food interactions) and gastroprotection (8). We should be aware of herbal medications with dabigatran, including gingko biloba and St. John's Wort. The results of our study suggest that DDIs are one of the most important problems in every day practice, and any drug interaction that influences the amount of drug that enters the bloodstream will have a much greater impact on dabigatran and increase the plasma concentrations of dabigatran enough to increase the risk of bleeding. The medications that inhibit P-glycoprotein (such as statins), can cause increases of up to 200% in plasma concentrations of dabigatran. Co-administration of statins with dabigatran worsens clinical outcomes and a similar interaction might be seen with verapamil and amiodarone (1).

The effects of DOACs may be prolonged in patients with underlying CKD. Therefore, important questions to ask a patient having some bleeding while on DOACs include the timing of their last DOAC ingestion and whether they have any underlying renal disorders. In patients having bleeding while taking dabigatran, a reversal agent, idarucizumab, is now available in the US and Europe and here in Croatia (9).

The decision to use a reversal agent must be made on a case by case basis with the help of a multi-disciplinary treatment team. Patients need to be on the right drug/right dose given the kidney function they have, with special care on DDIs (10,11). Adverse drug events (ADEs) have become an important public health problem. The real world population is sicker and more fragile than patients in randomized controlled trials. These sicker, more fragile group of patients are at higher risk of bleeding and need to receiving the lower dose of DOACs according to kidney function or concomitant medications with special care on drug-drug interactions.

CONCLUSION

The results of our study suggest that DDIs are one of the most important problems in every day practice and any drug interaction that influences the amount of drug that enters the bloodstream will have a much greater impact on dabigatran and increase the plasma concentrations of dabigatran enough to increase the risk of bleeding.

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Conflict of Interest: None to declare.

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