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Drug interaction as a predictor of direct oral anticoagulant drug levels in atrial fibrillation patients

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Abstract

Data are limited on the effects of drug interactions on direct-acting oral anticoagulant (DOAC) levels. We evaluated the effects of the use of interacting drugs on DOAC levels in patients with atrial fibrillation (AF). We reviewed data of AF patients tested for DOAC levels in 2013–2017. The primary outcomes were drug levels exceeding the expected steady-state range, and in the highest quartile. A multivariate analysis was performed to evaluate the correlation of treatment by the use of interacting drugs, CYP3A4 and P-glycoprotein (P-gp) inhibitors, with the primary outcomes. Overall, 147 patients underwent DOAC level measurement [dabigatran (n = 31), rivaroxaban (n = 29), apixaban (n = 87)]. Thirty-three (22.4%) had drug levels exceeding the expected range. Seventy-nine (53.7%) patients were treated with at least one interacting drug. In multivariate analysis, the concomitant use of interacting drugs was an independent predictor for drug levels exceeding the expected range (OR 3.3, 95% CI 1.20–9.05). The defined daily dose of the interacting drug correlated positively with DOAC levels (r = 0.29, P = 0.001). Co-treatment with interacting drugs was associated with extremely high levels of dabigatran, (OR 16.6, 95% CI 1.29–215.18) but not of the other DOAC examined. Concomitant use of interacting drugs is associated with high DOAC levels in patients with AF. Further investigation is warranted to establish the differences between specific DOAC, evaluate the effect on patient outcomes, and characterize the role of DOAC monitoring in this setting.

Keywords Drug interaction · Direct-acting oral anticoagulants · Drug levels · CYP3A4 inhibitors · P-gp inhibitors

Highlights

- Data are scarce regarding the effect of the co-administration of interacting drugs on DOAC levels
- We evaluated the effects of the use of interacting drugs on DOAC levels in patients with atrial fibrillation
- The concomitant use of interacting drugs was an independent predictor for drug levels exceeding the expected range
- Future studies are warranted to better delineate the role of DOAC monitoring for patients treated with interacting drugs, the effect on patient outcomes and the need of dose adjustment in this context

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Introduction

In recent years, direct-acting oral anticoagulants (DOAC) have emerged as alternatives to vitamin K antagonists in stroke prevention in patients with non-valvular atrial fibrillation (AF), and also in preventing and managing venous thromboembolism [1–3]. The introduction of DOAC represents a major advance in oral anticoagulation therapy. DOAC are characterized by a more predictable pharmacokinetics and pharmacodynamics profile, and less food and drug interactions are known. This enables their administration in fixed and near-uniform doses, eliminates the need for routine coagulation monitoring, and improves the efficacy-to-safety ratio [4].

Despite the above, DOAC have potential drug–drug interactions [4]. The two primary known mechanisms by which drugs may affect DOAC metabolism involve the intestinal P-glycoprotein (P-gp) transporter and the hepatic cytochrome P450 (CYP) 3A4. DOAC are substrates of P-gp efflux, which pumps substrates back into the intestinal lumen. P-gp is also involved in the renal tubular excretion of medications. Thus, inhibition of P-gp may enhance absorption and reduce excretion of DOAC, leading to an increase in their bioavailability [5]. CYP3A4 is expressed in the liver, kidney, and digestive tract, and has a significant role in the metabolism of some DOAC [6]. CYP3A4 is an important metabolic path for rivaroxaban, followed by apixaban, while it is not involved in the pharmacokinetics of dabigatran [7]. Several drugs used to treat AF, such as verapamil, dronedarone, amiodarone, and quinidine, are inhibitors of both CYP3A4 and P-gp, and their use can result in increased bioavailability of the substrates of these enzymes.

As DOAC have been certified and marketed to treat AF in fixed doses without the need of laboratory monitoring, data are limited regarding the effects of concomitant medications on the pharmacokinetic and pharmacodynamics of DOAC. A number of FDA-mandated and industry sponsored pharmacokinetic studies in healthy participants have demonstrated the potential of specific strong inhibitors of CYP3A4 and/or P-gp, such as ketoconazole, to increase the area under the curve (AUC) of DOAC [8, 9]. However, data are scarce concerning the potential impact of many other more commonly used inhibitors on DOAC levels among 'real-life' patients.

In this study we assessed the effect of the co-administration of interacting drugs on DOAC levels among AF patients.

Methods

Patients

We accessed data of all AF patients whose DOAC levels were tested at Hadassah Medical Center during the period January 1, 2013 (the initiation of DOAC level monitoring at our laboratory) and June 30, 2017. Patients were eligible for inclusion in the analysis if they received one of the following dosing regimens: dabigatran 150 mg twice a day (BID), dabigatran 110 mg BID, rivaroxaban 20 mg once a day (OD), rivaroxaban 15 mg OD, apixaban 5 mg BID, apixaban 2.5 mg BID. The study was approved by the institutional review board of Hadassah Medical Center and informed consent was waived.

Data collection

Data retrieved from patients' electronic medical records included: age, gender, weight, DOAC used (agent, dose), history of other anticoagulant treatment, or of bleeding or thrombosis during DOAC therapy, comorbidities, serum creatinine at DOAC testing, the indication for DOAC level testing, referring service, setting of testing (inpatient versus outpatient) and DOAC blood level. Calculation of the estimated glomerular filtration rate (eGFR) was according to the modified MDRD (Modification of Diet in Renal Disease) formula. Concomitant use of CYP3A4 and/or P-gp inhibitors included: verapamil, diltiazem, amiodarone, dronedarone, quinidine, ketoconazole, itraconazole, fluconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, ranolazine, cyclosporine, tacrolimus, felodipine, amlodipine, clarithromycin, erythromycin, azithromycin, and conivaptan [4, 10–14].

We compared DOAC blood levels to the expected steady-state range of levels, as delineated by pharmacokinetic data (Table S1) [15]. For each drug level we defined the following parameters:

1. Levels exceeding the expected range: a drug level exceeding the expected steady-state range of the specific DOAC levels (5th–95th percentile range, except for dabigatran 110 mg BID, for which the 10th–90th percentile range are presented) (Table S2).
2. Highest quartile level: for each DOAC level, the difference between the level measured and the expected steady-state median level was categorized into quartiles, from the lowest to the highest drug levels (Q1–Q4). Levels in Q4 were defined as "high levels".

The primary outcomes were the proportions of patients with DOAC blood levels exceeding the expected steady-state range and with drug levels in the highest quartile. In addition, according to DOAC dosage, weight, age, serum creatinine and eGFR, we categorized patients into three classes [9]:

1. Appropriate dose: patients dosed according to regulatory approved prescribing information [16–19].

2. Low-dose: patients who received lower than recommended dosing according to regulatory approved prescribing information (e.g. a patient prescribed rivaroxaban 15 mg/daily despite eGFR > 50 mL/min/1.73 m^2) [17, 18].
3. High-dose: patients who received higher than recommended dosing according to regulatory approved prescribing information (e.g. a patient prescribed rivaroxaban 20 mg/daily despite eGFR < 50 mL/min/1.73 m^2) [16, 19].

Detailed criteria used for determining appropriateness of dosing are provided in Table S2.

Drug level measurement

Venous blood was drawn to assess drug concentrations (Cmax or trough, Table S1). Measurements were performed as follows: dabigatran levels using the HemosIL® DTI assay (Instrumentation Laboratory, United States), rivaroxaban and apixaban levels using the HemosIL®Liquid Anti Xa kit (Instrumentation Laboratory, United States) with HemosIL®rivaroxaban calibrators (Instrumentation Laboratory, United States) and TECHNOVIEW®apixaban calibrators (Technoclone, Austria). These assays were all done on an ACL TOP 500 coagulometer (Instrumentation Laboratory, United States).

Data management and statistical analysis

All data were collected and introduced into a single database. Continuous variables were presented as means with standard deviation (SD), or median and interquartile (IQR) ranges for variables without a normal distribution. Categorical variables were presented as frequencies and percentages. Significance between groups was assessed by the independent sample *t* test for continuous variables with a normal distribution, Mann Whitney *U* test for continuous data without a normal distribution, and Chi square test and Fisher's exact test for categorical variables.

A multivariable logistic regression analysis, reported as odds ratios (OR) and 95% confidence intervals (CI), was done to assess associations of the presence of interacting drug with DOAC levels exceeding the expected range and in the highest quartile, adjusting for age, renal function, body weight and congestive heart failure, as these factors were previously found to affect DOAC levels [our previous study, and the relationship between amiodarone use and congestive heart failure] [20]. This analysis was performed for the cohort as a whole and separately for each of the DOAC evaluated. One-way ANOVA was also performed to assess variables affecting each DOAC level.

The interaction between specific DOAC and inhibitors was also adjusted to: ischemic heart disease, anticoagulant use history and a history of hemorrhagic stroke.

A two-sided P value < 0.05 was considered statistically significant. Software Package for Statistics and Simulation (IBM SPSS version 24, IBM Corp, Armonk, NY) was used to analyze the data.

Results

Demographic and clinical characteristics of the patients

Overall, 147 patients (49.6% males) underwent DOAC measurements [dabigatran (n = 31), rivaroxaban (n = 29), apixaban (n = 87)]. The median age was 80.5 [73.9–85.7] years and the median weight 75 [64–84] kg. At the time of DOAC testing, the median serum creatinine level was 97 [75–123] µmol/L and the median eGFR 56 [IQR 42–74] mL/min/1.73 m^2. 79 (53.7%) patients were treated with at least one interacting drug. The clinical characteristics of patients in relation to the co-administration of interacting drugs are summarized in Table 1. Baseline characteristics of patients were comparable between the groups except for a higher proportion of chronic renal failure, and lower proportions of kidney function and hypertension among those using interacting drugs. The distribution of patients receiving high, appropriate and low doses of DOAC were comparable between the groups.

Drug levels and interacting drugs

Of the 79 patients treated with at least one interacting drug at the time of DOAC measurement, 52 were treated with apixaban, 11 with rivaroxaban, and 15 with dabigatran. The most common inhibitor used was amiodarone (n = 42), followed by amlodipine (n = 31). Characteristics of the interacting drugs administered with each of the DOACs are summarized in Table 2.

A multivariable logistic regression model for the outcome of DOAC levels exceeding the expected range was created (Table 3). The administration of interacting drugs was shown to be the only independent predictor for drug levels exceeding the expected range (OR [95% CI] 3.3 (1.20, 9.05), P = 0.02).

Co-treatment with interacting drugs was associated with extremely elevated levels of dabigatran (OR [95% CI] 16.6 (1.29, 215.18), P = 0.02) but not with high levels of the other DOAC examined.

Table 1 Baseline characteristics of patients with atrial fibrillation treated with direct oral anticoagulants (DOAC)

Characteristics	All patients N = 147	Patients not treated with interacting drugs N = 68	Patients treated with interacting drugs N = 79
Age (years)	80.5 [73.9–85.7]	81.7 [75.7–86.5]	79.5 [72.0–84.5]
Males (%)	73 (49.6)	31 (45.6)	42 (53.2)
Weight (kg)	75 [64–84]	75.0 [63–84]	74.0 [63–84]
Indication for DOAC monitoring (%)			
Perioperative evaluation	35 (23.8)	17 (25.0)	18 (22.8)
Bleeding	31 (21.0)	14 (20.6)	17 (21.5)
Dose adjustment[b]	25 (17.0)	14 (20.6)	11 (13.9)
Breakthrough thrombosis	21 (14.3)	9 (13.2)	12 (15.2)
Renal failure	16 (10.9)	3 (4.4)	13 (16.4)
Concern for overdose	5 (3.4)	1 (1.5)	4 (5.1)
Drug-drug interaction	6 (4.1)	0 (0)	6 (7.6)
Dose verification[a]	4 (2.7)	3 (4.4)	1 (1.3)
Extreme body weight[c]	3 (2.0)	1 (1.5)	2 (2.5)
Liver failure	1 (0.7)	1 (1.5)	0 (0)
Inpatients (%)	91 (61.9)	49 (72.0)	42 (53.2)
DOAC type (%)			
Dabigatran	31 (21.1)	16 (23.5)	15 (19.0)
Rivaroxaban	29 (19.7)	17 (25.0)	12 (15.2)
Apixaban	87 (59.2)	35 (51.5)	52 (65.8)
Appropriate dose (%)			
Under dose	53 (36.1)	23 (33.8)	30 (38.0)
Appropriate dose	86 (58.5)	42 (61.8)	44 (55.7)
High dose	8 (5.4)	3 (4.4)	5 (6.3)
History of anticoagulation (%)			
Naïve	56 (38.1)	29 (42.6)	27 (34.2)
VKA	61 (41.5)	25 (36.8)	36 (45.6)
Other DOAC	15 (10.2)	7 (10.3)	8 (10.1)
LMWH	15 (10.2)	7 (10.3)	8 (10.1)
Serum creatinine (μmol/L)	97 [75.3–122.5]	87.5 [71.0–112.7]	107.0 [81.0–134.7]
MDRD eGFR (mL/min/1.73 m^2)[d]	55.7 [41.8–73.6]	60.1 [45.6–82.6]	52.7 [39.8–70.8]
Comorbidities (%)			
Hypertension	132 (89.8)	57 (83.8)	75 (94.9)*
Hyperlipidemia	125 (85.0)	56 (82.4)	69 (87.3)
Congestive heart failure	71 (48.3)	34 (50.0)	37 (46.8)
Ischemic heart disease	72 (49.0)	30 (44.1)	42 (49.0)
Diabetes mellitus	69 (46.9)	28(41.2)	41 (51.9)
Previous ischemic CVA/TIA	61 (41.5)	28 (41.2)	33 (41.8)
Chronic renal failure	49 (33.3)	15 (22.1)	34 (43.0)*
Active smoking	23 (15.6)	12 (17.6)	11 (13.9)

All continuous variables are expressed as medians [interquartile range] (mean)

CVA cerebrovascular accident, *DDD* defined daily dose, *eGFR* estimated glomerular filtration rate, *LMWH* low-molecular-weight heparin, *TIA* transient ischemic attack, *VKA* vitamin K antagonists, *DOAC* direct oral anticoagulants, *MDRD* modification of diet in renal disease

*$P < 0.05$

[a]Following change in the regimen of DOAC (either agent or dose) among patients who had lower or higher levels on previous DOAC monitoring or who had experienced thrombotic or bleeding complications under DOAC therapy or who had high risk for thrombotic or bleeding complications

[b]Following lowering of dosage of apixaban (2.5 mg twice daily) or rivaroxaban (15 mg once daily) among patients with atrial fibrillation who did not fulfill at least two of the following recommended criteria for apixaban: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 133 μmol/L and eGFR 15–50 mL/min for rivaroxaban

[c]Body mass index > 30 or < 18.5 kg/m^2

[d]MDRD study equation, $eGFR = 175 \times (SCr) - 1.154 \times (age) - 0.203 \times 0.742$ [if female] $\times 1.212$ [if Black]

Table 2 Inhibitors concomitantly used with each of the DOAC evaluated

P-gp/CYP 3A4 inhibitor drugs	N (%)	Apixaban n = 87	Rivaroxaban n = 29	Dabigatran n = 31
Any	79 (53.7)	52 (59.8)	12 (41.4)	15 (48.4)
Amiodarone	42 (28.6)	30 (34.5)	4 (13.8)	8 (25.0)
Amlodipine	31 (21.1)	20 (23.0)	6 (20.7)	6 (18.7)
Verapamil	7 (4.8)	2 (2.3)	1 (3.4)	4 (12.9)
Cyclosporine/tacrolimus	5 (3.4)	5 (5.7)	0 (0)	0 (0)
Dronedarone	2 (1.4)	1 (1.1)	1 (3.4)	0 (0)
Diltiazem	3 (2.0)	2 (2.3)	0 (0)	1 (3.1)

All co-administered interacting drugs encountered in the current cohort were previously found to inhibit both P-gp and CYP3A4 [4, 10–14]

Table 3 Multivariate analyses of factors associated with drug levels above the expected range

Patient characteristics	Levels above the expected range Multivariate analysis			Highest quartile of drug levels Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
CYP 3A4 or P-gp inhibitor administration[a]	3.3	1.20–9.05	0.020	2.4	0.93–6.08	0.071
Dabigatran inhibitor interaction[b]	3.6	0.51–26.08	0.20	16.6	1.29–215.18	0.031
Rivaroxaban inhibitor interaction[b]	2.0	0.34–12.25	0.44	0.7	0.12–4.41	0.723
Apixaban inhibitor interaction[b]	4.6	0.85–25.48	0.08	3.9	0.85–17.56	0.079

[a]Adjusted for age, estimated glomerular filtration rate, body weight, congestive heart failure

[b]Adjusted for age, estimated glomerular filtration rate, body weight, congestive heart failure, ischemic heart disease, anticoagulant use history, history of hemorrhagic stroke

Drug levels and correlation to bleeding as an indication for monitoring

Bleeding served as the indication for DOAC monitoring in 38 (25.8%) patients. Of them, 12 (31.6%) had drug levels exceeding the expected steady state range (OR [95% CI] 2.17 (0.91, 5.17), P = 0.08) and 13 (34.2%) had levels in the highest quartile (OR [95% CI] 2.01 (0.86, 4.69), P = 0.10).

Discussion

In this retrospective study, we show that the concomitant use of interacting drugs was associated with high DOAC levels in AF patients. Among the DOAC evaluated, the interactions of dabigatran with P-gp inhibitors was found to be a predictor for DOAC levels in the highest quartile.

DOAC have been shown to be effective for decreasing the risk of thromboembolic stroke in AF; the associated risk of hemorrhagic stroke is less than that of warfarin [21–24]. DOAC were presumed to have less drug–drug interactions than warfarin and not to require routine coagulation monitoring. However, concern as to the extent of anticoagulation when combinations of DOAC are administered with drugs that can modify DOAC concentrations still exists.

Amiodarone, verapamil, diltiazem, dronedarone, cyclosporine, tacrolimus and amlodipine moderately inhibit both CYP3A4 and P-gp. Moderate inhibition is defined as an increase in the AUC of a sensitive substrate by two- to five-fold [14]. Some of these drugs are commonly used in AF patients for rate and rhythm control.

Only a few pharmacokinetic studies addressed the impact of CYP3A4 and P-gp inhibitors on DOAC levels. The combination of erythromycin, which inhibits CYP3A4 and P-gp moderately, with rivaroxaban, resulted in a 1.3 fold increase in mean rivaroxaban AUC and Cmax [25]. Diltiazem, which is also considered a moderate CYP3A4 and a weak P-gp inhibitor, yielded a 1.4-fold increase in mean apixaban AUC and a 1.3-fold increase in Cmax [26]. Dabigatran bioavailability is less than that of other DOAC. Thus, small changes in absorption or elimination may have more influence on dabigatran's blood levels compared with the other DOAC [7]. In this manner, a recent report showed that simultaneous administration of dronedarone and dabigatran led to increases by about 2.4- and 2.3-fold in total dabigatran AUC and Cmax values, respectively [27]. In accordance with this finding, among the DOAC examined in the current study, only the concomitant use of dabigatran and interacting drugs was associated with extremely high drug levels.

Contrasting with controlled trials, the current cohort represents the complexity of real-world decision making in clinical practice. Over one-half of the patients were concomitantly given at least one drug known to interact with DOAC. This rate is relatively high, compared to patients enrolled in phase II, III clinical trials [21–25]. The effect of interacting drugs on DOAC levels can be additive to other common comorbidities, such as renal impairment; the latter was associated with an effect on DOAC levels in the current cohort. For example, in the setting of rivaroxaban treatment, compared to patients with normal renal function, the administration of erythromycin to patients with mild renal impairment led to a 1.8 fold increase in mean rivaroxaban AUC and a 1.6 fold increase in C max. Treatment with erythromycin for patients with moderate renal impairment resulted in a 2.0 fold increase in mean rivaroxaban AUC and a 1.6 fold increase in C max, when compared to individuals with normal renal function [18].

Our results may have implications for patient outcomes. Associations of drugs such as CYP3A4 and P-gp inhibitors with bleeding complications were investigated in a nationwide population-based cohort study. There, the use of medications such as amiodarone was associated with an elevated rate of major bleeding [28]. Although DOAC was not expected to require monitoring, the demonstration of associations of higher DOAC levels with bleeding may support DOAC monitoring for patients with particular situations such as the use of interacting drugs [29, 30].

This study has a number of limitations, due in large part to its retrospective design. In addition, our results reflect measurements at a single point as we did not obtain complete pharmacokinetic profiles. Further, drug levels were compared to the expected 'on-therapy' range, according to on phase II, III clinical trials. However, for the particular DOAC, therapeutic ranges have yet to be defined, and clinical guidelines to be established for determining DOAC dosages according to laboratory data. Moreover, as none of the patients in our cohort used edoxaban, the current study findings may not apply to this DOAC. Finally, the analysis in the current study considered all interacting drugs as inhibitors of both CYP3A4 and P-gp, as was previously shown for the co-administered drugs encountered [4, 10–14]; however, these drugs may have different inhibitory effects on P-gp, compared to CYP3A4, and thus levels of each of the DOAC studied may be differentially affected (i.e. dabigatran is primarily a substrate for P-gp but not metabolized by the hepatic CYP system).

Conclusion

The concomitant use of interacting drugs is associated with high DOAC levels in AF patients. More investigation is needed to better delineate the role of DOAC monitoring for patients treated with interacting drugs, the effect on patient outcomes and the need of dose adjustment in this context.

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Compliance with ethical standards

Conflict of interest The authors do not have any conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the local institutional review board of Hadassah Medical Center Helsinki Committee.

Informed consent Informed consent was waived by the by the institutional review board of Hadassah Medical Center.

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