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Brief observation

The impact of strong inducers on direct oral anticoagulant levels

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Clinical significance

- Patients taking strong P-gp and CYP3A4 inducers are at significant risk of lower-than-expected DOAC levels.
- Among them, patients without risk factors for accumulation (e.g. age, renal failure) appear more likely to present DOAC levels below the expected range.
- The concomitant use of strong P-gp and CYP3A4 inducers should be avoided in DOAC patients, unless laboratory measurement is performed.

Abstract

Purpose: The concomitant use of direct oral anticoagulants (DOAC) and strong P-gp and CYP3A4 inducers may lead to reduced DOAC levels and therapeutic failure. This study aimed to describe DOAC concentrations in patients receiving strong P-gp and CYP3A4 inducers, in relation to individual risk factors for high or low DOAC levels.

Methods: We retrospectively identified hospitalized patients receiving simultaneously a DOAC and carbamazepine, phenobarbital, phenytoin or rifampicin between 2016 and 2021. Among them, patients who underwent DOAC measurement at steady-state were included. DOAC peak or trough levels were compared to on-therapy ranges observed in pivotal trials. Individual risk factors for high or low DOAC levels were identified.

Results: We included 17 patients (median age 75 years), mainly receiving apixaban and carbamazepine. For 5 patients (29%), DOAC trough or peak level was below the expected range. Among the remaining 12 patients, 8 had at least one measurement in the lower quartile of the range. The median number of risk factors for drug accumulation was 0 (range 0-1) in patients with ≥1 measurement below the range and 2 (range 0-3) in other patients. DOAC measurement led to treatment adjustments in 9 patients (DOAC dose increase or switch).

Conclusion: Our data suggest a significant risk of reduced DOAC levels in patients taking strong P-gp and CYP3A4 inducers, especially those without risk factors for drug accumulation. DOAC measurement could help manage this relevant drug-drug interaction.

Keywords

Direct Oral Anticoagulants, Drug-Drug Interactions, Laboratory Measurement

Introduction

Direct oral anticoagulants (DOAC) are widely used in clinical practice. They are now recommended over warfarin in eligible patients, for stroke prevention in atrial fibrillation (SPAF) or the treatment of venous thromboembolism[1, 2]. Given their predictable dose response, DOAC have a fixed-dose regimen and do not require routine laboratory monitoring. However, inter-individual variability in DOAC plasma concentrations has been described. In phase 3 trials and registries, low and high DOAC levels were shown to correlate with thromboembolic and bleeding events respectively[3, 4].

All DOAC are substrates for the P-glycoprotein (P-gp) transporter, also called ABCB1 or MDR1. This active efflux pump limits intestinal drug absorption while it enhances biliary or renal excretion[5]. Additionally, rivaroxaban, apixaban and to a lesser extent edoxaban are metabolized by CYP450 (primarily CYP3A4). Several medications, mainly including older antiepileptic drugs, are known to strongly induce P-gp and CYP3A4. Guidelines and manufacturers recommend against their use in DOAC patients, as it may lead to reduced DOAC levels and therapeutic failure[2, 6, 7]. However, clinical evidence is currently limited to a few case reports[8].

Therefore, we aimed to describe DOAC plasma concentrations in patients receiving strong P-gp and CYP3A4 inducers, in relation to individual risk factors for high or low DOAC levels.

Methods

We retrospectively identified patients receiving concurrently a DOAC and a strong P-gp and CYP3A4 inducer during their hospitalization, between January 2016 and March 2021. Among them, patients who underwent DOAC measurement at peak or trough were eligible for inclusion. We excluded patients if body weight or renal function was missing, timing since the last DOAC intake was unclear or steady-state was not achieved (defined as three full days of DOAC intake). The patient flow diagram is presented in Figure 1. This work was approved by the local Ethics Committee (126/2019).

This study was performed at the CHU UCL Namur, a tertiary care hospital routinely involved in the prospective evaluation of DOAC prescriptions and their laboratory measurement. Apixaban, edoxaban and rivaroxaban plasma levels were estimated using a calibrated chromogenic anti-Xa assay, the STA®-Liquid anti-Xa (Diagnostica Stago®, Asnière, France). Dabigatran plasma levels were estimated with an ecarin-based assay (STA®-ECA II, Diagnostica Stago®).

Electronic medical records were reviewed to collect sociodemographic, clinical and medication data. For both DOAC and inducers, dose regimen, indication and duration of drug intake were recorded. Patient renal function was estimated using Cockcroft-Gault equation. For each patient, risk factors for high or low DOAC levels were identified (Figure 2).

DOAC plasma levels were compared to expected on-therapy ranges, based on DOAC pivotal trials[9]. The expected ranges were divided into quartiles, from Q1 (lower) to Q4 (upper). DOAC measurements were classified into four categories: below the on-therapy range, Q1, Q2 to Q4, or above the on-therapy range. Median numbers of risk factors for high or low DOAC levels were described for patients with and without ≥1 measurement below the expected range.

Results

We included 17 patients (median age 75 years), as presented in Figure 1 and Table 1. Apixaban was the most prescribed DOAC (n=8), followed by edoxaban (n=6). Main inducers were carbamazepine (n=9) and rifampicin (n=5). The main indication for anticoagulation was SPAF (n=13). Thirteen patients (76%) were taking their inducer treatment for ≥ 1 month, while 2 patients had less than 7 days of intake.

For 5 patients (29%), DOAC peak or trough measurement was below the expected on-therapy range. Among the remaining 12 patients, 8 had at least one measurement in the lower quartile of the range (Q1). The median number of risk factors for drug accumulation was 0 (range 0-1) for patients with measurement(s) below the range and 2 (range 0-3) for other patients. The median number of risk factors for low DOAC levels was 0 in both groups (range 0-1). All DOAC patients aged ≥ 75 years with renal impairment had plasma concentrations within the range. Four patients were taking concomitantly a P-gp or CYP3A4 inhibitor, as detailed in Figure 2.

DOAC measurement led to treatment adjustments in 9 patients (53%). It resulted in DOAC dose increase (n=4) or switch to another anticoagulant (low-molecular-weight heparin (n=3), vitamin-K antagonist (n=1), another DOAC (n=1)). Several examples of clinical management are presented in Table 2.

Discussion

We observed lower-than-expected DOAC levels in almost a third of patients taking strong P-gp and CYP3A4 inducers. Patients without risk factors for DOAC accumulation seemed to be primarily concerned.

To our knowledge, this is the second retrospective study to assess the impact of strong inducers on DOAC plasma concentrations. Previously, Perlman et al showed that 1.4% of 1596 hospitalized DOAC patients were co-treated with an enzyme inducer (mainly phenytoin and carbamazepine). DOAC peak levels were below the expected range in 6 out of the 11 patients for whom measurement was performed[10]. Clinical observations were nevertheless lacking regarding the concomitant use of rifampicin, which was shown to decrease DOAC exposure by 34 to 67% in healthy volunteers[7].

An original aspect of this work was the consideration of individual risk factors for high or low DOAC levels. In the same way as the management of DOAC interactions with moderate inhibitors depends on comorbidities and comedications[6], we can hypothesize that there is not a one-size-fits-all answer to the concomitant use of strong inducers. Patients with several risk factors for accumulation (e.g. age, renal failure) are more likely to present higher baseline DOAC levels, with a potentially less relevant clinical impact of inducers. Further studies are needed to confirm this preliminary observation.

Laboratory measurement may provide valuable assistance to manage DOAC interactions. However, several pitfalls have to be avoided. First, enzyme induction can take several weeks to develop or disappear, with a delayed effect on DOAC levels. In a single-dose pharmacokinetic study, edoxaban exposure was reduced after 7 days of rifampicin treatment[11]. Conversely, when adding DOAC to an ongoing inducer therapy, measurement can be performed as soon as steady-state DOAC concentrations are achieved (i.e. 2 to 4 days

of intake, depending on renal function). Second, time to reach the peak may differ between patients. It would therefore be better to measure DOAC at least at trough, especially since low trough levels were previously associated with a high risk of thrombotic complications in AF patients with a high CHA_2DS_2-VASc score[4].

The principal limitation of this study is its retrospective design, without further investigation of subsequent clinical outcomes. Moreover, we did not measure the pharmacodynamically metabolites of edoxaban (M4, M6 and M8), whose exposure is increased after rifampicin administration and which could interfere with chromogenic assays[11, 12]. Finally, the impact of weak or moderate inducers, such as dexamethasone, was not investigated.

In conclusion, the use of strong P-gp and CYP3A4 inducers should be avoided in DOAC patients, especially in the absence of risk factors for DOAC accumulation. Laboratory measurement could help manage this relevant drug-drug interaction.

Authorship

All authors had access to the data and a role in writing the manuscript.

Declaration of Competing interest

JD is the CEO and founder of QUALIblood s.a., a Belgian Contract Research Organization, and reports personal fees from Daiichi-Sankyo, DOASense, Mithra Pharmaceuticals, Norgine, Portola, Stago, Roche and Roche Diagnostics outside the submitted work. FM reports institutional fees from Stago, Werfen, Nodia, Roche Sysmex and Bayer all outside the submitted work. FM also reports speaker fees from Boehringer Ingelheim, Bayer Healthcare, Bristol-Myers Squibb-Pfizer, Stago, Sysmex, Werfen and Aspen all outside the submitted work.

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Figure 1: flow chart of the inclusion process

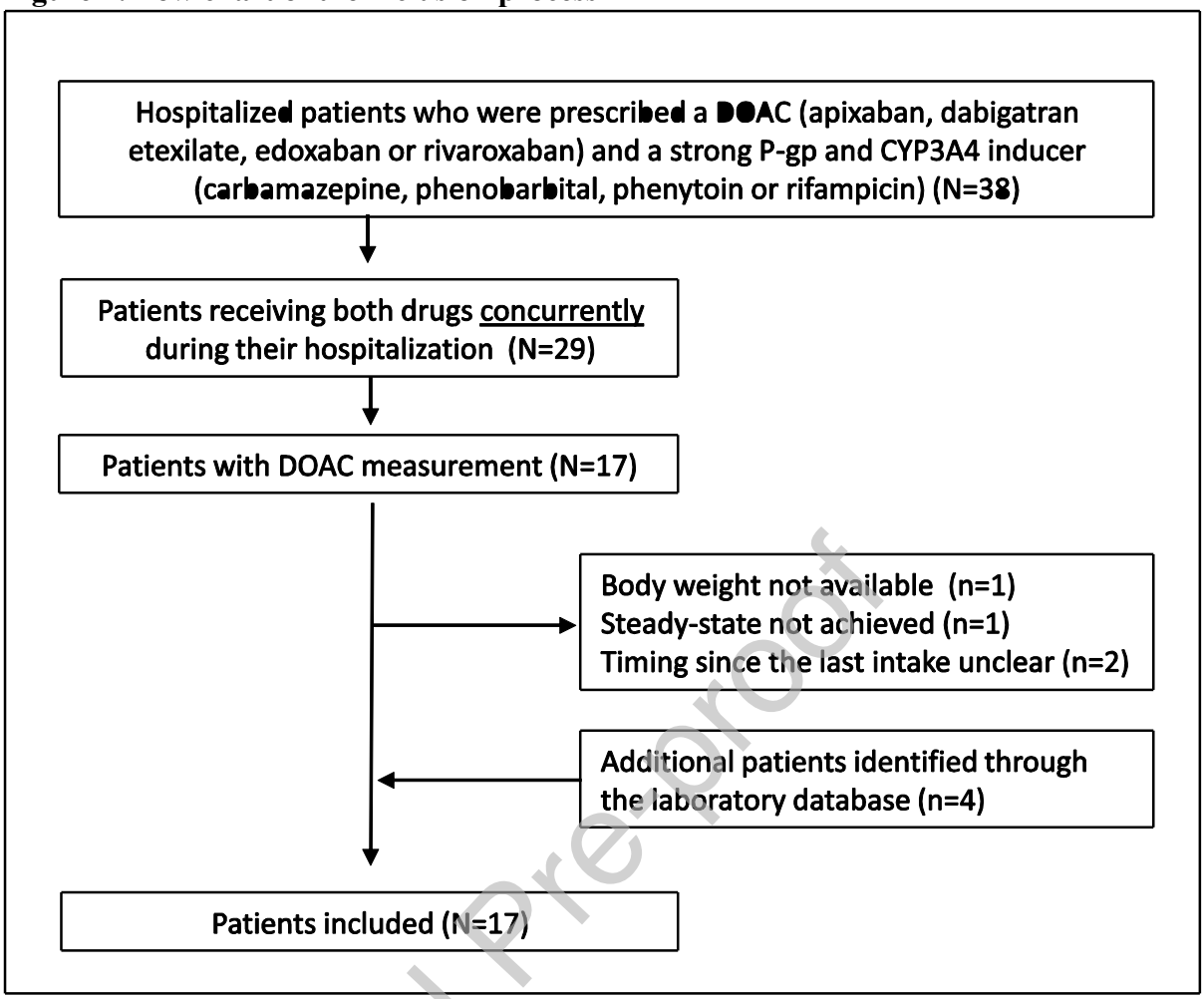
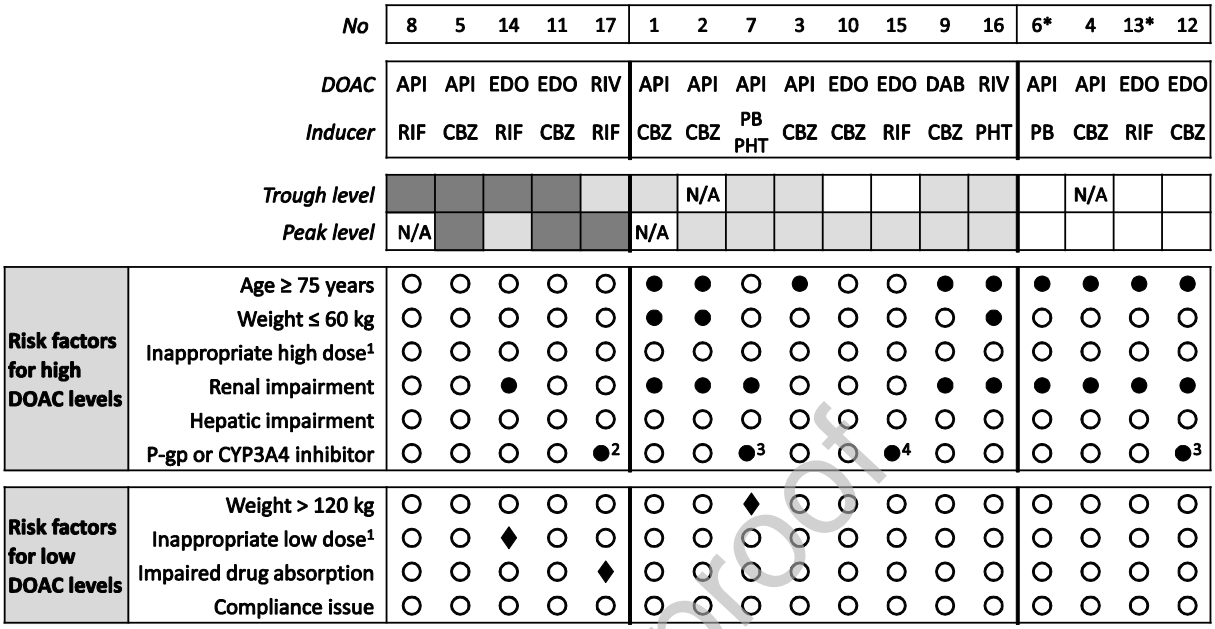


Figure 2: individual risk factors for high or low DOAC plasma levels



DOAC: API: apixaban, DAB: dabigatran etexilate, EDO: edoxaban, RIV: rivaroxaban
Strong inducers: CBZ: carbamazepine, PB: phenobarbital, PHT: phenytoin, RIF: rifampicin
○: Absence of the risk factor, ● or ♦: Presence of the risk factor, *: < 7 days of intake, N/A: not applicable
[1] Based on drug labeling, [2] azithromycin, [3] amiodarone, [4] diltiazem

Comparison to the expected on-therapy range: Below | Within (Q1) | Within (Q2-Q4) | Above

Table 1: patient characteristics and DOAC plasma levels

No	Age (years)	Sex	Weight (kg)	CrCL (ml/min)	DOAC	Dose regimen	Indication	CHA_2DS_2-VASC	Inducer	Daily dose	Trough		Peak	
											DOAC cc (ng/ml)	Range **	DOAC cc (ng/ml)	Range **
1	82	F	57	53	**API**	2.5mg BID	SPAF	7	**CBZ**	400mg	36	Q1	N/A	N/A
2	95	F	55	18	**API**	2.5mg BID	SPAF	4	**CBZ**	400mg	N/A	N/A	105	Q1
3	93	M	90	92	**API**	5mg BID	SPAF	5	**CBZ**	800mg	65	Q1	115	Q1
4	75	F	74	58	**API**	5mg BID	SPAF	5	**CBZ**	200mg	N/A	N/A	222	Q2-Q4
5	51	M	78	170	**API**	5mg BID	SPAF	3	**CBZ**	800mg	**19**	**Below**	**66**	**Below**
6	85	F	76	40	**API**	2.5mg BID	VTE	N/A	**PB***	100mg	62	Q2-Q4	176	Above
7	71	M	136	116	**API**	5mg BID	SPAF	4	**PHT/PB**	200/100 mg	42	Q1	135	Q1
8	67	M	85	104	**API**	5mg BID	SPAF	4	**RIF**	900mg	**25**	**Below**	N/A	N/A
9	77	F	79	62	**DAB**	150mg BID	SPAF	6	**CBZ**	800mg	42	Q1	108	Q1
10	65	M	83	170	**EDO**	60mg OD	VTE	N/A	**CBZ**	600mg	26	Q2-Q4	176	Q1
11	59	M	71	117	**EDO**	60mg OD	VTE	N/A	**CBZ**	400mg	**≤ 14**	**Below**	**120**	**Below**
12	89	M	82	38	**EDO**	30mg OD	SPAF	5	**CBZ**	400mg	30	Q2-Q4	92	Q2-Q4
13	85	M	72	28	**EDO**	30mg OD	SPAF	N/K	**RIF***	600mg	27	Q2-Q4	80	Q2-Q4
14	62	M	95	79	**EDO**	30mg OD	SPAF	N/K	**RIF**	900mg	**≤ 14**	**Below**	73	Q2-Q4
15	58	M	102	136	**EDO**	60mg OD	VTE	N/A	**RIF**	900mg	20	Q2-Q4	167	Q1
16	87	F	59	49	**RIV**	15mg OD	SPAF	6	**PHT**	100mg	20	Q1	209	Q1
17	74	M	72	102	**RIV**	20mg OD	SPAF	2	**RIF**	300mg	20	Q1	**112**	**Below**

DOAC: API: apixaban, DAB: dabigatran etexilate, EDO: edoxaban, RIV: rivaroxaban
Strong inducers: CBZ: carbamazepine, PB: phenobarbital, PHT: phenytoin, RIF: rifampicin.
*: < 7 days of intake. **: as compared to the expected on-therapy range based on DOAC pivotal trials (Q1= lower quartile, Q4= upper quartile)

BID: twice-daily, cc: concentration, CrCL: creatinine clearance (Cockcroft-Gault equation), F: female, M: male, N/A: not applicable, N/K: not known, OD: once-daily, SPAF: stroke prevention in atrial fibrillation, VTE: venous thromboembolism

Table 2: examples of clinical management

No	DOAC	DOAC plasma level	Action	Details
1	Apixaban 2.5mg BID	**Trough: 36 ng/ml** Range: 34-162 ng/ml	DOAC dose increase	**Carbamazepine** 200mg BID had been started for > 1 month, for epilepsy. Given a CHA_2DS_2-VASc score of 7, apixaban dose regimen was increased to 5mg BID. A new specific assay was performed after 3 days of intake, with an apixaban trough level of 139 ng/ml.
8	Apixaban 5mg BID	**Trough: 25 ng/ml** Range: 41-230 ng/ml	Switch to LMWH	**Rifampicin** 450mg BID had been started for 8 days, for prosthetic material infection. The patient was switched to enoxaparin 80mg BID, until two weeks after rifampicin discontinuation.
5	Apixaban 5mg BID	**Trough: 19 ng/ml** Range: 41-230 ng/ml **Peak: 66 ng/ml** Range: 91-321 ng/ml	Switch to VKA	**Carbamazepine** 400mg BID had been started for > 1 month, for migraine. Apixaban treatment started 3 days before measurement, in a context of postoperative atrial fibrillation. The patient was switched to acenocoumarol (no history of labile INR).
17	Rivaroxaban 20mg OD	**Trough: 20 ng/ml** Range: 12-137 ng/ml **Peak: 112 ng/ml** Range: 184-343 ng/ml	Switch to another DOAC	**Rifampicin** 300mg OD had been started for > 1 month, for mycobacteriosis. Given eating disorders limiting rivaroxaban absorption, the patient was switched to edoxaban 60mg OD. A new specific assay was performed after 3 days of intake, with an edoxaban trough level of 18 ng/ml and peak level of 218 ng/ml. The patient was also switched from azithromycin to clarithromycin (for a more potent inhibitory effect).