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Letter to the Editors-in-Chief

Effect of dexamethasone on direct Xa-inhibitor oral anticoagulant plasma levels in patients with COVID-19

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To the editor.

Dexamethasone, administered at a dose of 6 mg once daily for 10 days or until hospital discharge, was shown to significantly reduce mortality among COVID-19 patients receiving either invasive mechanical ventilation or oxygen alone, and it has therefore become standard-of-care [1]. Additionally, since COVID-19 patients are at considerably high risk of venous and arterial thromboembolism, adequate anticoagulation is crucial [1].

Direct oral anticoagulants (DOACs), comprising the factor-Xa inhibitors apixaban, edoxaban and rivaroxaban and the thrombin inhibitor dabigatran, are primarily eliminated through metabolization via CYP3A4 (rivaroxaban and apixaban), excretion via the xenobiotic transporter P-glycoprotein (apixaban, rivaroxaban, edoxaban and dabigatran), and renal excretion [2]. Dexamethasone is an inducer of both CYP3A4 and P-glycoprotein, which potentially reduces bioavailability and increases clearance leading to reduced plasma levels of DOACs [2]. Therefore, DOACs are generally not recommended in patients on dexamethasone due to this potential drug-drug interaction [2], and current guidelines recommend low-molecular-weight heparins for the prophylaxis and treatment of venous and arterial thromboembolism in hospitalized COVID-19 patients [1]. However, the magnitude of dexamethasone effects on DOAC plasma levels is uncertain and to date, no pharmacokinetic data has been published on the interaction between these two classes of drugs [2,3]. These data are needed since, in many centres, COVID-19 patients receiving dexamethasone are also treated with DOACs. The aim of this study was to assess DOAC plasma levels in hospitalized COVID-19 patients on concomitant dexamethasone therapy.

Hospitalized COVID-19 patients from two centres, in Italy and in the Netherlands, receiving simultaneously dexamethasone and DOACs were eligible. Analysis was restricted to a non-intensive-care unit setting. Patients could either start DOAC treatment during hospitalization or already receive anticoagulants before admission. Plasma samples were collected after a minimum of 3 days intake of both dexamethasone and DOAC to be able to reach steady state of both drugs. Trough samples were collected 30 min before DOAC and dexamethasone administration and peak samples were collected on the same day within 2–4 h after the DOAC administration, during which the peak concentration value is expected for all DOACs [4]. DOAC levels were expressed as activated anti-factor X activity in ng/ml and were measured using a chromogenic assay calibrated for apixaban, rivaroxaban and edoxaban (*Biophen Heparin LRT* and *Biophen DiXal CoaChrom, Hyphen Biomed, France*). Reference values from pharmacokinetic studies on DOAC plasma levels were used to assess whether observed values were within expected range (Table 1) [4–6].

Sixteen Caucasian COVID-19 patients admitted to general wards were included (Table 2). All included patients were using factor-Xa inhibitors and where on a therapeutic dose. Six patients used apixaban, seven rivaroxaban, and three edoxaban. Four patients were chronic users (≥90 days) and twelve started anticoagulant treatment within 14 days of anti-Xa measurement. The indication for anticoagulation therapy was venous thromboembolism in six cases, atrial fibrillation in nine, and myocardial infarction in one. The entire cohort was initially treated

Table 1
Reference ranges for DOACs by dose and indication.

	Number of patients included	Trough reference range, ng/ml	Peak reference range, ng/ml
Apixaban [6]			
Atrial fibrillation			
2.5 mg BID	3	34–162	69–221
5 mg BID	1	41–230	91–321
Venous thromboembolism			
5 mg BID	1	22–177	59–302
10 mg BID	1	41–335	111–572
Rivaroxaban [4]			
10 mg OD	1	1–37	91–195
15 mg OD	1	9–143	157–317
20 mg OD	4	9–147	177–361
15 mg BID	1	6–87	189–419
Edoxaban [5]			
60 mg OD	3	10–39	149–317

Abbreviations: BID: twice daily; OD: once daily.

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Table 2
DOAC plasma levels and characteristics per patient.

Factor-Xa inhibitor	Dose	Indication	New/ chronic users	DXM dose*	Days of DXM*	Age	Sex	Weight, kg	BMI	eGFR, ml/min*	Hepatic impairment†	CRP mg/l‡	Other P-gp/ CYP3A4 inducers/ inhibitors	Factor-Xa trough level	Trough level §	Factor-Xa peak level	Peak level §
Apixaban	2.5 mg bid	AF	New	2 mg	21	88	M	78	25.8	35	No	34	No	179	High	227	High
Apixaban	2.5 mg bid	AF	New	6 mg	6	95	M	66	21.1	19	No	131	No	36	–	69	–
Apixaban	2.5 mg bid	AF	New	4 mg	24	80	M	79	27.3	56	No	152	No	150	–	170	–
Apixaban	5 mg bid	AF	Chronic	6 mg	4	84	F	109	41	80	No	125	No	122	–	182	–
Apixaban	5 mg bid	VTE	New	4 mg	18	66	M	87	27.5	132	No	215	No	32	–	110	–
Apixaban	10 mg bid	VTE	New	6 mg	9	82	M	69	27	41	No	136	No	192	–	308	–
Rivaroxaban	10 mg od	Post AMI	Chronic	6 mg	7	78	M	78	26.1	82	No	132	No	41	High	125	–
Rivaroxaban	15 mg od	AF	New	6 mg	7	86	F	67	25.5	43	No	99	No	52	–	283	–
Rivaroxaban	20 mg od	AF	Chronic	6 mg	4	86	M	68	23.5	66	No	129	No	81	–	545	High
Rivaroxaban	20 mg od	AF	New	6 mg	6	83	M	90	27.2	89	No	89	Remdesivir	64	–	306	–
Rivaroxaban	20 mg od	AF	New	6 mg	5	74	M	110	32.8	75	No	100	Remdesivir	76	–	263	–
Rivaroxaban	20 mg od	AF	New	6 mg	6	71	M	116	35.8	90	No	152	Remdesivir	26	–	158	Low
Rivaroxaban	15 mg bid	VTE	New	6 mg	7	77	F	62	24.2	88	Yes	148	Remdesivir	79	–	256	–
Edoxaban	60 mg od	VTE	Chronic	6 mg	5	79	M	94	26.9	61	No	70	No	64	High	347	High
Edoxaban	60 mg od	VTE	New	4 mg	21	84	F	76	29	61	No	37	No	35	–	388	High
Edoxaban	60 mg od	VTE	New	6 mg	3	72	M	80	26.1	90	Yes	26	No	28	–	223	–

*At the time of factor-Xa measurement. No DXM dose indicates control patient, †At the time of factor-Xa measurement, defined as AST or ALT >3 times upper value. ‡ Measured on day of admission. § factor-Xa inhibitor plasma level above (High) or below (Low) expected range. Abbreviations DOAC: direct oral anticoagulants, DXM: dexamethasone; BMI: body mass index, eGFR: estimated glomerular filtration rate, P-gp: P-glycoprotein, bid: twice daily, od: once daily, AF: atrial fibrillation, VTE: venous thromboembolism, AMI: acute myocardial infarction, M: male, F: female.

with dexamethasone in a dose of 6 mg once daily. At the time of blood collection, four patients were receiving a lower dexamethasone dose as a part of corticosteroid tapering. Three patients were receiving 4 mg once daily, and one patient 2 mg once daily. Four patients were also receiving remdesivir. No other drug potentially interfering with CYP3A4/P-glycoprotein activity was administered.

None had trough factor-Xa inhibitor plasma levels below reference values (Table 2). One patient (6.2%), who was using rivaroxaban 20 mg once daily since three days, had a peak plasma level below the reference range (158 ng/ml, reference: 177–361 ng/ml). Five patients (31.3%) had trough or peak levels above the reference ranges, and two of those patients (12.5%) had both high trough and peak levels. Of the five patients with high trough or peak levels, three were chronic users while two were new users. No bleeding events or venous or arterial thrombosis occurred in the included patients in up to four weeks after inclusion.

Current guidelines on COVID-19 and antithrombotic treatment recommend to avoid DOACs in case of potential drug-drug interactions, and low-molecular-weight heparins are the preferred suggested as the anticoagulant drug of choice [1,3]. The impact of dexamethasone on DOACs levels has not been clinically evaluated before. Our data suggests no evidence of low factor-Xa inhibitor plasma levels in patients on concomitant dexamethasone therapy.

Previous clinical and pre-clinical studies have analysed the effects of dexamethasone on the activity of CYP3A4 and P-glycoprotein. In a study in 30 hospitalized patients, oral dexamethasone of up to 32 mg once daily for 2 to 9 days increased CYP3A4 activity by 55% [7]. Nonetheless, this increase may not be clinically relevant as suggested by the results of another study that found no statistically significant difference in plasma levels of the sensitive CYP3A4 substrate bortezomib in patients with multiple myeloma after co-administration of high doses of dexamethasone (40 mg once daily for 4 days) compared to patients with no concomitant dexamethasone [8]. These studies show that the effect of dexamethasone on CYP3A4 is rapid, however it remains unclear which dose and length of exposure to dexamethasone are sufficient to induce clinically relevant changes in CYP3A4 activity. Changes of relevant effects in COVID-19 patients could be even lower due to the lower dose of dexamethasone used in these patients. Additionally, dexamethasone can increase P-glycoprotein activity in-vivo in rodent intestines already after several hours of treatment, in a time and dose dependant manner [9]. To our knowledge, there are no human studies evaluating dexamethasone effects on plasma levels of P-glycoprotein substrates, therefore the magnitude of this effect in human intestinal tissue remains unknown. Furthermore, it is worth pointing out that severe acute respiratory syndrome coronavirus 2 may directly or indirectly (e.g. through activation of inflammatory pathways) affect the activity of both CYP3A4 and P-glycoprotein. Therefore the effect of dexamethasone might be counteracted by the disease itself.

Our data, despite several limitations, suggest that a short course of low-dose dexamethasone exerts a limited effect on CYP3A4 and P-glycoprotein, as shown by the DOAC plasma levels in hospitalized patients with COVID-19.

While it remains possible that a longer exposure to dexamethasone may result in a clinically significant induction of CYP3A4 and P-glycoprotein and, thus, lower factor-Xa inhibitor plasma levels, this was not observed in our study. In fact, out of four patients treated with dexamethasone for more than ten days, two had peak factor-Xa inhibitor plasma levels just above the reference range, and two had both trough and peak levels within range (Table 2). Notably, these patients were receiving a reduced dexamethasone dose at the time of measurement as part of corticosteroid tapering but all received a dose of 6 mg per day during the first ten days.

Unfortunately, we could not obtain repeated measurements of factor-Xa inhibitor plasma levels of patients before and after dexamethasone therapy. Nonetheless, it is reassuring that all but one trough and peak values were above the minimum range of the reference values. Five patients had higher trough or peak factor-Xa inhibitor levels, where the increase was marginal in four cases, and substantial in one patient on rivaroxaban 20 mg once daily, whose peak level was 545 ng/ml (i.e. 1.5 times above the maximum reference peak level). In patients with higher factor-Xa inhibitor levels, there was no hepatic impairment, no concomitant use of CYP3A4 or P-glycoprotein inhibitors, all had a body weight above 60 kg, and all but one patient had an estimated glomerular filtration rate of >60 ml/min (Table 2). One patient with a decreased estimated glomerular filtration rate received an adjusted dose of apixaban (2.5 mg twice daily). These increased factor-Xa inhibitor plasma levels could possibly be due to the large intra-individual variation which can be observed in patients treated with factor-Xa inhibitors [10]. Especially in the elderly population, high factor-Xa inhibitor plasma levels are not uncommon, and all our patients with high plasma levels were 78 years or older. Although the reference ranges for different factor-Xa inhibitors are well documented in literature, it should be stressed that it is unclear whether these ranges also represent the optimal therapeutic window. These data merely reflect an expected factor-Xa inhibitor plasma level, observed in patients with therapeutic dose anticoagulation, but do not strictly correlate with outcomes such as bleeding or thrombosis. Another important limitation of this study is that different types and doses of factor-Xa inhibitors were not sufficiently represented in our study population. Additionally, the small sample size of our study and the lack of adequately matched controls do not allow to definitely exclude any clinically relevant effect of dexamethasone on factor-Xa inhibitor plasma levels. Nonetheless, our results are in line with the expected effects of a short course of low-dose dexamethasone on CYP3A4 and P-glycoprotein.

In conclusion, we found no evidence of systematically decreased anti-Xa levels in non-critically ill patients with COVID-19 treated with a direct Xa-inhibitor anticoagulant concomitantly with a short course of low-dose dexamethasone, indicating that the effects of dexamethasone on DOAC plasma levels might be of limited clinical relevance. While randomized controlled trials evaluating the optimal anticoagulation strategy for the treatment of venous and arterial thromboembolism in COVID-19 are on the way, our preliminary findings may help clinicians decide whether to continue or start factor-Xa inhibitor treatment in hospitalized non-critically ill COVID-19 patients treated with dexamethasone.

CRediT authorship contribution statement

All authors made a substantial contribution to the data collection and the manuscript. F.T.M.B. and M.C. wrote the first draft; All authors critically revised the paper for important intellectual content, approved the final version, and agree with the submission.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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