DR SOPHIE TESTA (Orcid ID : 0000-0002-3512-0243)

Direct oral anticoagulant plasma levels striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents. The Cremona experience

Running title: Severe COVID-19 syndrome and direct oral anticoagulant

Sophie Testa*, Paolo Prandoni†, Oriana Paoletti*, Rossella Morandini*, Maurizio Tala*, Claudia Dellanoce*, Matteo Giorgi-Pierfranceschi‡, Monia Betti§, Gian Battista Danzi¶, Angelo Pan**, Gualtiero Palareti†,

*Haemostasis and Thrombosis Center, Cremona Hospital, Italy

†Arianna Foundation, Bologna, Italy

‡Division of Internal Medicine, Cremona Hospital, Italy

§Division of Pneumology, Cremona Hospital, Italy

¶Division of Cardiology, Cremona Hospital, Italy

**Division of Infectious Disease, Cremona Hospital, Italy

Correspondence to: Sophie Testa, MD

                        Hemostasis and Thrombosis Center

                        Ospedale di Cremona

                        Viale Concordia 1, 26100 Cremona, Italy

                        tel. +390372405453

                        fax +390372405457

e-mail: s.testa@asst-cremona.it

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Essential

- Antiviral agents potentially increases DOAC (direct oral anticoagulant) plasma concentration

- Patients on DOAC with severe COVID-19 respiratory syndrome started antiviral drugs in hospital

- DOAC plasma levels were measured and compared with those recorded before hospitalization

- DOAC patients treated with antiviral drugs show an alarming increase in DOAC plasma levels

- Physicians should consider withholding DOACs replacing with parenteral antithrombotic strategies

Summary

Background Antiviral drugs are administered in patients with severe COVID-19 respiratory syndrome (SARS-CoV-2), including those treated with direct oral anticoagulants (DOACs). Concomitant administration of antiviral agents has the potential to increase their plasma concentration. A series of patients managed in the Cremona Thrombosis Center were admitted at Cremona Hospital for SARS-CoV-2 and started antiviral drugs without stopping DOAC therapy. DOAC plasma levels were measured in-hospital and results compared with those recorded before hospitalization.

Methods All consecutive patients on DOACs were candidates for administration of antiviral agents (lopinavir, ritonavir or darunavir). Plasma samples for DOAC measurement were collected 2-4 days after starting antiviral treatment, at 12 hours from the last dose intake in patients on dabigatran and apixaban, and at 24 hours in those on rivaroxaban and edoxaban. For each patient, C-trough DOAC level , expressed as ng/mL, was compared with the one measured before hospitalization.

Results Of the 1039 patients hospitalized between February 22th and March 15th 2020 with SARS-CoV-2 and candidates for antiviral therapy, 32 were on treatment with a DOAC. DOAC was stopped in 20, and continued in the remaining 12. On average, C-trough levels were 6.14 times higher during hospitalization than in pre-hospitalization period.

Conclusion DOAC patients treated with antiviral drugs show an alarming increase in DOAC plasma levels. In order to prevent bleeding complications, we believe that physicians should consider withholding DOACs from patients with SARS-CoV-2 and replacing them with alternative parenteral antithrombotic strategies for as long as antiviral agents are deemed necessary and until discharge.

Keywords: Anticoagulant**;** Antiviral Agents**;** COVID-19 ; DOAC; plasma level

Introduction

The World Health Organization on March 11th 2020 declared the novel coronavirus infection COVID-19 a global pandemic (1,2). Italy, particularly the area of Cremona located in the northern region, was notified as the first European country where severe acute respiratory syndrome due to COVID-19 (SARS-CoV-2) was spreading (2). Currently, we are observing an increasing number of patients treated with direct oral anticoagulants (DOACs) - dabigatran, apixaban, rivaroxaban and edoxaban - hospitalized with severe COVID-19 infection. DOACs are indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the prevention and treatment of venous thromboembolism (3). At present DOACs are administered at fixed dose without indications for dose adjustment based on laboratory testing (3, 4), even if an high inter-individual variability in drug blood levels was shown and an association between DOAC plasma levels and thrombotic and bleeding complications was observed (5-12).

Patients treated with DOACs should receive multiple drug treatment during hospitalization for severe COVID-19 respiratory syndrome that may include antiviral therapies (lopinavir/ritonavir, darunavir), tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor), chloroquine or hydroxychloroquine, antibiotics, steroids, nonsteroidal anti-inflammatory drugs, bronchodilators and immunosuppressive drugs (13-16). As previously reported, antiviral therapies strongly interact with DOACs, because both are substrates of the P-glycoprotein and/or cytochrome P450-based metabolic pathways (17,18). Therefore the concomitant administration of DOACs and antiviral drugs has the potential to sharply increase DOAC anticoagulant plasma level, thus increasing hemorrhagic risk.

In addition to multiple drug-drug interactions, also metabolic alterations induced by the acute disease can cause unpredictable and unstable DOAC anticoagulant effects, exposing patients to the risk of uncontrolled bleeding or thrombotic complications (17-20).

A series of patients, chronically managed in the Cremona Thrombosis Center for anticoagulant treatment with DOAC, were hospitalized at Cremona Hospital for severe SARS-CoV-2 respiratory syndrome. They started antiviral drugs without stopping DOAC therapy.

During hospitalization DOAC plasma levels were measured and the results were compared with those recorded in the same patients at the Thrombosis Center before hospitalization.

Methods

All consecutive patients admitted to Cremona Hospital (Northern Italy) with SARS-CoV-2 were eligible for this investigation, provided they were on anticoagulant treatment with a DOAC (apixaban, rivaroxaban, edoxaban or dabigatran) for prevention or treatment of cardiovascular disorders and were candidates for administration of antiviral agents (lopinavir, ritonavir or darunavir).

Plasma samples were collected within 2-4 days after starting antiviral treatment, at 12 hours from the last dose intake in patients on dabigatran and apixaban, and at 24 hours in those on rivaroxaban and edoxaban. DOAC levels, expressed as drug concentration-equivalent (ng/ml), were measured using echarin chromogenic assay calibrated for dabigatran, and specific anti-FXa assays calibrated for apixaban and rivaroxaban (Stago, France) (21).

For each patient, C-trough DOAC level was compared with the one measured at our Thrombosis Center before hospitalization where a structured follow-up is applied, including periodical clinical evaluation, laboratory tests for renal function, blood cell count and DOAC plasma measurement at steady state (11,12).

The study has been approved by the local Ethics Committee. All patients give their written informed consent before enrollment and the research is conducted according to the World Medical Association Declaration of Helsinki

Results

Of the 1039 patients hospitalized between February 22th and March 15th 2020 with SARS-CoV-2 and candidates for antiviral therapy, 32 were on treatment with a DOAC. Based on the decision of attending physicians, the drug was discontinued in 20, and continued in the remaining 12 (5 patients on apixaban, 3 patients on rivaroxaban, 3 patients on edoxaban and 1 patient on dabigatran). Eight out of twelve were males, mean age was 80 years (69-89y); half of

them were on low DOAC doses. They all had concomitant administration of hydroxycloroquine and azithromycin or levofloxacin.

Table 1 details for each patient the main characteristics as well as C-trough DOAC plasma levels before and during hospitalization, also shown in Figure 1. On average, C-trough levels were 6.14 times higher during hospitalization than in pre-hospitalization period.

Discussion

In the emergency critical situation, such as we lived in the first weeks of the outbreak of COVID-19 pandemic in our hospital, we had the opportunity to observe and learn from direct experience on DOAC patients. The pandemic SARS-COV-2 is causing hospitalization of thousands of persons, especially the elderly, many of them are treated with oral anticoagulants for cardiovascular diseases. Treatment of COVID-19 infection is currently based on antiviral and immunosuppressive drugs (13-18). Several drugs, particularly those that strongly interact with P-glycoprotein and/or cytochrome P450-based metabolic pathways, such as antiviral agents, can modify DOAC pharmacokinetic and pharmacodynamic prophile, consequently changing their plasma anticoagulant activity (7-10, 17-19).

In all 12 examined patients, an alarming increase in DOAC plasma levels compared to pre-hospitalization phase was observed after hospital admission. Although we cannot exclude a possible role of concomitant drugs or disease-related organ dysfunctions, our results are consistent with those coming from several studies addressing interferences between DOAC and antiviral agents (17-20). Although the potential of antiviral agents to increase the plasmatic concentration of DOACs, as well as their bleeding risk, is well known there is no agreement on the most appropriate clinical management in these circumstances. Accordingly, some physicians continue DOAC treatment while others do not, as was the case in our Hospital.

An alternative option could be adjusting dosage (where available) according to plasma values, as is often done in situations like bleeding and thromboembolic complications, need of surgery or invasive procedure(22). However, we think that in critical conditions, such as severe SARS-CoV-2 respiratory syndrome, DOAC level adjustment is both impractical and unlikely to offer the desirable protection against thromboembolic and haemorrhagic complications.

In order to prevent bleeding complications, we believe that physicians should consider withholding DOACs from patients with SARS-CoV-2 and replacing them with alternative

parenteral antithrombotic strategies for as long as antiviral agents are deemed necessary and until discharge.

Conflicts of interest

None declared

Addendum

Role of each Author: S.Testa: study design, first draft manuscript preparation; O. Paoletti: patient identification and manuscript approval; C.Dellanoce: patient identification and data analysis; M. Betti, G. Danzi, R. Morandini, M. Tala, acquisition of data; M. Giorgi Pierfranceschi, A. Pan acquisition of data and manuscript approval; G.Palareti, P. Prandoni: final manuscript revision an approval

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Table 1. Main clinical characteristics and C-trough DOAC levels in the cohort of patients

| Number	Age	Sex	Clinical indication	DOAC	Dose mg/day	Antiviral drugs	C-trough (ng/mL) Pre-hospitalization	C-trough (ng/mL) In-hospital	Δ %
1	86	M	NVAF	dabigatran	110 x 2	lopinavir/ritonavir	54	221	+309.3
2	89	F	NVAF	apixaban	2.5 x 2	lopinavir/ritonavir	71	420	+491.5
3	74	M	NVAF	apixaban	5 x 2	darunavir/ritonavir	112	185	+65.2
4	69	F	NVAF	apixaban	5 x 2	lopinavir/ritonavir	85	326	+283.5
5	77	M	VTE	apixaban	5 x 2	darunavir/ritonavir	78	142	+82
6	73	M	NVAF	apixaban	5 x 2	lopinavir/ritonavir	92	163	+77.2
7	80	F	NVAF	edoxaban	60	lopinavir/ritonavir	102	473	+363.7
8	89	M	NVAF	edoxaban	30	darunavir/ritonavir	25	112	+348
9	85	M	NVAF	edoxaban	30	darunavir/ritonavir	11	71	+545.5
10	82	M	NVAF	rivaroxaban	15	lopinavir/ritonavir	12	143	+1091.7
11	77	M	NVAF	rivaroxaban	20	lopinavir/ritonavir	16	505	+3056.2
12	79	F	NVAF	rivaroxaban	15	lopinavir/ritonavir	13	99	+661.5
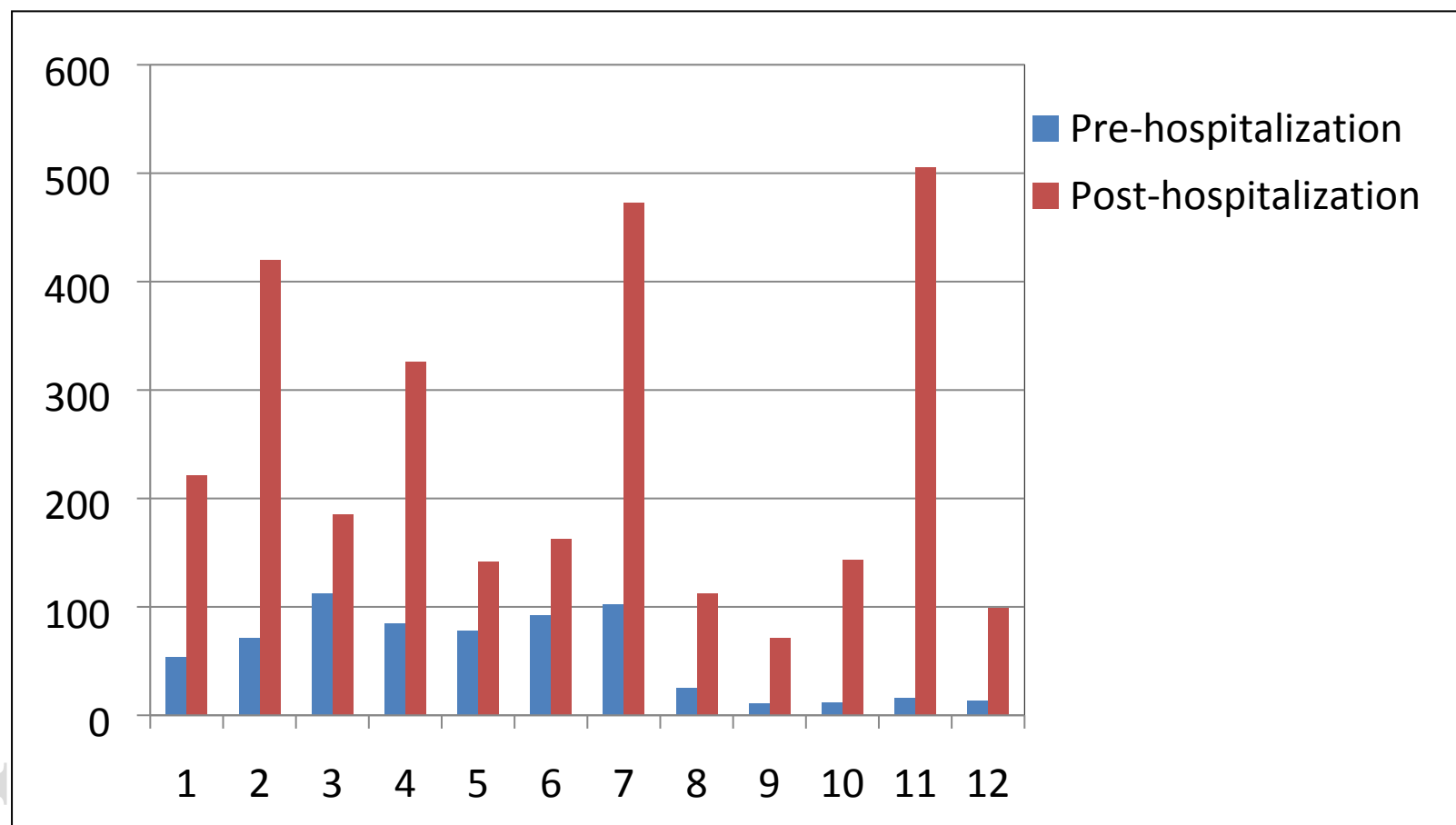
Fig.1: Changes in C-trough plasma levels, expressed as ng/mL, between pre- and in-hospital , in the twelve patients observed.