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Anticoagulation in COVID-19: DDI Perspective

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To The Editors

The novel 2019 coronavirus disease (COVID-19) creates a hypercoagulable state in which thrombotic microangiopathy, and a local disseminated intravascular coagulation (DIC) tends to be the principle cause of death. The COVID-19 hyper-inflammatory state, and inflammatory cytokine releasing, mainly IL-6, is associated with the down-regulation of drug-metabolizing enzymes and transporters activity. During the 1980 influenza epidemic, a clinically significant inflammation-induced loss of CYP1A2 activity led to theophylline toxicity in children.[1-4] Notably, drug-drug interactions (DDIs) described here are mainly based on proposed mechanisms of CYP and transporter inhibitory/induction properties.

Considering the key role of the inflammation in the pathogenesis of COVID-19, several immunomodulatory agents are being investigated. TNF-α, IL-1, and IL-6 blocker agents decrease the effects of anticoagulants due to cytochrome P450 enzymes induction. Among them, DDIs of IL-6 inhibitors have attracted the greatest interest. The American Society of Hematology recommended that apixaban and rivaroxaban should not be used with sarilumab and tocilizumab. Moreover, interferon-induced suppression effects on hepatic CYP450 enzymes and consequent drug interactions should be also considered. For example, warfarin dose reduction may be needed. Furthermore, Dexamethasone an inducer of P-glycoprotein in pre-clinical models, and a moderate inducer of CYP3A4. Consequently, its DDIs with anticoagulants should be considered. In the coadministration of warfarin with methylprednisolone, a decreasing dose of warfarin may be required.

Protease inhibitors such as ritonavir/lopinavir and atazanavir have been considered for off-label use in the treatment of COVID-19. These active substances are strong inhibitors of both CYP3A4 and P-glycoprotein and therefore may increase plasma concentrations of factor Xa (FXa) inhibitors to a clinically relevant degree, leading to an increased bleeding risk. Rivaroxaban should be avoided in this treatment scenario, while dose adjustment of warfarin edoxaban, apixaban, and betrixaban may be considered based on the current labeling.

Anti-hepatitis C virus nucleoside analogs including ribavirin, sofosbuvir, and daclatasvir are being investigated for the COVID-19 management. Among them, ribavirin may reduce the anticoagulant effect of warfarin through decreasing warfarin absorption. There is no predicted DDI between daclatasvir and warfarin; however, daclatasvir is a P-glycoprotein inhibitor, and predicted to decrease the metabolism of FXa inhibitors and dabigatran.

Azithromycin could increase the serum concentrations of dabigatran, betrixaban, and edoxaban through P-glycoprotein/ABCB1 inhibition, and the serum concentration of warfarin through unknown mechanisms. Furthermore, among antiparasitic agents, nitazoxanide with probable effects in COVID-19 could increase the warfarin level through protein binding competition (Table 1).

To date, no major DDI has been identified between the COVID-19 investigational agents and parenteral anticoagulants including heparin, low molecular weight heparin, fondaparinux, desirudin, danaparoid, bivalirudin, and argatroban due to their non-CYP-mediated metabolism. Besides, no major DDI has been recognized between other agents including remdesivir, favipiravir, sofosbuvir, chloroquine/hydroxychloroquine, pirfenidone, losartan, fingolimod, bevacizumab, and eculizumab with oral anticoagulants.[5-10]

Taken together, based on current evidence, parenteral anticoagulants have lower DDIs than oral anticoagulants. Besides, considering metabolism pathways of oral anticoagulants, edoxaban, betrixaban, and dabigatran are less likely to interact with COVID-19 drugs. Finally, hospitalized patients with COVID-19 should be monitored regarding anticoagulation using clinical and laboratory criteria and potential DDIs.

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Table 1. Potential Drug Interactions of Oral Anticoagulants With Investigational Agents in COVID-19.

Oral anticoagulant agents	Metabolism pathway	Inhibitors of IL-1, IL-6,[#] and TNFα	Ribavirin	Azithromycin	Lopinavir/ritonavir	Atazanavir	Daclatasvir
Warfarin	CYP2C9 * (major), CYP1A2,3A4,2C19	Restoring or normalizing CYP450 enzymes. Increasing dose may be needed	Possibly decreasing absorption Increasing dose may be needed [€]	Unknown mechanism Decreasing dose may be needed Monitor INR	CYP2C9 inducer CYP3A inhibitor Increasing dose may be needed Adjust dose based on INR.	CYP3A inhibitor Decreasing dose may be needed Adjust dose based on INR.	No interaction expected
Rivaroxaban	CYP3A4 (major), 2J2 BCRP/ABCG2 P-gp/ABCB1	Restoring or normalizing CYP450 enzyme levels. [f]	No interaction expected	P-gp/ABCB1 inhibitor No a priori dose modification is recommended	CYP3A, P-gp /ABCB1 inhibitor Do not coadminister	CYP3A, P-gp/ABCB1, and BCRP/ABCG2 inhibitor Do not coadminister.	P-gp/ABCB1 inhibitor. Monitoring is suggested
Apixaban	CYP3A4 (major), CYP1A2,2C19,2C8,2C9, BCRP/ABCG2P-gp/ABCB1	Restoring or normalizing CYP450 enzyme levels [f]	No interaction expected	P-gp/ABCB1 inhibitor No a priori dose modification is recommended	CYP3A, p-gp /ABCB1 inhibitor Administer at 50% of dose (do not administer if initial dose is 2.5 mg twice daily) [§]	CYP3A, P-gp/ABCB1, and BCRP/ABCG2 inhibitor Do not coadminister	P-gp/ABCB1 inhibitor. Monitoring is suggested
Edoxaban	P-gp/ABCB1	No interaction expected	No interaction expected	P-gp/ABCB1 inhibitor VTE: Limit dose to 30 mg daily Nonvalvular AF: No dose suggested	P-gp/ABCB1 inhibitor Reduce dose reduction from 60 mg to 30 mg [£]	P-gp /ABCB1 inhibitor Reduce dose reduction from 60 mg to 30 mg[£]	P-gp/ABCB1 inhibitor. Monitoring is suggested
Betrixaban	P-gp/ABCB1	No interaction expected	No interaction expected	P-gp/ABCB1 inhibitor Decrease dose to 80 mg once followed by 40 mg daily	P-gp/ABCB1 inhibitor Decrease dose to 80 mg once followed by 40 mg daily [¥]	P-gp/ABCB1 inhibitor Decrease dose to 80 mg once followed by 40 mg daily [¥]	P-gp/ABCB1 inhibitor. Monitoring is suggested
Dabigatran	P-gp/ABCB1	No interaction expected	No interaction expected	P-gp/ABCB1 inhibitor No dose adjustment recommended	P-gp /ABCB1 inhibitor No dose adjustment recommended	P-gp/ABCB1 inhibitor No dose adjustment recommended	P-gp/ABCB1 inhibitor. Monitoring is suggested

*S-warfarin (more potent) is metabolized by CYP2C9; whereas, R-warfarin is primarily metabolized by CYP1A2 and CYP3A4. [#]IL-1 inhibitor is anakinra. IL-6 inhibitors include tocilizumab, sarilimab, and siltuximab. TNF-α inhibitors includes etanercept, infliximab, rituximab, adalimumab, and golimumab. Among them, drug interactions of IL-6 inhibitors have attracted the greatest interest. [f] No dose adjustment recommended. Monitoring for possible dose increasing. € Considering ribavirin long half-life, any potential for interactions may persist for up to 2 months after cessation of ribavirin therapy. [§] These recommendations are based on the U.S. package insert. The Canadian package insert considers the combination of these agents to be contraindicated. [£]The European product label recommended dose reduction from 60 ng to 30 mg; however, the US product label recommend no dosage adjustment. [¥] The US product label recommended dose reduction and use an initial dose of 80 mg followed by 40 mg once daily and monitoring considering blood loss. P-gp indicates P-glycoprotein; INF, interferon; IL, interleukin; TNF, tumor necrosis factor; INR, international normalized ratio; VTE, venous thromboembolism; AF, atrial fibrillation.

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