

## Drug-Drug Interactions of Antithrombotic Medications During Treatment of COVID-19

Oğuzhan Fırat, Burcu Kelleci Çakır, Kutay Demirkan

Department Of Clinical Pharmacy, Hacettepe University Faculty Of Pharmacy, Ankara, Turkey

### Corresponding Author Information

Oğuzhan Fırat

[ogzhnfrt@gmail.com](mailto:ogzhnfrt@gmail.com)

+905414894206

<https://orcid.org/0000-0002-8726-8530>

14.09.2020

22.09.2020

**Keywords:** COVID-19, antithrombotics, drug-drug interactions

Dear Editor,

Coronavirus Disease 2019 (COVID-19), as an outbreak has high morbidity and mortality (1). Since COVID-19 is affecting elderly more than other age groups, intensive care requirement, cardiovascular diseases and stroke becomes important due to widely antithrombotic medications usage. These high risk medications may cause gastrointestinal bleeding as a result of potential drug-drug interactions (2). We believe that identifying drug-drug interactions between COVID-19 and antithrombotic medications which commonly used in intensive care units in patients that suffer from cardiovascular diseases or stroke will be beneficial to ensure appropriate and safe treatment.

First-line treatment option for COVID-19, hydroxychloroquine has a few drug interactions with antithrombotics. While hydroxychloroquine can increase blood levels of apixaban (low-risk), dabigatran (moderate-risk), edoxaban (moderate-risk) and rivaroxaban (low risk), there is no drug-drug interaction with other antithrombotics (such as heparin, enoxaparin, aspirin, clopidogrel, warfarin) (3).

Lopinavir/Ritonavir (LPV/r) combination, strong cytochrome-3A4 and P glycoprotein inhibitor, may enhance blood levels of apixaban (high risk), edoxaban (moderate risk), rivaroxaban (high-risk), ticagrelor (high-risk). It is recommended to adjust the dose of apixaban to 2.5 mg twice daily during concomitant use with LPV/r. Additionally, serum concentrations of clopidogrel (high-risk), dabigatran (moderate-risk), dipyridamole (moderate-risk) and warfarin (moderate-risk) may decrease with concurrent use of LPV/r. In patients using clopidogrel together with LPV/r, switching to prasugrel is recommended, if possible (3).

The concurrent use of oseltamivir and warfarin (low-risk) can lead to increase serum concentration of warfarin. However this interaction does not require any intervention except monitoring INR (International Normalized Ratio). Additionally, clopidogrel (moderate-risk may decrease serum concentrations of the active metabolites of oseltamivir (4).

Among the treatment options of COVID-19, the use of azithromycin in combination with hydroxychloroquine is common approach in some countries. In case of concomitant use of azithromycin during the treatment of venous thromboembolism with edoxaban, serum

concentration of edoxaban may significantly increase which leads to risk of exceeding maximum daily dose (30 mg) of edoxaban. The use with azithromycin and apixaban (minor risk), rivaroxaban (low-risk), dabigatran (moderate-risk) or warfarin (moderate-risk) may enhance serum concentration of these antithrombotic drugs (5).

At the moment due to limited data available, favipiravir seems to be the safest option among other medications used in COVID-19 treatment in terms of interaction with antithrombotics.

The interaction of favipiravir with antithrombotic drugs has not been established (3).

During the treatment of COVID-19, concomitans use of high risk medications such as antitrombotics should be assessed carefully in terms of drug-drug interactions to avoid any negative outcomes in the treatment process.

## **Declarations**

**Funding:** No funding

**Competing Interests:** There is no conflict of interest

**Ethical Approval:** Not required

## **References:**

1. Aggarwal, G., Lippi, G., & Michael Henry, B. (2020). Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): A pooled analysis of published literature. *International Journal of Stroke*, 1747493020921664.
2. Delaney, J. A., Opatrny, L., Brophy, J. M., & Suissa, S. (2007). Drug–drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *Cmaj*, 177(4), 347-351.
3. Interactions with Experimental COVID-19 Therapies, Liverpool Drug Interaction Group, 2020. (Accessed March 13, 2020 at <https://www.covid19-druginteractions.org/>).
4. Drugs.com [Internet]. Oseltamivir Drug Interactions from Drugs.com; c1996-2020 [Updated: 10 April 2020; Cited: 27 April 2020]. Available from: <https://www.drugs.com/drug-interactions/oseltamivir.html>
5. Azithromycin. In: Lexi-drugs online [database on the Internet]. Hudson (OH): Lexicomp, Inc.; 2020 [accessed 27 April 2020]. Available from: [https://www.uptodate.com/contents/azithromycin-systemic-drug-information?search=azithromycin&source=panel\\_search\\_result&selectedTitle=1~145&usage\\_type=panel&display\\_rank=1](https://www.uptodate.com/contents/azithromycin-systemic-drug-information?search=azithromycin&source=panel_search_result&selectedTitle=1~145&usage_type=panel&display_rank=1)