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LETTER
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Does therapeutic drug monitoring of hydroxychloroquine improve treatment outcome in intensive care unit patients with COVID-19?

To The Editor,

COVID-19 is a newly emerging human infectious disease of SARS-CoV-2 origin that has spread from China. The global COVID-19 situation was described as a pandemic by the WHO on 11 March 2020. Several treatment strategies are being considered and evaluated in numerous clinical trials. Among several treatment strategies, hydroxychloroquine (HCQ) has been suggested as potential treatment option for COVID-19. However, it has very long half-life (5-40 days) and large volume of distribution into blood and tissues which causes variability in treatment response. It is known that, the steady-state concentration is reached within weeks and differs according to individual factors (eg, obesity, sepsis, burn, ascites, pregnancy, critical illness) even at the same dose regime especially in the treatment of rheumatic diseases.[1] In contrast, the usage of HCQ is limited to 5 days and the mean time to reach the minimum therapeutic drug concentration (1 mg/L) is 3-4 days in patients with COVID-19.[2]

Patients in intensive care unit (ICU) present certain characteristics such as presence of sepsis, obesity, extracorporeal membrane oxygenation that may cause an increase in the volume of distribution of drugs.[3] The presence of these factors may prevent to achieve the desired concentration of HCQ in this special population.

There is little information about the efficacy of HCQ and modalities of administration of this drug in ICU patients with COVID-19. The therapeutic level of HCQ in patients with COVID-19 has not yet been established. According to the studies, HCQ trough levels between 1-2 mg/L were considered to be therapeutic.[4,5] Yao et al suggested HCQ dosage of 400 mg twice a day for day-1, followed by 200 mg twice daily in the following 4 days for COVID-19 treatment.[5] In many countries, this dosage regimen is used primarily for patients with COVID-19, including patients in ICU. To the best of our knowledge, there are no data established yet that assess the number of ICU patients have reached the target level in this dosage regimen.

In contrast, Perinel et al indicated that only 61% of patients reached the therapeutic level at 200 mg three times daily dosing regimen.[2] However, no information was provided on potential drug interactions with HCQ which might affect the level of HCQ. Cytochrome P450 (CYP) enzymes (particularly CYP2C8 and CYP3A4/5) play a role in HCQ metabolism, hence may results in drug interactions.[1] Therefore, co-administration of CYP2C8 inhibitors (eg, gemfibrozil and clopidogrel) and CYP 3A4/5 inhibitors (eg, verapamil, diltiazem, azole antifungal agents, most macrolide antibiotics, ciprofloxacin) may potentially raise the blood level of HCQ, whereas inducers of CYP3A4/5 (eg, carbamazepine, rifampicin, phenytoin) may potentially decrease the blood level of HCQ.[6] Given the fact that a majority of patients in ICUs are elderly people (>65 years old), as seen in the Perinel et al study,[2] it can be assumed that these patients are at greater risk of drug interactions because of the existence of several comorbid conditions and administration of many drugs concurrently.[7] Therefore, these issues should also be considered and monitored during HCQ treatment in patients with COVID-19.

The most commonly seen adverse effect of HCQ in patients with COVID-19 is cardiac toxicity. The relation between cardiac toxicity and HCQ concentration has not been determined; however, it is known that HCQ concentration should not exceed 2 mg/L in order to avoid ocular toxicity.[8] In Perinel et al study, two patients experienced cardiac toxicity at high HCQ concentrations. Although a high dose of HCQ is given initially during the COVID-19 treatment, it should be remembered that a high drug exposure is likely to cause unwanted effects in vulnerable patients at critical circumstances, therefore therapeutic drug monitoring of HCQ may reduce the risk of its occurrence.

In addition, the day of HCQ initiation during the COVID-19 infection was not indicated in the study by Perinel et al[2] As it known that liver and kidney functions can be damaged in patients in ICU which may result in delays in reaching the therapeutic drug concentration and increase the risk of adverse drug reactions, particularly in patients with COVID-19.[9,10]

Existence of high mortality rates in the ICU and uncertainty around reaching the therapeutic concentration, we suggest that individual dose modification by therapeutic drug monitoring for HCQ until its concentration reaches the therapeutic level (mean duration of 3-4 days) in ICU patients with COVID-19 can help to achieve optimal outcomes and reduce the risk of drug interactions. Further pharmacokinetic and pharmacodynamic (virological) studies are also warranted.

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DISCLOSURE

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Kamer Tecen-Yucel
Elif Aras-Atik
Aygin Bayraktar-Ekincioglu

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

Correspondence
Kamer Tecen-Yucel, Hacettepe University Faculty of Pharmacy, Department of Clinical Pharmacy, 06100 Sihhiye, Ankara, Turkey.
Email: kamertecen@hacettepe.edu.tr

ORCID

Kamer Tecen-Yucel https://orcid.org/0000-0002-5381-0950

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