Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

The significance of correct dosing of hydroxychloroquine in clinical trials of COVID-19

Dear Sir,

d'Arminio Monforte et al. report the findings from a cohort of 159 hospitalized patients with COVID-19 and shows that the effectiveness of hydroxychloroquine (HCQ) is greater for individuals with the milder form of the disease (d'Arminio Monforte et al., 2020). However, the authors have not mentioned the dose, frequency, or duration of treatment with HCQ or any of the other medications received by the patients.

HCQ has been in use as an antimalarial since 1955. The universally recommended loading dose of HCQ for the management of uncomplicated malaria is 800 mg. It is noteworthy that in the dosing regimen of the HCQ arm for all the three major global trials — Solidarity, RECOVERY, and DisCoVeRy — the recommended loading dose for treatment of COVID-19 was 1600 mg (two oral loading doses of 800 mg each, 6 h apart), exactly double the antimalarial dose. Notably, the HCQ arms in all of these trials have been discontinued (Recovery trial, 2020; World Health Organization, 2020; Inserm, 2020). But why is there a need for such a high loading dose?

For a drug with a large volume of distribution such as HCQ (5522 L) (Tett et al., 1988), a high loading dose is required to achieve a plasma concentration above the minimum effective concentration (MEC), so that the therapeutic effects are obtained. The maintenance dose, given further, ensures that the trough concentration remains above the MEC. The loading dose of a drug is calculated by multiplying the target plasma concentration of the drug for its therapeutic effect by the volume of distribution. For hydroxychloroquine sulfate (HCQS), if its median effective concentration (EC_{50}) value for SARS-CoV-2 is taken as the target plasma concentration, two different values of loading dose are obtained. While one in vitro study has found the EC_{50} to be 0.72 μM (241.2 ng/mL) (Yao et al., 2020), another proposed it to be 4.51 μM (1510.85 ng/mL) (Liu et al., 2020), which is almost six times higher, both at the same multiplicity of infection (MOI) of 0.01. Calculating with these two values as target plasma concentrations, the approximate loading doses come out as 1331 mg and 8338 mg, respectively. Thus, there is a definite and large discrepancy in the magnitude of loading doses for COVID-19.

Considering that a 200 mg HCQS formulation contains 155 mg hydroxychloroquine base, if the lesser loading dose of 1331 mg is selected, then approximately 8.5 tablets/capsules of 200 mg strength need to be administered. In the three aforementioned major trials, four tablets of 200 mg each were to be administered twice, 6 h apart, as a loading dose; eight tablets in total, amounting to a 1240 mg HCQ base. This is 91 mg lower than the required loading dose. Hence, another half a tablet (77.5 mg of HCQ base) should have been given, which was actually not included in the trial protocols. Plaquenil (HCQS) 200 mg tablets cannot be cut in half to solve this issue since they are film-coated, so a solution could have been to administer an additional 100 mg HCQS (77.5 mg base) tablet; the loading dose should ideally have been four tablets of 200 mg HCQS × 2, along with a single 100 mg tablet. Although the rationale for a loading dose of HCQ in COVID-19 has been discussed (Lê et al., 2020), we could not find any mention of this dose discrepancy.

Could this disparity in the loading dose have led to HCQ not meeting the desired efficacy endpoints in the unsuccessful trials? However, increasing the dose also compromises safety, mainly relating to cardiac conduction defects. The benefit-to-risk ratios were not found to be favorable for all the three aforementioned trials. Additionally, since the elimination half-life ($t_1/_2$) of HCQ is about 50 days (Tett et al., 1989), the metabolites would remain for a prolonged period after such a high loading dose, compromising the safety profile even further. Moreover, the rationale for a continuous dosing regimen of HCQ in light of its long elimination half-life, and the fact that the COVID-19 illness lasts for about 10 days for most persons (Centers for Disease Control and Prevention, 2020), is debatable.

We therefore request the authors to share the entire dosing regimen of HCQ that was administered to the patients and ask for their opinion on whether it played any role in their findings on the effectiveness of HCQ for COVID-19.

Conflicts of interest

We declare no conflicts of interest.

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Author contributions

Conception and design: BS, SA.
Analysis and interpretation of the data: AR, SS.
Collection and assembly of data: AR, SS.
Drafting of the article: AR, SS.
Critical revision for important intellectual content: SA, AR, SS.
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