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

Recommendations for use of a hydroxychloroquine loading dose in patients with COVID-19

Sir,

Discussions and confusion continue regarding the use, effectiveness and adverse effects of hydroxychloroquine (HCQ) use in the treatment of coronavirus disease 2019 (COVID-19). One of the uncertainties regarding HCQ use is about the dosage of the drug. There are inadequate data to guide dosing for HCQ treatment, and dosing regimens may vary according to its indication (e.g. malaria, rheumatological disorders). Several approaches are available for these indications, both in terms of what the maintenance and loading dose should be and whether a loading dose should be used. In addition, HCQ-related adverse events may increase with dosing regimens that result in supratherapeutic concentrations. However, there are no clinical trials evaluating this issue and there is variability in dosing between centres when being used in patients with COVID-19.

HCQ has a large volume of distribution (47.5 L) and a long elimination half-life (40–50 days). Overdose and toxicity risk may be higher especially in critically ill patients with impaired renal and/or hepatic function. Pharmacokinetic parameters of HCQ have been learned from studies in patients with rheumatic diseases and in healthy volunteers [1,2].

In an integrative modelling study by Garcia-Cremades et al., it was found that effective HCQ treatment either with a loading dose [800 mg twice a day (b.i.d.) loading dose for 1–2 days followed by 400 mg b.i.d. maintenance dose] or without a loading dose (400 mg b.i.d. maintenance dose) for a 7-day regimen could be tolerated safely. Besides their safety, their effectiveness in terms of reducing the time of detectable viral load and improving treatment outcomes was also analysed. It was predicted that higher daily doses of HCQ (such as 800 mg b.i.d.) could result in an increased risk of QT prolongation [3]. Similar to the use of high doses, a loading dose may also increase the risk of QT prolongation and other cardiovascular problems, and the use of other drugs that prolong the QT interval may reinforce this reaction. In another simulation modelling study by Al-Kofahi et al., simulations predicted that 89% of patients could reach the target concentration [trough concentration above half maximal effective concentration (EC_{50}) of 0.72 μM] on the first day of treatment when an 800 mg/day loading dose was given followed by a 400 mg/day maintenance dose, however 400 mg/day without a loading dose could achieve the target in only 8% of patients [4]. Yao et al. recommended HCQ 400 mg b.i.d. for the first day, followed by 200 mg b.i.d. for an additional 4 days to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection according to physiologically-based pharmacokinetic models [5].

Distribution of appropriate drug concentrations into the lungs is crucial for the treatment of pulmonary infections such as COVID-19. Therefore, in cases such as empyema or pleural effusion, a loading dose may increase the probability of achieving adequate drug concentration in the lungs. Obesity, sepsis, burn, ascites and pregnancy may cause an increase in the volume of distribution of drugs. In addition to the high volume of distribution of HCQ, the presence of these factors may reduce the achievement of the desired concentrations and thus a loading dose could be beneficial to overcome these problems.

Considering the need for rapid achievement of therapeutic concentrations during the acute phase of the infection and the short treatment course, loading doses may be beneficial. Some suggestions can be made for the use of a loading dose (Table 1). Although these suggestions do not apply to all patients, clinicians need to consider the necessity of a loading dose for their patients individually. Clinicians should consider the effect of individual patient con-

Table 1
Suggestions regarding a loading dose of hydroxychloroquine in its use for the treatment of COVID-19.

Patients who are not eligible for a loading dose	Patients who do not need a loading dose	Patients who are eligible for a loading dose
Patients at risk of cardiovascular disease: QT prolongation Torsades de pointes Ventricular arrhythmia Patients who use drugs with high risk of QT prolongation	Patients with mild COVID-19 Patients without risk of change in volume of distribution of the drug Patients in whom 1–2 days of delay can be tolerated to reach the therapeutic dose	Patients with severe COVID-19 Patients at risk for severe disease (e.g. advanced age, asthma, diabetes) Patients with oral intake/bioavailability problems Patients with features that can increase the volume of distribution of the drug (e.g. obesity, sepsis, burn, ascites, pregnancy) Patients with increased metabolism or excretion of the drug (e.g. drug interactions) Patients at risk of poor distribution of the drug to the lungs or decreased drug concentration in the lungs (e.g. empyema, pleural effusion)

COVID-19, coronavirus disease 2019.

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ditions (e.g. obesity, sepsis, burn, ascites, pregnancy, critical illness) and changes in pharmacokinetic (e.g. increased drug volume of distribution) and pharmacodynamic (e.g. decreased effectiveness, increased adverse effects) parameters on HCQ prescribing. We believe that randomised controlled studies should be conducted to evaluate HCQ use with and without a loading dose in terms of effectiveness and safety.

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Ethical approval

Not required.

Declaration of Competing Interest

None declared.

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