DOI: 10.4103/0971-5916.290075

Quick Response Code:

Authors' response

We thank the authors[1] for their interest in the case-control investigation[2] we conducted and also acknowledge the importance of using preventive strategies, such as social distancing and utilization of personal protective equipment for preventing SARS-CoV-2 infection in healthcare workers. They mention that the previous *in vitro* experiments with quaternary ammonium compounds such as ammonium chloride have documented an increase in endosomal *p*H in specific cell lines as is observed with hydroxychloroquine (HCQ). However, we would like to emphasize that the referred study reported on SARS-CoV, not on SARS-CoV-2[3]. It is also vital to consider that the stated evidence is derived from an *in vitro* study, which has shown increased antibody-mediated infection of specific cell lines expressing Fc receptors in the presence of ammonium chloride. But importantly, the antibody-dependent enhancement (ADE) only led to abortive infection in the experiments described in the quoted article. In addition, the increase in infection was only seen in the ADE pathway and not in the angiotensin-converting enzyme 2 (ACE2) receptor pathway. For SARS-CoV-2, while the ACE2 receptor pathway has been shown to be relevant, the importance of ADE pathway is not clear[4]. Contrary to the claim by authors[1], the *in vitro* results for the effect of ammonium chloride on *in vitro* infection for SARS-CoV in the quoted study did not biologically explain why short duration of HCQ should increase the risk of infection for SARS-CoV-2. The extrapolation to our study therefore, seems inappropriate.

The authors[1] have suggested an alternate dosing schedule for prophylaxis, which is higher than the current schedule. Before any such changes in the dosing schedule are considered, the safety of the proposed schedule must be proven through clinical studies. The pharmacological activity of HCQ against SARS-CoV-2 has been assessed *in vitro,* and the loading dose of 400 mg twice daily followed by twice daily maintenance dose of 200 mg has been assessed in physiology-based pharmacokinetics (PBPK) models for concentrations in the lungs[5]. Further, models describing the highly compartmentalized distribution of chloroquine in humans have been developed, which show that if the prophylactic effect is considered to be based on the pulmonary exposure of HCQ, then once weekly dosing could prove effective[6]. We agree that the dosing schedule suggested by the authors[1] should be based on the available *in vitro* or *in vivo* data derived from PBPK models or on clinical studies of safety and efficacy.

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