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Letter to the editor

Chloroquine paradox may cause more damage than help fight COVID-19

A B S T R A C T

Novel coronavirus disease 2019 (COVID-19) pandemic is the most recent health care crisis without specific prophylactic or therapeutic drugs. Antimalarial drug chloroquine (CHL) and its safer derivative hydroxychloroquine (HCHL) have been proposed to be repurposed to treat SARS coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19. CHL/HCHL have anti-inflammatory activity and are used to treat rheumatoid arthritis, osteoarthritis and lupus. Although, CHL/HCHL have an anti-viral activity against several viruses in cell-cultures, the anti-viral activity in-vivo is questionable. Repurposing of CHL/HCHL to treat SARS-CoV-2 infection is appealing. However, there is empirical evidence from animal studies with other viruses suggesting that CHL/HCHL may have an untoward paradoxical effect. One thus cannot exclude the possibility that CHL may increase the severity of the disease and prove deleterious both for the patients and public health efforts to contain the highly contagious and explosive spread of SARS-CoV-2.

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1. Main text

As the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak reaches pandemic proportions, there is a frantic search for effective anti-SARS-CoV-2 drug. Recently, among others, chloroquine (CHL) and its safer derivative hydroxychloroquine (HCHL) [1] have been propelled as anti-SARS-CoV-2 drugs as CHL inhibited the virus in cell cultures [2] and appear to reduce virus load in patients in an open label non-randomized trial [3]. The U.S. Food and Drug Administration has given an emergency use authorization for use of HCHL for treatment of novel coronavirus disease 2019 (COVID-19). CHL/HCHL are excellent anti-viral drugs in-vitro, as they increase endosomal and lysosomal pH [4] and interfere with the glycosylation of the proteins [5]. Acidic pH of endosomes and lysosomes aids in virus fusion to cells as well as release of their genetic material in the cells to initiate active virus replication [4]. Modification of the protein glycosylation including that of the viral envelope proteins interferes with virus assembly and release of mature virus particles. By inhibiting these two crucial steps, it’s not surprising that CHL/HCHL have indeed been found to be effective anti-viral agents in-vitro, including that of the SARS-CoV [6]. In fact there is no report of CHL/HCHL being not effective as an anti-viral agent when tested against any virus in cell cultures (in vitro).

However, in-vivo, CHL/HCHL have been shown to either have no effect on virus replication or have increased the viral replication and disease severity such as that of influenza [7], dengue [8,9], Semliki forest virus (SFV) [10,11], encephalomyocarditis virus (EMCV) [10], Nipah and Hendra viruses [12], chikungunya virus [13] and Ebola virus [14]. In clinical trials, CHL treatment failed to prevent influenza and chikungunya virus infections in human subjects and was suggested to increase the risk of infection as well as symptom severity [7,15]. In children treated with CHL following malarial infection, the incidence of Herpes zoster virus (HZV) was markedly enhanced, which otherwise is not common in children [16]. Similar association was later reported in adults suggesting high incidences of HZV in dermatomyositis/polymyositis patients treated with chloroquine [17]. For treatment of plasmodium infection, CHL/HCHL blocks the intra-erythrocytic stage of the plasmodium but, has no activity against the hepatic stage of plasmodium life cycle [18]. The hepatic stage (sporozoite) of plasmodium, which can cause relapsing malaria, is treated by other quinolone drugs such as mefloquine and primaquine [19]. Treatment with gamma interferon (IFN-γ) alone is effective against exo-erythritic stage of the Plasmodium cynomolgi infection in monkeys and prevented relapse of parasitemia [20]. However, when combined with CHL, the anti-sporozoite activity of IFN-γ was abolished resulting in parasitemia relapse. More importantly, CHL was shown to abolish the anti-viral activity of IFN in mice against Semliki forest virus [11]. Note that IFN is the earliest defense response presented to virus infections and such immunomodulatory activity of CHL may help virus infections [21]. In context of coronaviruses (CoV) that causes milder disease in humans, protection of the newborn mice from human CoV-OC43 induced death after treatment of mother mice with CHL have been shown [22]. However, newborns were presumed to acquire CHL transplacentally or via mother’s milk which, limits the extrapolation of results to anti-CoV activity by direct treatment of animals with CHL/HCHL. Against SARS-CoV, which causes severe respiratory syndrome involving lower respiratory tract, CHL did not show anti-viral activity in mice [23].
Due to the anti-inflammatory activity of CHL/HCHL, these drugs are used to treat variety of disease where inflammation is central to disease pathogenesis such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and osteoarthritis [24]. As SARS-CoV-2 causes an acute inflammation in the lungs, a condition central to the pathology of COVID-19, a potential beneficial effect of CHL/HCHL due to an anti-inflammatory activity is postulated. Although encouraging, the difference of treating inflammation of COVID-19 vs SLE or RA is the presence of an infectious agent, i.e., SARS-CoV-2. In animal studies, CHL enhanced severity of the inflammatory viral disease such as that of SFV and EMCV, and increased arthritic symptoms in CHIKV infected patients [10,25]. Therefore, beneficial anti-inflammatory effect of CHL may not translate as it is, into SARS-CoV-2 infected patients. Only a carefully planned animal study and/or clinical trials will be able to answer this important question.

Preliminary findings of a non-randomized open-label trial showed reduction in SARS-CoV-2 viral RNA load in HCHL and HCHL combined with azithromycin treatment [3]. However, HCHL treatment was started in 26 patients of which, six were not included in the final analysis as the drug treatment was not completed in these patients. Of these six, four (15.3% of the total patients) patients experienced severe COVID-19 including one death, and additionally another patient experienced adverse symptoms during treatment and did not complete the trial. Control patients did not experience severe form of COVID-19 [3]. Adverse effect of HCHL treatment in patients and virus titer data from patients which progressed into more severe disease after treatment with HCHL was not available, limiting the ability to conclude with certainty the beneficial effect of HCHL and the potential exacerbation of the disease by HCHL treatment in four patients cannot be ruled out. Contradictory results on the protective efficacy of CHL/HCHL in COVID-19 patients have been reported in other recent clinical reports and trials [26 – 29]. In a separate study, treatment of COVID-19 patients with HCHL in combination with azithromycin was found to be beneficial. However, no direct comparison with non-drug treated COVID-19 patients was made. Although most patients recovered, three HCHL treated COVID-19 patients progressed to severe disease including one death [26]. A randomized clinical study in with 62 COVID-19 patients reported beneficial effect of HCHL treatment compared to standard clinical care of COVID-19 [29]. In contrast, a small cohort study with 11 patients found no protective efficacy of HCHL and azithromycin in COVID-19 patients and reported one death and one adverse effect (18.1%) after initiation of HCHL treatment [27]. Progression of disease severity in HCHL treated COVID-19 patient was also observed in another study, which otherwise showed no beneficial effect of HCHL treatment on prognosis of COVID-19 patients [28].

The paradoxical studies on the effect of CHL/HCHL on virus replication are of particular importance from a public health perspective. Animal studies indicate that CHL/HCHL can increase the severity of some viruses including those where inflammation is at the core of disease pathology. Although controversial, some clinical reports have indicated beneficial effect of HCHL against COVID-19, but progression of disease severity in HCHL treated COVID-19 patients over that of non-drug treated COVID19 patients have also been observed in these studies. A cautious and thorough review of antiviral activity of CHL/HCHL before widespread use of the drugs to treat COVID19 is needed [30,31]. Hasty application of CHL/HCHL to treat COVID19 may end up in exacerbating the disease and increasing morbidity. Drawbacks of self-administration of CHL/ HCHL are highlighted by the overdose toxicity and fatal outcome of self-administration of CHL [32,33]. Therefore, extreme caution is needed while extrapolating the anti-viral activity of CHL/HCHL to SARS-CoV-2 in these testing times.

Opinions expressed herewith are those of the author and are not necessarily representative of those of the USUHS, DoD, or the United States Army, Navy or Air Force.

Declaration of Competing Interest

Author declare no conflict of interest.

References

[1] McChesney EW. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. Am J Med 1983;75:11–8.
[2] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269–71.
[3] Gautret P, Lagier JC, Parola P, Hoang VT, Me debit L, Maille M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949.
[4] Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res Perspect 2017;5:600293.
[5] Thorens B, Vassali P. Chloroquine and ammonium chloride prevent terminal glycosylation of immunoglobulins in plasma cells without affecting secretion. Nature 1986;321:618–20.
[6] Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69.
[7] Paton NI, Lee L, Xu Y, Ooi EE, Cheung YB, Archuleta S, et al. Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. Lancet Infect Dis 2011;11:677–83.
[8] Tricou V, Minh NN, TP, Lee SJ, Farrar J, Wills B, et al. A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults. PLoS Neglected Trop Dis 2010;4:e785.
[9] Borges MC, Castro LA, Fonseca BA. Chloroquine use improves dengue-related symptoms. Mem Inst Oswaldo Cruz 2013;108:596–9.
[10] Maheshwari RK, Srikantan V, Bhatiya D. Chloroquine enhances replication of Semiliki Forest virus and encephalomyocarditis virus in mice. J Virol 1991;65:990–5.
[11] Maheshwari RK, Srikantan V, Bhatiya D, Puri SK, Dutta GP, Bhawan BN. Effects of interferon in malaria infection. Immunol Lett 1990;25:53–7.
[12] Falletier J, Middleton D, Crameris G, Yamada M, Klein R, Hancock TJ, et al. Chloroquine administration does not prevent Nipah virus infection and disease in ferrets. J Virol 2009;83:11979–82.
[13] Roques P, Thiberville SD, Dupuis-Maguiraga I, Lem FM, Labade K, Martinon F, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. Virus Res 2018;261:268.
[14] Dowall SD, Bosworth A, Watson R, Bewley K, Taylor I, Rayner E, et al. Chloroquine inhibited E bola virus replication in vitro but failed to protect against infection and disease in the in vivo Guinea pig model. J Gen Virol 2015;96:3484–92.
[15] De Lamballerie X, Brionnais V, Reynier JC, Enault S, Charrel RN, Flahault A, et al. On chikungunya acute infection and chloroquine treatment. Vector Borne Zoonotic Dis 2008;8:337–9.
[16] Cook IF. Herpes zoster in children following malaria. J Trop Med Hyg 1985;88:207–14.
[17] Slater AF. Chloroquine: mechanism of drug action and resistance in Plasmodium falciparum. Pharmacol Ther 1993;57:203–35.
[18] Anjum MU, Naveed AK, Mahmood SN, Naveed OK. Single dose tafenoquine for preventing relapse in people with plasmodium vivax malaria-an updated meta-analysis. Trav Med Infect Dis 2020;101576.
[19] Puri SK, Maheshwari RK, Dutta GP, Friedman RM, Dhar MM. Human interferon-gamma protects rhesus monkeys against sporozoite-induced Plasmodium cynomolgi malaria infection. J Interferon Res 1988;8:201–6.
[20] Sticherling C, Pouget N. Stimulation of innate immunity by host and viral RNAs. Trends Immunol 2019;40:1134–48.
[21] Keyaerts E, Li S, Vijgen L, Ryman E, Verbeeck J, Van Ranst M, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother 2009;53:3416–21.
[22] Barnard DL, Day CW, Bailey K, Heiner M, Montgomery R, Lauridsen L, et al. Evaluation of immunomodulators, interferons and known in vitro SARS-cov inhibitors for inhibition of SARS-cov replication in BALB/c mice. Antivir Chem Chemother 2006;17:275–84.
[23] Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology 2015;23:231–60.
[24] Seth P, Mani H, Singh AK, Banaudha RK, Madhavan S, Sidhu GS, et al. Acceleration of viral replication and up-regulation of cytokine levels by antimalarials: implications in malaria-endemic areas. Ann J Trop Med Hyg 1999;61:180–6.
[26] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow-up: an observational study. Travel Med Infect Dis 2020 Apr 11;101663. In press.
[27] Jean MM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020 Mar 30. In press, pii: S0399-077X(20)30085-8.2.
[28] Chen Jun LD, Liu Li, Liu Ping, Xu Qingnian, Lu XIA, Yun LING, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ 2020;49.
[29] Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020. https://doi.org/10.1101/2020.03.22.200407583.
[30] Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antivir Res 2020;177:104762.

[31] Guastalegname M, Vallone A. Could chloroquine/hydroxychloroquine be harmful in Coronavirus Disease 2019 (COVID-19) treatment? Clin Infect Dis 2020 Mar 24. pii: ciaa321.
[32] Waldrop T, Alsup D, Elliott CM. Fearing coronavirus, Arizona man dies after taking a form of chloroquine used to treat aquariums. 2020.
[33] Salo J. Nigeria reports poisonings from possible coronavirus drug chloroquine. March 22, 2020.

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