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Title

Hydroxychloroquine as an aerosol might markedly reduce and even prevent severe clinical symptoms after SARS-CoV-2 infection

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Abstract

Covid-19 is a new coronavirus disease first described in December 2019. This respiratory illness is severe and potentially fatal. Severe cases make up to 15%, lethality ranges between 1.5 and more than 10 %. What is urgently needed is an efficient pharmacological treatment for the treatment of severe cases. During the infection of alveolar epithelial cells of the lung, the ACE2 receptor has a central function. The antimalarial drugs chloroquine phosphate (CQ) and hydroxychloroquine (HCQ) impair in vitro the terminal glycosylation of ACE2 without significant change of cell-surface ACE2 and, therefore, might be potent inhibitors of SARS-CoV-2 infections. Starting inhibition at 0.1 µM, CQ completely prevented in vitro infections at 10 µM, suggesting a prophylactic effect and preventing the virus spread 5 hours after infection. In a first clinical trial, CQ was effective in inhibiting exacerbation of pneumonia, improving lung imaging findings, promotion of virus-negative conversion, and shortening the disease. In addition, HCQ, which is three times more potent than CQ in SARS-CoV-2 infected cells (EC50 0.72 µM), was significantly associated with viral load reduction/disappearance in COVID-19 patients compared to controls. Theoretically, CQ and HCQ could thus be effectively used in the treatment of SARS-CoV pneumonia. From a pharmacological standpoint, however, the major problems of oral treatment with these drugs are possible severe side effects and toxicity. Concretely, this relates to (a) the inconsistent individual bioavailability of these drugs at the alveolar target cells, depending on intestinal resorption, hepatic first-pass metabolism and accumulation in liver, spleen and lung, and (b) the need for a relatively high concentration of 1-5 µM at the alveolar surface.
Therefore, we propose in a first dose estimation the use of HCQ as an aerosol in a dosage of 2-4 mg per inhalation in order to reach sufficient therapeutic levels at the alveolar epithelial cells. By using a low-dose non-systemic aerosol, adverse drug reactions will markedly be reduced compared with oral application. This increase in tolerability enables a broader use for prevention and after contact with an infected person, which would be an advantage especially for the high-risk, often multi-morbid and elderly patients.
Empirical data on self-medication with a one-week aerosol application by two of the authors is presented. Inhalation was well tolerated without relevant side effects.

Keywords

COVID-19, hydroxychloroquine aerosol, pharmacotherapy, prevention, SARS-CoV-2

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Introduction/Background

The 2019-nCoV pandemic is rapidly spreading with currently more than a million reported cases and 57.000 deaths worldwide (https://coronavirus.jhu.edu/map.html, downloaded April 3, 2020). While the majority of infections with Covid-19 are asymptomatic or show a mild course (Novel, 2020; Wu & McGoogan, 2020), up to 15% of patients develop a severe and potentially fatal respiratory illness with an estimated lethality ranging between 1.5 and more than 10 % (Baud et al., 2020). Currently, as no effective antiviral pharmacological treatment is available, lethality seems to depend on individual risk factors including age, gender and hypertonia and regarding the course of the disease in cases of severe pneumonia, on the availability of large-scale intensive care units and extracorporeal membrane oxygenation (ECMO) (Hamer et al., 2020; Zhou et al., 2020).

Regarding pharmacological treatment, several clinical trials have recently been initiated, e.g. with lopinavir/ritonavir (Cao et al., 2020), remdesivir peptide (EK1) (Lai et al., 2020) and interferon alpha (Dong et al., 2020). The latter originally being used for the treatment of hepatitis B (novaferon, Beijing Genova Biotech). However, the clinical efficacy of these new drugs for COVID-19 has not been proven and their safety has not been extensively tested.

Further, CQ and HCQ have been discussed as promising, cost-effective and easily available agents in the treatment of COVID-19 (Colson et al., 2020; Gao et al., 2020; Gautret et al., 2020). These are relatively old agents, introduced primarily for prophylaxis and treatment of malaria and also for rheumatic diseases (Lu, 2020). In vitro cell cultures, HCQ seems to be a more potent inhibitor of infection with SARS-CoV-2 than chloroquine (Wang et al., 2020; Yao et al., 2020). Both drugs, taken orally, may cause severe side effects (Goel and Gerriets., 2019) ranging from psychiatric symptoms (Good et al., 1982) to ocular toxicity (Schwartzman and Samson, 2019) to myocardial dysfunction (Blignaut et al., 2019), even at only low overdosage (Firsk-Holmberg et al., 1979). These side effects may be severe and, therefore, limit widespread application in vivo, at least at the present time. As Drosten (2020) pointed out, a major limiting factor of oral hydrochloroquine treatment lies in the fact that the drug may not reach the target, i.e. the surface of the lungs (https://www.pharmazeutische-zeitung.de/virologe-drosten-nimmt-stellung-zu-chloroquin; downloaded 04.02.2020) Instead, it is metabolized internally, requiring treatment dosages which, in turn, may cause toxic and sometimes even lethal side effects.

Here, we propose a different approach to the investigation of the effectiveness of the hydrochloroquine drug that would imply a direct application of the active agent to the respiratory tract.

The Hypothesis

We hypothesize that HCQ especially ***as an aerosol application*** will prevent or at least markedly reduce the replication rate of the SARS-CoV-2 virus ***in the early phase of the infection*** and subsequently substantially lower the number of severe pneumonias and casualties.

Why this hypothesis is different from current thinking

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This hypothesis is new since the major assumption in ongoing clinical studies and actual recommendations is that HCQ and CQ should be used in oral application form in patients with severe covid-19 pneumonia and only when other treatment strategies have failed. However, the typical clinical course of this infection suggests that the virus load in the respiratory tract increases stepwise starting with mild symptoms and ending in up to 15 % of patients with severe and potentially life-threatening pneumonia (Baud et al., 2020). Therefore, the treatment with a drug which inactivates the cell receptor for the virus should start after exposition with high risk, e.g., when one person was infected very recently with the virus or is in the early phase of the disease. Moreover, our hypothesis differs from the standard recommendation to try HCQ/CQ in a late phase of the disease when other antiviral drugs failed. We believe that a respiratory virus infection should be treated very early because the severe acute respiratory syndrome is caused by ion channel activity of the viroporin 3a which activates the NLRP3 inflammasome (Chen et al., 2019). Unfortunately, as of now, there is no evidence yet that HCQ/CQ has any inhibiting effect on this inflammasome activation.

How has this idea evolved?

The idea to propose application of HCQ/CQ as aerosol is generated because one major objection against the clinical efficacy of these drugs is that they have to be administered in relatively high oral dosages. Such high dosages may have several toxic side effects, strongly limiting their utilizability as preventive treatment. An aerosol application of drugs which are primarily intended to act on the respiratory system is well established for several drugs, e.g. in the treatment of asthma with corticosteroids (e.g. budesonide, Chen et al., 2019; Pauwels et al., 1997) and beta mimetica (e.g. fenoterol, Salome et al., 1981) and in the early treatment of influenza (during the first 48 hours) with neuraminidase blockers like zanamivir (Cass et al., 1999). Moreover, there are reports of undergoing clinical studies of aerosol interferon alpha (novaferon) for treatment of COVID-19 (Qiu et al., 2020) leading us to advocate a clinical trial to evaluate also HCQ/CQ in this application form.

Evaluation of the hypothesis

Why hydroxychloroquine might be efficacious in COVID-19

It has been demonstrated that the SARS-CoV-2 virus enters ACE2-expressing cells including alveolar epithelial cells of the lung and in other organs (Gentile and Abenavoli, 2020; Jia et al., 2005; Zhang et al., 2020), which has been shown before also for SARS-CoV-1. Therefore, during the infection of alveolar epithelial cells of the lung, the ACE2 receptor has a central function (Su and Wu, 2020).

The antimalarial drugs CQ and HCQ impair the terminal glycosylation of ACE2 without significant change of cell-surface. ACE2 increases the local pH value, which reduces the activity of cathepsin L needed for hydrolysis of the viral S protein and might influence the generation of pro-inflammatory cytokines (Devaux et al., 2020). Therefore CQ might be a potent inhibitor of SARS-CoV infection (Jia et al., 2005; Kearney, 2020; Keyaerts et al., 2004).

In vitro, CQ, starting with 0.1 µM inhibited and, moreover, completely prevented SARS-CoV infections in cell cultures at 10 µM, suggesting a prophylactic effect and preventing the virus spread 5 hours after infection. HCQ is threefold more potent than

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CQ in SARS-CoV-2 infected cells, resulting in the clinical recommendation to treat orally with 800 mg at the first day and at 400 mg on the following four days (Qiu et al., 2020).

Two major points of action are postulated for CQ/HCQ in the treatment of COVID-19: (1) they perturb the terminal glycosylation of the ACE2 protein and inhibit cell-binding of the virus, (2) the alkalizing medication elevates the pH value of the endosomes. Since Cathepsin L requires an acidic environment to crack the viral S protein, virus induced activities are reduced. Other possible explanations for the antiviral effect include a reduction in MAK kinase activation or a disruption of the maturation of the viral M protein. Further, CD8+ cells directed against the virus may be activated and thereby lead to a decrease of pro-inflammatory cytokines (Devaux et al. 2020).

Chinese scientists from Peking University found low inhibitory concentrations of 0.72 µM for the hydroxy derivative in direct comparison to chloroquine (5.47 µM) in cell culture experiments with the pathogen SARS-CoV-2. Both figures are EC50 values, that is, concentrations that cause half-maximal inhibition of virus replication. They calculated that with an initial dose of 400 mg twice daily and a subsequent dose of 200 mg hydroxychloroquine sulfate twice daily there should be significantly higher concentrations in the lung tissue than needed for in vitro inhibition. However, the concentrations have not been measured and clinical studies that examine the possible benefit of such treatment are not yet available (Yao et al., 2020).

Another group of Chinese virologists published slightly different EC50 values for the in vitro inhibition of viral replication by CQ and HCQ (3.8 µM and 4.1 µM at 0.02 MOI = multiplicities of infection). As the results depend on the type of cell culture, the cells used, the amount of viruses used for infection, the time of evaluation and other factors, this is not surprising (Wang et al., 2020; Liu et al., 2020).

Moreover, a first clinical study with more than 100 patients demonstrated superiority of chloroquine phosphate to controls in inhibiting exacerbation of pneumonia, improving lung imaging findings, promotion of virus-negative conversion, and shortening the disease without severe adverse reactions (Gao et al., 2020). In a non-randomized open-label trial in 20 patients, hydroxychloroquine treatment was significantly associated with viral load reduction/disappearance in COVID-19 patients compared to controls (Gautret et al., 2020).

Why the oral application form might have disadvantages

From a pharmacological standpoint, one major problem of oral treatment with chloroquine phosphate or hydroxychloroquine is that relatively high concentrations between 1-10 μM are needed to inhibit the glycosylation of the soluble ACE2 receptor at the alveolar surface in the lung. Therefore, the bioavailability of these drugs in the pulmonic target regions depends individually on intestinal resorption, hepatic first-pass metabolism and diffusion from the blood to the alveolar cells. This could in part be compensated by higher oral dosages, which are, however, limited by adverse and potentially toxic side effects.

Another problem can be that CQ and HCQ are accumulated in the liver, spleen, kidney, lungs and other organs. 100 to 500 times of the chloroquine plasma concentration is found in parenchyma cells and 1000 times in pigmented cells. Around 55% of it is bound to plasma proteins (pharmaceutical product information).

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From a clinical standpoint, potential fatal arrhythmias and drug-induced sudden cardiac death in rare cases or in case of overdose can be a resulting problem.

How can clinically be evaluated whether HCQ/CQ as aerosol is clinically efficacious for prevention and dampening severity of the course of illness?

Our hypothesis prompts to be tested in controlled randomized clinical studies. Currently, an aerosol preparation of HCQ is not commercially available. Therefore, experimental data is needed to examine whether it is possible to achieve and maintain an antiviral concentration of 1-5 μM in the alveolar cells which has been proven effective in vitro. In a first approximation, one can assume that in the normal adult, the lungs weigh approximately 1.000 g which is 0.014 of the whole body weight of 70 kg. Although it is difficult to predict in the lung the effects of blood perfusion and on the other hand accumulation of HCQ, it seems reasonable to substitute 2-400 mg HCQ b.i.d. in oral form (as recommended) and a bioavailability of 0.79 (McLachlan et al., 1994) with 2.2-4.4 mg HCQ b.i.d. per inhalation.

Since HCQ/CQ is an old drug with a known profile of side effects, also for much higher dosages, it might also be appropriate to perform open pilot studies with higher numbers of cases and compare (in a non-randomized study) the clinical course and final result in patients with similar symptoms but without HCQ inhalation.

For objective testing of the preventive potential, persons at risks like therapeutic staff following direct unprotected contact with corona patients as well as relatives of patients who have tested positive for SARS-CoV-2 and who are living in the same household should inhale HCQ in comparison to placebo during the incubation period of 5-7 days without symptoms. We would predict that the number of subsequent infections of the contact persons will be significantly lower in the verum group.

To test whether HCQ as aerosol lowers the severity of the course, a randomized comparison should be performed including patients with beginning mild symptoms who were actually tested SARS-CoV-2 positive in order to evaluate the effect on clinical symptoms including fever, cough, beginning pneumonia and other complications.

Finally, HCQ as aerosol could be tested preferentially as co-medication in more severely ill patients where an indication for oral HCQ treatment is given. The prediction would be that those with the co-medication will have a better treatment outcome than those in oral monotherapy with HCQ.

Empirical (own) data

Since there is currently no commercial aerosol application available, two of the authors (A.K., clinical director and B.W., medical student working at an ICU with acute COVID-19 patients) decided to test tolerability and possible side effects of the inhalation of HCQ, starting with a dosage of 1 mg b.i.d (dissolved in 2 ml of 0.9 % NaCl solution) which was stepwise increased up to 4 mg per day over a period of one week. Inhalation was well tolerated without relevant side effects. The only observation was after 4 days the feeling of a transient bitter taste in the mouth which lasted 2-3 hours after the inhalations.

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Consequences of the hypothesis and discussion

Why this treatment strategy is of potential great importance

If our hypothesis is true, HCQ as an aerosol might not only reduce the side effect potential of the oral application form but can also be clinically used as an efficient antiviral agent in the early phase of COVID-19 and eventually lower the rate of severely ill patients and fatalities. This might have great relevance for further prognosis and treatment of this often fatal disease.

Baud, D., Qi, X., Nielsen-Saines, K., Musso, D., Pomar, L., & Favre, G. (2020). Real estimates of mortality following COVID-19 infection. *The Lancet Infectious Diseases*.

Bai, Y., Yao, L., Wei, T., Tian, F., Jin, D. Y., Chen, L., & Wang, M. (2020). Presumed asymptomatic carrier transmission of COVID-19. *Jama*.

Battegay, M., Kuehl, R., Tschudin-Sutter, S., Hirsch, H. H., Widmer, A. F., & Neher, R. A. (2020). 2019-novel Coronavirus (2019-nCoV): estimating the case fatality rate–a word of caution. *Swiss medical weekly*, *150*(0506).

Blignaut, M., Espach, Y., van Vuuren, M., Dhanabalan, K., & Huisamen, B. (2019). Revisiting the Cardiotoxic Effect of Chloroquine. *Cardiovascular drugs and therapy*, *33*(1), 1-11.

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., ... & Li, X. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*.

Cass, L. M., Efthymiopoulos, C., & Bye, A. (1999). Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. *Clinical pharmacokinetics*, *36*(1), 1-11.

Chen, I. Y., Moriyama, M., Chang, M. F., & Ichinohe, T. (2019). Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. *Frontiers in microbiology*, *10*.

Chen Y. Adjunctive Corticosteroid Therapy for Patients with Severe Novel Coronavirus Pneumonia (COVID-19): a Randomized Controlled Trial. http://www.chictr.org.cn/showproj.aspx?proj=48777 [Accessed 03 April 2020].

Colson, P., Rolain, J. M., Lagier, J. C., Brouqui, P., & Raoult, D. (2020). Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*, *105932*.

Devaux, C. A., Rolain, J. M., Colson, P., & Raoult, D. (2020). New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?. *International Journal of Antimicrobial Agents*, 105938.

Dong, L., Hu, S., Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discoveries & Therapeutics*, *14*(1), 58-60.

Frisk-Holmberg, M., Bergkvist, Y., Domeij-Nyberg, B., Hellström, L., & Jansson, F. (1979). Chloroquine serum concentration and side effects: Evidence for dose-dependent kinetics. *Clinical Pharmacology & Therapeutics*, *25*(3), 345-350.

Gao, J., Tian, Z., & Yang, X. (2020). Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience trends*.

Gautret, P., Lagier, J. C., Parola, P., Meddeb, L., Mailhe, M., Doudier, B (…) & Honoré, S. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*, 105949.

Gentile, I., & Abenavoli, L. (2020). COVID-19: Perspectives on the Potential Novel Global Threat. *Reviews on Recent Clinical Trials*, *15*(2), 1.

Goel, P., & Gerriets, V. (2019). Chloroquine. In *StatPearls [Internet]*. StatPearls Publishing.

Good, M. I., & Shader, R. I. (1982). Lethality and behavioral side effects of chloroquine. *Journal of clinical psychopharmacology*, *2*(1), 40-47.

Hamer, O. W., Salzberger, B., Gebauer, J., Stroszczynski, C., & Pfeifer, M. (2020, March). CT morphology of COVID-19: Case report and review of literature. In *RöFo-Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren*. © Georg Thieme Verlag KG.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020. doi: 10.1016/S0140-6736(20)30183-5

Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, Farzan M, Wohlford-Lenane C, Perlman S, McCray PB Jr. (2005). ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. Journal of Virology 79(23), 14614-21.

Kearney, J. (2020). Chloroquine as a Potential Treatment and Prevention Measure for the 2019 Novel Coronavirus: A Review.

Keyaerts, E., Vijgen, L., Maes, P., Neyts, J., & Van Ranst, M. (2004). In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochemical and biophysical research communications*, *323*(1), 264-268.

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *International journal of antimicrobial agents*, 105924.

Lu, H. (2020). Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Bioscience trends*, *14*(1), 69-71.

Novel, C. P. E. R. E. (2020). The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi*, *41*(2), 145.

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *International journal of antimicrobial agents*, 105924.

McLachlan, AJ, Tett SE, Cutler DJ, Day RO (1994) Bioavalibility of hydroxychlorquine tablets in patients with rheumatoid arthritis. *Rheumatology*, Volume 33(3): 235–239

Pan, F., Ye, T., Sun, P., Gui, S., Liang, B., Li, L, (…) & Zheng, C. (2020). Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology*, 200370.

Pauwels, R. A., Löfdahl, C. G., Postma, D. S., Tattersfield, A. E., O'Byrne, P., Barnes, P. J., & Ullman, A. (1997). Effect of inhaled formoterol and budesonide on exacerbations of asthma. *New England Journal of Medicine*, *337*(20), 1405-1411.

Qiu, R., Wei, X., Zhao, M., Zhong, C., Zhao, C., Hu, J., ... & Chen, J. (2020). Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review. *medRxiv*.

Salome, C. M., Schoeffel, R. E., & Woolcock, A. J. (1981). Effect of aerosol and oral fenoterol on histamine and methacholine challenge in asthmatic subjects. *Thorax*, *36*(8), 580-584.

Schwartzman, S., & Samson, C. M. (2019). Are the Current Recommendations for Chloroquine and Hydroxychloroquine Screening Appropriate?. *Rheumatic Disease Clinics*, *45*(3), 359-367.

Su, Z., & Wu, Y. (2020). A Multiscale and Comparative Model for Receptor Binding of 2019 Novel Coronavirus and the Implication of its Life Cycle in Host Cells. *bioRxiv*.

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., ... & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research*, *30*(3), 269-271.

Wu, Z., & McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama*.

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P (…) & Zhan, S. (2020). In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*.

Zhang Z. Therapeutic effect of hydroxychloroquine on novel coronavirus pneumonia (COVID-19). http://www.chictr.org.cn/showproj.aspx?proj=48880 [Accessed 14 Feb 2020].

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... & Guan, L. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*.