

A MINI REVIEW OF STUDIES THAT INCLUDE THE THERAPEUTIC ROLE OF CHLOROQUINE AND HYDROXYCHLOROQUINE IN CORONAVIRUS DISEASE-19 (COVID-19)

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Recibido para publicación: 19-10-2020 - Versión corregida: 10-11-2020 - Aprobado para publicación: 11-11-2020

Al-msaoudi G, Sako J, Alzahrani M, Al-Hindi Y. **A mini review of studies that include the therapeutic role of Chloroquine and Hydroxychloroquine in coronavirus disease-19 (COVID-19).** *Arch Med (Manizales)*. 2021; 21(1):279-284. <https://doi.org/10.30554/archmed.21.1.4008.2021>

Summary

COVID-19 (Coronavirus Disease-2019) is now considered a public health emergency of that concerns the whole globe. Despite it is still not approved, the use of aminoquinoline drugs such as chloroquine and hydroxychloroquine are now in increasing, especially with the pandemic of coronavirus disease 2019 (COVID-19). This mini review highlights the main information's gathered of using the therapeutic purpose of both these medications in the extraordinary situation of coronavirus disease -19.

Keywords: Covid-19; therapeutics; Chloroquine; Hydroxychloroquine; review.

Una mini revisión de estudios que incluyen el papel terapéutico de la cloroquina y la hidroxiclороquina en la enfermedad por coronavirus-19 (COVID-19)

Resumen

COVID-19 (Enfermedad por coronavirus-2019) ahora se considera una emergencia de salud pública que afecta a todo el mundo. A pesar de que todavía no está aprobado, el uso de medicamentos de aminoquinolina como la cloroquina y la hidroxiclороquina ahora está aumentando, especialmente con la pandemia de la enfermedad por corona-

Archivos de Medicina (Manizales) Volumen 21 N° 1, Enero-Junio 2021, ISSN versión impresa 1657-320X, ISSN versión en línea 2339-3874, Al-msaoudi G, Sako J, Alzahrani M, Al-Hindi Y.

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virus 2019 (COVID-19). Esta mini revisión destaca la principal información recopilada sobre el uso del propósito terapéutico de estos dos medicamentos en la extraordinaria situación de la enfermedad por coronavirus -19.

Palabras clave: Covid-19; terapéutica; cloroquina; hidroxicloroquina; revisión.

Introduction

COVID-19 (Coronavirus Disease-2019) that is an emergency health situation that became a global issue [1]. The first instances of the brand-new coronavirus 2019 disease (COVID-19) have been suggested in December 2019 whilst a collection of sufferers turned into admitted to hospitals in Wuhan, with a preliminary analysis of pneumonia of unknown etiology. Initially, the outbreak of extreme acute respiration syndrome coronavirus 2 (SARS-CoV-2) turned into constrained to Hubei province, however it hastily unfolds to many different countries, compelling the World Health Organization to formally claim an international pandemic on March 11, 2020. Most deaths concerned older adults, lots of whom had underlying persistent diseases [2].

COVID-19 may be brought on through the virus (SARS-CoV-2) [3]. The disorder is transmitted through inhalation or touch with inflamed droplets and the incubation duration tiers from 2 to fourteen days. The signs are normally fever, cough, sore throat, breathlessness, fatigue, malaise amongst others. In maximum sufferers the disorder route is normally mild; however, in sufferers together with the aged and who suffers from comorbidities it could development to pneumonia, acute breathing misery syndrome (ARDS) and multi organ dysfunction [3]. It additionally been said a few sufferers with asymptomatic pattern [4]. Patients contracting the intense shape of the disorder represent about 15% of the cases [5]. The Specific analysis is through precise molecular assessments on breathing samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). Virus can also be detected withinside the stool and in intense cases, the blood [4].

There are numerous tablets had been used to deal with COVID-19 along with remdesivir, favipiravir, ribavirin, lopinavir-ritonavir (utilized in combination), and aminoquinoline (chloroquine (CQ) and hydroxychloroquine (HCQ)) [3]. The aminoquinoline tablets (chloroquine and hydroxychloroquine) at the moment are in expanded use globally as a potential, albeit unproven, remedy choice for coronavirus disorder 2019 (COVID-19). Both are artificial anti-malarial tablets with fast absorption [6,7].

The in vitro antiviral interest of CQ changed into first recognized withinside the overdue 1960s. Two research have proven anti-SARS-CoV interest, with excessive concentrations wished for antiviral impact. CQ impact changed into very clean to have a higher motion in inhibiting pneumonia complications, that ends in a higher pulmonary outcome, with excessive charge of lowering the period of the disease [4]. Hydroxychloroquine, a spinoff of CQ first synthesized in 1946, proved to be much less poisonous and greater potent [6]. Both capsules are water soluble, HCQ is greater soluble because of presence of hydroxyl organization and possesses plasma half-existence of 900 h and 1300 h. Chronic use of those capsules may also result in accumulation in tissues [8].

Method

We aimed to consist of posted scientific research that examine the healing position of CQ and HCQ in COVID-19. Pre-scientific research, case reports, case series, meta-evaluation and reviews. We searched those questions: What are the negative results which could seem whilst the usage of the CQ and HCQ? Can all and sundry use CQ and HCQ? What is an appropriate

dose that may be used for CQ and HCQ? what are the contraindications of CQ and HCQ?

Uses of Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine mainly used as antimalarial drugs. They are effective in reducing viral replication in other infections involving the SARS-associated coronavirus (CoV) and MERS-CoV [3]. HCQ is most commonly utilized in persistent inflammatory diseases, which includes systemic lupus erythematosus and rheumatoid arthritis [12-14].

Mechanism of action

In general, CQ and HCQ have more than one *mechanism* of movement and perhaps one or greater act towards viral infections and decrease mortality [10,11]. The ability drug goals depend upon the herbal cycle of this virus. The virus relies upon on pH-structured internalization and fusion with lysosomes. The pathway of each HCQ and CQ is displaying an elevation of pH. This, in turn, impacts viral replication. and facilitates in immune law and inhibition of the host cytokine typhoon because the antigen presentation is affected [12].

Chloroquine increases the pH of intracellular vacuoles. Inside the lysosomes it changes the catalysis activity of protein break-up pathways via acidic hydrolysis. It also alters endosomal macromolecule synthesis and in Golgi apparatus it affects post-translational modifications. It decreases the pH and interferes with the viral fusion process. chloroquine binds to the cellular receptors and changes the glycosylation. Chloroquine possesses selective and reversible immunomodulatory effect through its action on human CD4+ T-cells which is mediated by inhibition of JNK catalytic activity [10], and could be used to decrease the viral load in respiratory seconds, allowing less nosocomial and post discharge transmission [5].

Hydroxychloroquine exerts similar mechanism of antiviral action and some of the key

features are increases the pH, modulation of activated immune cells, downregulation of expression of Toll-like receptors (TLR), down-regulation of TLR-mediated signal transduction, interleukin-6 formation drops, reduces the formation of proinflammatory cytokines and other mediators to control inflammation [10].

Adverse effects

There are many aspect results of those tablets that can have an effect on the coronary heart, neurons, eye and ear. Both medicines extend the QTc language (extra than 500 milliseconds may want to cause extreme arrhythmias, rhabdomyolysis) and thus might also additionally placed sufferers at multiplied threat for torsade's de pointes and surprising death, the electrocardiographic (ECG) marker of behind schedule ventricular repolarization. Delayed repolarization allows early after depolarizations, that can cause a in all likelihood deadly ventricular arrhythmia referred to as torsade de pointes [10,11]. Amionquinolines, act via way of means of binding to and inhibiting the potassium channel protein manufactured from the gene KCNH2 (additionally referred to as hERG), thereby blockading the fast aspect of the behind schedule rectifier potassium current (IKr). Repolarization is likewise maintained via way of means of different currents, and its miles believed that human beings with impaired feature of those extra currents (consisting of IKs) are at extra threat for drug-brought about QT prolongation and torsade. This situation is taken into consideration as a lower in repolarization compensation, it could arise because of a situation like inherited lengthy QT c language syndrome, lower in potassium and magnesium levels. Bradycardia and coronary heart failure are different threat elements that sell torsade [10]. The use of CQ and HCQ might also additionally purpose vacuolization of cardiac and skeletal muscle cells via way of means of inhibit the interest of lysosomal phospholipases , and additionally each those tablets own affinity for melanin and have an effect on the macular cones ,The phagocytic interest of lysosomes

is declined at the photoreceptors and that they migrate closer to critical and peripheral areas in addition to induces epithelial atrophy and irreversible changes in photoreceptors [10]. Multiple research proven that the ones tablets can purpose a poisonous impact to the ear via way of means of unfavorable internal structures, that can cause lack of the experience of hearing, also can purpose tinnitus or imbalance stature. In addition, it turned into pronounced that pregnant ladies who obtained chloroquine remedy their newborns suffered from unusual cochleovestibular [11].

Who use it?

Patients elderly 18 to sixty-five years with mild, moderate, or extreme pneumonia [3]. Secondary to COVID-19 and normally used for greater than 70 years to deal with malaria. However, withinside the context of sufferers with extreme COVID-19, there's a look at increases sufficient crimson flags to prevent the usage of a high-dosage regimen (ie, 12 g of CQ at some stage in 10 days), due to the fact the dangers of poisonous outcomes overcame the benefits [6].

Interaction

There are pills recognized to lengthen the QT interval (i.e. quinolones, macrolides, ondansetron) in addition to numerous antiarrhythmic, antidepressant and antipsychotic pills [8]. Cytochrome P-450 gadget inhibitors, in addition to with different pills being recommended or evaluated in COVID-19 which include azithromycin and protease inhibitors [14].

CQ and HCQ is thought to have a CYP metabolism movement that arise via way of means of those enzymes CYPs 2C8, 3A4 and 2D6. Co-management with inhibitors and inducers of those isoenzymes may also growth or lower publicity to them, respectively, and dose modifications or extra tracking might be considered. Fluoxetine and paroxetine are inhibitors of each CYP3A4 and CYP2D6 and might consequently result in expanded degrees of CQ and HCQ, in flip growing the chance of QTc prolongation.

Other psychotropics which can be vital inhibitors of CYP2D6 consist of amitriptyline, bupropion and duloxetine. Carbamazepine induces CYP3A4 and might result in decreased degrees of CQ and HCQ [5].

Precaution

Blood trying out to rule out the improvement of anemia, thrombocytopenia or leukopenia in addition to serum electrolyte disturbances and/or hepatic and renal feature dysfunction. electrocardiography investigates any cardiovascular signs and affected person interviews to searching for the advent of visible and/or intellectual disturbance/deterioration [8].

Dose

Chloroquine became rather powerful in lowering viral replication, with an Effective Concentration (EC) 90 of 6.90 μ M that may be without problems attainable with widespread dosing, because of its favorable penetration in tissues, along with withinside the lung [8]. According to a consensus announcement from a multicenter collaboration institution in China, they advise a CQ-phosphate tablet, 500 mg two times consistent with day for 10 days for sufferers recognized as having mild, slight or excessive instances of novel coronavirus pneumonia and without contraindications to CQ [5]. The Dutch Center of Disease control (CDC), in a public report on its website, cautioned to deal with excessive infections requiring admission to the health center and oxygen remedy or admitted to the ICU with chloroquine, The cautioned routine in adults with most effective supportive care includes six hundred mg of chloroquine base (6 drugs A-CQ one hundred mg) accompanied with the aid of using three hundred mg after 12 h on day 1, then three hundred mg \times 2/die consistent with os on days 2–five days. the wishes for preventing the remedy at day five to lessen the hazard of facet effects, thinking about the lengthy half-existence of the drug, the want to distinguish among regimens primarily based totally on chloroquine phosphate and chloroquine base on account

that 500 mg of the primary correspond to three hundred mg of the second [12].

HCQ is suggested with a loading dose of 1200 mg each day for 3 days accompanied with the aid of using a renovation dose of 800 mg each day for the subsequent weeks mainly in sufferers with excessive sample of the disease [2].

Indian Council of Medical studies hurriedly issued a guiding principle and moreover endorsed using CQ and HCQ as a prophylactic agent withinside the near contacts, along with the fitness care workers [8]. Vero cellular strains highlighted using an excessive loading dose of CQ accompanied with the aid of using a low renovation dose to aid its pharmacokinetic belongings of better mobile accumulation and extended removal half-existence, HCQ exhibited a higher in vitro anti-SARS-CoV-2 pastime than CQ. CQ functioned at each access and post-access degrees of the SARS-CoV-2 contamination in Vero E6 cells. China researchers discovered that HCQ may have a useful impact over CQ for prophylactic use, the most each day dose of CQ is 500 mg, even as HCQ may be given at a better each day dose 1200 mg, that is equal to 750 mg of CQ, however it appears untimely to advise CQ and HCQ as prophylaxis of COVID-19 [14].

Contraindications

For sufferers have been age underneath 18 years; sufferers with extreme situations together with malignancies, heart, liver, or kidney disorder or poorly managed metabolic diseases, being pregnant or lactation [3]. In a few examine they observed short-time period HCQ remedy has been taken into consideration secure in being pregnant [13], sufferers have allergic reaction to CQ or HCQ; extreme hepatic impairment (for example, Child Pugh grade C, alanine aminotransferase extra than fivefold the top limit); and extreme renal impairment (predicted glomerular filtration rate ≤ 30 mL/min/1.73 m²) or receipt of non-stop renal substitute therapy, hemodialysis, or peritoneal dialysis [3].

Conclusion

Off-label use of chloroquine can be observed with the aid of using numerous concerns; the primary is affected person protection. Such use ought to be observed with the aid of using near tracking. An epidemic is rarely an appropriate placing to do this. The moral method to off-label drug use additionally differs among countries, elevating questions concerning equity. Finally, chloroquine stays a pivotal drug withinside the remedy of Malaria in lots of locations withinside the world. Off label drug use can create essential drug shortages [8].

HCQ, at a better dose, can also additionally have a stronger antiviral interest compared to that of CQ. Furthermore, HCQ has a higher protection profile because of decrease tissue accumulation compared to CQ. An extra benefit of HCQ is its protection in being pregnant in contrast to CQ. Thus, if tested beneficial, HCQ can be a prophylactic drug towards COVID-19 [14].

The tracking of aspect outcomes desires to be endured even after discontinuation of remedy because of extend half-existence of chloroquine and hydroxychloroquine [11].

Ethics Approval: was approved from Umm Al-Qura University.

Availability of Data and Materials: research data can be provided upon request.

Authors' Contribution: Ghdi Al-msaoudi, Jumana Sako and Maha Alzahrani conceptualization; methodology; writing - review and editing manuscript; Yosra Al-Hindi: writing - reviewing and editing.

Acknowledgment

We thank Umm Al-Qura pharmacy collage for all the support given.

Conflicts of interest: competing Interest Author declares that there are no significant competing financial, professional, or personal interests.

Sources of funding: no funding source was available.

Cited literature

1. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. **A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19.** *J Crit Care.* 2020; 57:279-283. <https://doi.org/10.1016/j.jcrc.2020.03.005>
2. Borba MG, Val FF, Sampaio VS, Alexandre MA, Melo GC, Brito M, et al. **Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial.** *JAMA network open.* 2020; 3(4):1-14. DOI: 10.1001/jamanetworkopen.2020.8857
3. Tang D, Li J, Zhang R, Kang R, Klionsky DJ. **Chloroquine in fighting COVID-19: good, bad, or both?.** *Autophagy.* 2020; 25:1-3. <https://doi.org/10.1080/15548627.2020.1796014>
4. Singh AK, Singh A, Singh R, Misra A. **Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis.** *Diabetes Metab Syndr.* 2020; 14(4):589-596. <https://doi.org/10.1016/j.dsx.2020.05.017>
5. Bishara D, Kalafatis C, Taylor D. **Emerging and experimental treatments for COVID-19 and drug interactions with psychotropic agents.** *Ther Adv Psychopharmacol.* 2020;10:1-15. DOI: 10.1177/ 2045125320935306
6. Colson P, Rolain JM, Raoult D. **Chloroquine for the 2019 novel coronavirus SARS-CoV-2.** *Int J Antimicrob Agents.* 2020; 55(3):1-2. <https://doi.org/10.1016/j.ijantimicag.2020.105923>
7. Das S, Bhowmick S, Tiwari S, Sen S. **An Updated Systematic Review of the Therapeutic Role of Hydroxychloroquine in Coronavirus Disease-19 (COVID-19).** *Clin Drug Investig.* 2020; 2020:1-11. <https://doi.org/10.1007/s40261-020-00927-1>
8. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. **QT prolongation, torsades de pointes and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review.** *Heart Rhythm.* 2020; 17(9):1472-1479. <https://doi.org/10.1016/j.hrthm.2020.05.008>
9. Patil VM, Singhal S, Masand N. **A systematic review on use of aminoquinolines for the therapeutic management of COVID-19: Efficacy, safety and clinical trials.** *Life Sciences.* 2020;117775. <https://doi.org/10.1016/j.lfs.2020.117775>
10. Prayuenyong, P, Kasbekar, AV, Baguley, DM. **Clinical Implications of Chloroquine and Hydroxychloroquine Ototoxicity for COVID-19 Treatment: A Mini-Review.** *Front Public Health.* 2020; 8:1-6. DOI:10.3389/fpubh.2020.00252
11. Sarma P, Kaur H, Kumar H, Mahendru D, Avti P, Bhattacharyya A, et al. **Virological and clinical cure in COVID 19 patients treated with hydroxychloroquine: a systematic review and meta-analysis.** *J Med Virol.* 2020; 92(7):776-785. DOI: 10.1002/jmv.25898
12. Shah S, Das S, Jain A, Misra DP, Negi VS. **A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease 19 (COVID19).** *Int J Rheum Dis.* 2020; 23(5):613-619. DOI: 10.1111/1756-185X.13842
13. Ji LN, Chao S, Wang YJ, Li XJ, Mu XD, Lin MG, et al. **Clinical features of pediatric patients with COVID-19: a report of two-family cluster cases.** *World Journal of Pediatrics.* 2020;16:267-270. <https://doi.org/10.1007/s12519-020-00356-2>
14. Tripathy S, Dassarma B, Roy S, Chabalala H, Matsabisa MG. **A review on possible modes of actions of Chloroquine/Hydroxychloroquine: Repurposing against SAR-COV-2 (COVID 19) pandemic.** *Int J Antimicrob Agents.* 2020; 56(2):1-7. <https://doi.org/10.1016/j.ijantimicag.2020.106028>

