Activity of the chloroquine/hydroxychloroquine and mefloquine in front of the SARS-CoV-2

Abstract

Introduction: Identifying the main advances in the pharmacological and clinical management of the pandemic COVID-19 and SARS-CoV-2, the most recent and currently taking lives worldwide, is to priority of the scientific community that to date have rehearsed and joined efforts in order to respond with effective treatments that stop the progression of the viral infection and manage to recover the patient.

Objective: To document available information on the effects of the antimalarials chloroquine / hydroxychloroquine and mefloquine in severe acute respiratory syndrome, generated by SARS CoV-2, according to updates of the best scientific evidence, according to the evolution of the epidemic.

Material and Methods: Descriptive documentary study consisting of the selection and review of scientific material whose subject is COVID-19 and SARS-CoV-2 based on published evidence from bibliographic sources seeking different therapeutic options to combat the disease at the same time ace necessary preventive measures plough implemented worldwide. The databases consulted were Scopus, Head office Pubmed and Scielo.

Results: 132 articles related to the search were obtained in the first instance, of which they were filtered and prioritized by thematic relevance until 60 articles with to broad relationship were located. The largest number of articles was published between 2015 and 2020 (n = 26; 43.3%). It have been shown that the mechanism of today’s SARS-CoV-2 is similar to that of SARS-CoV and MERS-CoV, in the same way; they share the symptoms shown by patients with COVID-19 such ace: fever, non-productive cough, dyspnea, myalgia, fatigue, normal or decreased white blood cell counts.

Conclusions: The activity of hydroxychloroquine and chloroquine in viruses is the same since the mechanism of action of these two molecules is identical. Given the pandemic, the use of these drugs is suggested in the management of patients with SARS CoV-2 / COVID-19 infection that have no contraindication for their use and the cardiac toxicity derived from these ace to cause of mortality should not be forgotten, due to what therapy must be individualized. The mefloquine is not recommended due to its neurotoxic effect and association with neuropsychiatric adverse reactions.

Keywords: COVID-19, SARS-CoV-2, therapeutic option and pandemic

Introduction

The SARS-CoV-2, was discovered in 2019 in Wuhan, province of Hubei of China and was sequencer and isolator in January of 2020.1 SARS-CoV-2 is associated with a continuous shout of atypical pneumonia designated Covid-19, that has affected to more than 2 millions of people and has left more than 200 one thousand died in the world to April of the 2020, enciphers that it can increase even more. On 30 January 2020, the WHO declared the public epidemic of SARS-CoV-2 like a sanitary emergency of international interest.1,2 So much the SARS-CoV like the SARS-CoV-2 are closely related and origin Aron in bats, that probably servant like reservoirs for these two viruses, but the intermediate guest SARS-CoV-2 keeps on being unknown.3,4 Like result of the big impact generated, look for different therapeutic options to combat the illness at the same time that they implement the measures of necessary prevention all over the world. By the previous, the present review centers in the study of drugs antimalarics as they are: chloroquine/hydroxychloroquine, at present used; initiating with a review of the structure of SARS-CoV-2 and gives a look to the drug mefloquine like therapeutic option in front of the pandemic.

Material and methods

Descriptive study is the consistent documentary in the selection and review of scientific material whose subject is COVID-19 and SARS-CoV-2 with bibliographic sources that look for different therapeutic options to combat the illness and warn all over the world. The databases consulted were Scopus, Pubmed central and Scielo. The review applied took into account scientific sources of the years 2015 to the 2020 for builder on the structure of the virus, genome and virulence, besides mechanisms of action of the antimalarics and clinical essays for evidentiary the action antiviral cloroquine/ hidroxicloroquine and mefloquine. The terms of research employed for the obtaining of the information were: COVID-19, SARS-CoV-2, therapeutic option and pandemic. , the research allowed the achievement of 132 articles related with the research, of which were filtered and prioritised by thematic relevance until situating 45 articles with wide relation on the effects of the antimalaric cloroquine/ hidroxicloroquine and mefloquine in the acute respiratory syndrome severe, generated by the SARS-CoV-2.
Development

Pathogenesis of the infection by SARS-CoV-2

The SARS-CoV-2 belongs to the gender β of the coronavirus (CoV) which are virus wrapped with a genome of positive RNA, pertaining to the family Coronavirus of the order Nidovirales. His genome is similar to the of the CoV and contains at least ten frames of reading opened (ORF). The ORFs of SARS-CoV-2 in a third of the genome encode four structural proteins main: spike (Spike) (S), wrapping (And), nucleocápside (N) and proteins of membrane (M), as well as several proteins accessories with unknown functions that do not participate in the replication viral. Between these proteins, Spike (S), is a glycoprotein transmembrane that forms homotrímers and projects of the surface viral, it comprises two subunited functional managers of the union to the receptor of the cell guest (subunited S1) and fusion of the virus and the cellular membranes (subunited S2). On the other hand, the structural proteins (ns1-ns16) form the complex replicase-transcriptase viral and reorganize the membranes that originate of the reticle endoplasmic rugs (RER) in vesicles of double membrane where produces the replication viral and the transcription (Figure 1).

Although the pathogenesis of COVID-19 today day is object of study, the mechanisms are very similar to the ones of SARS-CoV and MERS-CoV and in fact the symptomatology showed by the patients with COVID-19 as they are: fever, cough no productive, dyspnea, myalgia, fatigue, headcounts of normal leucocytes or diminished and radiographic evidence of pneumonia is similar to the associated with SARS-CoV and MERS-CoV. It has reported that the protein S game a paper determinant in the entrance of virus in the cells guest. Being the union of the protein S to ACE2 for the SARS-CoV and DPP4 for MERS-CoV and the back negative regulation of this receptor what contribute to the pulmonary injury during the SARS-CoV and MERS-CoV.

The union of the virus with the receptors of the cell guest is a determinant in the pathogenesis of the infection and also governs the tropism viral of the virus. The glycoprotein S of SARS-CoV-2 joins to his cellular receptor, ACE2 of the human cells. After the fusion of the membrane, already was directly with the membrane of the cell guest or with the membrane of the endosome, the genome viral of RNA frees in the cytoplasm, and the RNA revisited to allow the translation of the two polyproteíns, the transcription of the RNA subgenomics and the replication of the virus. After the replication and the synthesis of RNA sub-genomic, the structural proteins virals, S, and M translate and insert in the reticle endoplásomic (RE). These proteins move along the road secretor to the reticle endoplásomic-intermediate compartment of Golgi (ERGIC). There, the genomes virals encapsulated by the protein N sprout in the membranes of the ERGIC that contain structural proteins virals, forming virions mature (Figure 2).

Figure 1

The coronavirus have a genome of RNA single chain (ssRNA) of positive sense and size 26and32 kb of size. In SARS-CoV, MERS-CoV and SARS-CoV-2, ORF1 to / b encode polyproteíns that form the complex of the replicase l transcriptase viral. The others ORF encode four structural proteins main: proteins of spike (S), wrapping (And), nucleocápside (N) and membrane (M), as well as several proteins accessories.

Source: X. Li Et al., Molecular immune pathogenesis and diagnosis of COVID-19, Journal of Pharmaceutical Analysis.

After the assembling, the virions are transported to the cellular surface in vesicles and freed by exocytosis. In several coronavirus, the protein S that does not assemble in virions happens to the cellular surface where mediates the fusion cell-cell between the cells infected and the adjacent cells no infected. This drives to the training of giant cells multinucleated, what allows that the virus propagate inside an organism infected without being detected or neutralized by specific antibodies of the virus.

The antimalarial like alternative of treatment antiviral

At present it does not exist a medicine or specific treatment for the illness caused by the SARS-CoV-2; for which employs and looks
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for test if the existent drugs, like the antimalarials and some antivirals are effective in the treatment of the illness, the previous due to the fact that develop new specific medicines from zero could take several years. Inviter, the chloroquine/hidroxicloroquine has showed activity antiviral against virus DNA and RNA, activity that has related mainly to his capacity to affect the entrance of the viruses to the cell guest for being east a step dependent pH and inhibit the replication viral. unfortunately no always the results have been reproducible in the clinical essays.

Figure 2 Process of union to the receptor of the human cell, process of replication, assembling and release of the virión from the cell infected and key places of action of the chloroquine/hidroxicloroquine Source: Of Wit, And., they Go Doremalen et al.,N., SARS and MERS: Recent insights into emerging coronaviruses. Nature Reviews Microbiology.

In spite of the studies invitro made by Keyaerts and Masakazu with HCoV-OC43 and HCoV-229 respectively to show the therapeutic profits of the inhibition viral by chloroquine the results even are not conclusive and even consider controversial, in front of the absence of better evidence and the situation of public health, authorised the use of chloroquine like line of treatment in the patients with COVID-19 and according to the Chinese authorities report improvement in the symptomatology and images tomográfics in the patients infected by which at present carry out clinical essays to evaluate the chloroquine like a therapy anti-COVID-19.

Activity antiviral of the chloroquine/hidroxicloroquine

The chloroquine (CQ), is a 4- aminoquinoline known from 1934. In addition to his known effects antimalaric, the medicine has biochemical properties that they could apply against some infections virales. The chloroquine/ hidroxicloroquine belong to the same molecular family; but in spite of having a pharmaco-cinética similar the clinical indications and the doses toxicas of these drugs differ slightly. It is characteristic of these drugs the variability interindividual in the absorption, sand distribute widely in the muscular fabric, liver, spleen, kidneys, lungs, blood cells, glands pituitaria and suprarenal and fabrics that contain melanin, sand metabolizan in the liver and excrete by renal road. So much the chloroquine like the hidroxicloroquine are feeble bases that affect the sour vesicles that drive to the dysfunction of several enzymes. Extracelular, the chloroquine/hidroxicloroquine is present mainly in a form protonate that, because of his positive load, is unable to cross the membrane plasmática. However, the portion no protonate can increase to the intracellular compartment, where, to his time, proton of way inversely proportional to the pH, in accordance with the law of Henderson-Hasselbach. Once inside, the nitrogen’s of the chloroquine (and quinines in general) warn the acidification when absorbing a big quantity of hydrogens that simply interaction with the nitrogen and afterwards the chloroquine loads positively, an ionic interaction that hampers that the endosome acidify. Therefore, the chloroquine goes to have preference by the organelles where the pH is low like the endosome, the vesicles of Golgi and the lysosomes.

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The result is a tampon that keeps it to a higher pH and avoids that it go back the sufficiently sour as to be functional. The enzymes of the organelle cannot work because the group donor will be an ion of hydrogen, disabled the hydrolysis required for the replication of the coronavirus. This means that all type of events in the cell are unable to work of optimum way, including the replication viral.\textsuperscript{28,29}

Having In account these characteristics has n described different mechanisms through the drugs can affect the cycle viral (Figure 2):

A. The cloroquine can inhibit the start of the cycle viral when interfering in the union of the virus with his receptor in the cellular surface. The previous has associated to his capacity of indigo the quinone reductase \textsuperscript{2,28} that are involved in the biosynthesis of the acids siálicos which find presents in the proteins transmembrane cellular and is a compose you critical of the recognition of ligands. This possible interference with the biosynthesis of acid siálico could explain the wide spectrum antiviral of these drugs, since the viruses like the coronavirus human hCoV-0x43 and the ortomixovirus use rests of acid siálico like receptors.\textsuperscript{31} It is possible that the cloroquine interfere with the glycosylation of the receptor ACE2, avoiding like this the union of the SARS-CoV-2 to the objective cells.\textsuperscript{32}

B. The cloroquine also can interfere with the entrance viral mediated by the endosome dependent of the pH of the viruses wrapped like the virus Dengue or the virus Chikungunya probably by the inhibition of endocytosis and/or the fast elevation of the pH endosómico and the cancellation of the fusion virus-endosome, inhibiting like this the training of the car phagosome.\textsuperscript{33,34}

C. Blockade of the cycle of replication viral; and absence of a drug antiviral, the virus directs to the compartment lysosome where the low pH, together with the action of the enzymes, allows the release of the nucleic acid infectious and, in several cases, the necessary enzymes for his replication, Sand discovered that the inhibition of the virus of the hepatitis To mediated by cloroquine associates with the elimination of the coating, blocking like this all his cycle of replication.\textsuperscript{29,30}

D. The cloroquine also can interfere with the modification poststructural of the proteins viral. These modifications postaducionales, that involve proteases and glyclosytransferases, occur inside the reticle endoplasmic or the vesicles of the network trans-Golgi and can require a low pH.\textsuperscript{35} Using the coronavirus no human, showed that the intracelular place of the gemanation of the coronavirus is determined by the location of his proteins M of membrane that accumulate in the complex of Golgi further of the place of the gemanation of the virión, what suggests a possible action of l to cloroquine in SARS-CoV-2 in this step of the cycle of replication.\textsuperscript{37}

E. In addition to affecting the process of maduration of the virus, the modulation of the pH by the action of the cloroquine can alter the maduration of the protein viral M and interfere with the assembling and the training of viriones and the recognition of the antigeno viral by the cells dendriticas, what occurs through a dependent road of the receptor type Toll-like (TLR)\textsuperscript{39} the cloroquine inhibits the phosphorylation (activation) of the protein quinase activated by mitogen p38 (MAPK) in the cells THP-1, as well as the caspasa-1.\textsuperscript{40}

Mefloquine

The mefloquine is an analogous synthetic of the quinine indicated for the prevention and the treatment of the malaria. As they have registered it several news means is being employed in clinical essays to verify his efficiency and security in the control in the illness COVID-19, but still does not have conclusive results. In spite of the previous also have made multiple studies of his activity antiviral standing out the made by Brickelmaier et al in the year 2009 where showed invitro that this drug inhibits the replication of the DNA viral, of the JCV (virus John Cunningham) after the entrance of the virus to the cell, but is not able to inhibit the entrance of the virus.\textsuperscript{41} During the 2017 the mefloquine was employ to in different essays invitro to test if it was able to block the infection of human cells by virus Zika (ZIKV), but did not obtain conclusive results.\textsuperscript{42} In spite of the existence of diverse clinical essays where has showed the activity antiviral of the mefloquine\textsuperscript{43,44} it is important to take into account that this medicine is neurotóxic, causes adverse reactions severe neuropsychiatric like anxiety, confusion, convulsions, attacks of panic, nightmares, aggressiveness, agitation, depression, paranoia, cognitive deterioration, psychosis.\textsuperscript{45} Until where knows today day to being object of investigation his effectiveness like medicine for the current pandemic of COVID-19, therefore, his use still is not recommended.

Conclusion

The activity of the hidroxicloroquine in the viruses is the same that the one of the cloroquine since the mechanism of action of these two molecules is identical. In front of the pandemic suggests the use of hidroxicloroquine or cloroquine in the handle of patients with infection by SARS CoV-2/ COVID-19 that do not have contraindication for his use and does not have to forget the derivative cardiac toxicity to these drugs like cause of mortality, by what the therapy has to be individualized. On the other hand, it does not recommend the use of mefloquine by his effect neurotoxic and association to adverse reactions neuropsychiatric. In the actuality develop of simultaneous way and in multiple international cooperation clinical essays on the efficiency of the at present used drugs, and in spite of the enormous scientific evidence around the drugs studied greater fault compression on the virus and therefore only it remains to recommend preventive measures.

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Conflicts of interest

Author declares that there is no conflict of interest.
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