Chloroquine Related To Malaria and Its Promising Appications for Codiv-19 Treatment

Abstract: Aim: this article describes the use of chloroquine as an antimalarial agent with potential antivirotic indications for COVID-19 infections. Methods: On line searches and gray literature have been used in the construction of this articles, whose database include PUBMED Central, BVS/BIREME, Web of Science, Science Direct, Higher Level Personnel Improvement Coordinator (CAPES), Periodic Door (Portal de Periódicos da CAPES, The Cochrane Library and PROSPERO). Results: chloroquine and hydroxychloroquine has shown appropriate clinical reports when associated with the antibiotic Azithromycin. It has been authorized for the clinical treatment of grave acute forms of COVID infections by countries like Brazil and USA. Conclusions: Chloroquine seems to have potential antivirotic properties that may be useful in the treatment of the grave acute forms of COVID-19 associated with Azithromycin. Nevertheless, its indication must include ECG monitoring due to the risk of cardiac QT prolongation able to cause sudden death.

Keywords: Mitotic depressor; DNA.

INTRODUCTION

The first reports of the plant that originated chloroquine appeared in Peru, used by Indians who used the bark of the trees of the chincona officinalis plant, used as teas, to combat chills and fever in the 17th century (FERN, 2020). As trade between the Americas and Europe increased, the early reports of this plant appeared in 1633, being indicated for the treatment against malaria basically. It is estimated that in Africa alone, more than 200 million people suffer from malaria, and that more than 1 million deaths per year are in fact caused by malaria (FOYE, 1995). Even today, there is a constant search for the discovery and development of insecticides and vaccines of practical use that are effective and safe in the tireless fight against this protozoan disease (BRUCE-CHWATT, 1988). The drug that preceded chloroquine was quinine, and it was first isolated from the extract in 1820. In this way, antimalarial drugs have on the road of science for nearly 200 years.

The search for and improvement of antimalarial drugs is not new and began in the years of the rise of Nazism just before World War II. Chloroquine was officially discovered in 1934 by Hans Andersaq and collaborators under the name "Resochin", developed by Beyer laboratories (KRAFTS, 2012). It remained virtually ignored for a decade, as it was considered by some researchers to be too toxic for use in humans, and therefore had virtually been forgotten. Instead, a similar drug was used, 3-methyl-chloroquine, which entered the market under the name of Sontochin, in the middle of World War II. After the definitive entry of allied forces in North Africa, more specifically in Tunisia, the drug Sontochin fell into the hands of the Americans, who sent the material back to the USA to be analyzed and researched, leading to the definitive rediscovery of the chloroquine to be used in the parasitic infections that affected their soldiers. Thus, at the end of the worldwide conflict, chloroquine entered in clinical practice in 1947, indicated for the prophylactic treatment of malaria (SNEADER, 2005).

In the mid-1950s, the world scientific community definitively indicated chloroquine to be used in malaria chemotherapy, and also concluded that its congeners; primaquine and quinine; in addition to dihydropholate reductase inhibitors, such as pyrimethamine, were at the time the best options, more specifically when associated with sulfonamides, sulfonas and tetracycline (OROLKOVAS, 1975).

In 2019, the COVID-19 pandemic was established, an acute respiratory disease caused by severe acute respiratory syndrome 2 coronavirus (SARS-CoV-2). In the development of this work, the pandemic is still ongoing.
disease was first identified in Wuhan, Hubei Province, People’s Republic of China, on December 1, 2019, and the first case was reported on December 31 of the same year (OMS, 2020; International Health Regulations Emergency Committee, 2019) The virus is believed to have a zoonotic origin, because the first confirmed cases were mainly linked to the Huanan Seafood Wholesale Market, which also sold live animals (BJ News, 2020; Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020).

The objective of this work was to relate chloroquine in the treatment of infections caused by CODIV-19 through a literature review.

The biology of malaria infection

Human malaria is basically caused by five species of mandatory intracellular protozoa, of the genus Plasmodium, which reproduce asexually in humans, and sexually in females of transmitting mosquitoes, of the genus Anopheles (INDER, 1973). Each species has peculiar morphological characteristics, in the same way that the disease caused by each of them is also; namely: Plasmodium falciparum (1); causes malignant 48 hour malaria, which is considered the most dangerous form of human malaria capable of producing a fulminant infection in non-immunized individuals, and may certainly lead to death if not adequately treated. If treatment is only started after the proof of parasitemia, such delay may lead to an irreversible state of shock, and death may occur even after peripheral blood is free of the parasite. Therefore, early treatment causes the infection to respond promptly without recurrences (VERBEECK, 2005).

Plasmodium vivax (2); producer of benign 48 hour malaria, presents much milder clinical symptoms than its homonym falciparum, with low mortality rate in untreated adults, with relapse characteristics that may occur up to two years or more of primary infection. Plasmodium ovale (3) produces rare malaria infections, with periodicity and recurrences similar to those of P. vivax, but clinically milder and more easily curable. In turn, Plasmodium malariae (4) causes 72 hour malaria, a very common infection in certain areas of the tropics. Its clinical manifestations may occur years after primary infection, but are much rarer than in cases of P. vivax infection (VERBEECK, 2005). (5) The last parasite discovered as able to cause malaria was Plasmodium knowlesi. It is a malaria parasite found in macaques from Malasia (long-tailed and pig-tailed) that was reported in 2004, in Sarawak, Malasian Borneo. Infections concerning this parasite have been reported throughout Southeast Asia. It was thought that it was only able to infect macaques. In this way, human infections were unknown and remained undiagnosed until molecular detection methods that could distinguish it became available (WHITE, 2008).

Although malaria can be transmitted via blood transfusion from infected patients, humans typically contract the disease through sporozoites injected by the bite of infected females. Parasites quickly leave the bloodstream and are located in the cells of the hepatic parenchyma, where they multiply, develop and become tissue schizontes. This tissue state (pre-erythrocyte or exoerythrocyte) is asymptomatic, and lasts from 5 to 16 days, depending on the plasmodium species. The tissue schizontes then break down the cells that contain them, each releasing thousands of merozoites. Afterwards they enter the bloodstream; invade erythrocytes, and initiate the erythrocyte phase or stage of infection. After this stage, it no longer invades other tissues, so there is no tissue phase in blood transfusion-induced malaria infections. Within erythrocytes, most parasites develop asexually from young annular forms to trophozoites and, finally, mature schizontes. Erythrocytes containing schizontes within end up breaking, each releasing from 6 to 24 merozoites that cause intense febrile clinical attack. The released merozoites infect other erythrocytes that continue the cycle until they cause the death of the host, or until the infection is halted by medications or by adaptive immunity. The periodicity of parasitemia and febrile clinical manifestations in 48 hour or 72 hour malaria therefore depends on the synchronization of schizogonia of the erythrocyte phase of a generation of parasites (STECK, 1971).

Some erythrocyte parasites differ in sexual forms known as gametocytes. After the blood has been ingested by a female of the anopheline mosquito, the loss of the male gametocyte flagellum takes place, followed by male gametogenesis and fertilization of the female gametocyte in the digestive tract of the insect, resulting in the zygote that develops in the wall of the digestive tract, in the form of oocyst, ending up giving life to the infecting form, which is the sporozoite that invades the salivary glands of the insect. Thus, the mosquito can finally infect another human host by exerting hematophagy through bite (ORGANIZACION MUNDIAL DE LA SALUD, 1964).

The duration of the erythrocytic cycle depends directly on the species of plasmodium responsible for the illness. Plasmodium: P. knowlesi apparently has the shortest cycle, around 24 hours, while for P. falciparum, P. vivax, and P. ovale, it is virtually 48 hours, while P. malariae, has the longest cycle; of 72 hours (GAMHAM, 1966).

Chloroquine and Its Congeners
Chloroquine is part of a large series of 4-amino-quinolines that have been thoroughly studied in the vast interwestern antimalarial research program conducted in the United States in the middle of World War II, being considered a relatively already known for having its clinical effects evaluated by years of clinical practice (WALACE, 1994). The aim of the American program was to discover and use suppressive drugs that were more effective and less toxic than quinacrine, an acridine derivative that is no longer used in malaria chemotherapy due to its toxicity and the inability to cure malaria caused by P. vivax, or acting as a causal prophylactic (RYNES, 1998). Although 4-aminoquinolines had been previously described as potential antimalarials by Russian researchers, no greater attention was paid to this chemical group; until the French reported that 3-methyl-7-chlorine-4 (4-diethylamino-1-methylbutylamino) quinoline (SN-6911; SONTCHIN, SONTQVIN) was well tolerated and had great activity in human malaria (PETERS, 1970). Hence, in 1943, thousands of these compounds were synthesized and tested for malaria activity in birds and toxicity in mammals. From this series, ten of them were then studied in human volunteers with experimentally induced malaria. From these, chloroquine has been shown to be the most promising drug and has been released for clinical trials. When the war ended, it was discovered that the substance had been synthesized and studied by the Germans since 1934, under the name RESOCHIN, being presented as diphosphate in the form of white powder, bitter, soluble in water. Their solutions, however, were considered stable (ROCKWELL, 1978).

Chloroquine has the same alkyl lateral chain as quinacrine, differing from having a quinoline nucleus instead of acridine, and also because it does not have the methoxy radical. Chloroquine also bears much resemblance to paquine, and pentaquin (obsolete antimalarials derived from 8-aminoquinoline); differing from them in the position of the alkyl lateral chain and by having a chlorine atom in place of the nucleus methoxy radical (PINDER, 1973). Chloroquine forms d, l and dl were indistinguishable in the potency tests in duck malaria, but the isomer d is slightly less toxic than the l isomer in mammals. The 4-aminoquinolines that show more pronounced antimalarial activity in both poultry malaria and human malaria have a chlorine atom at position 7 of quinoline. Substitution by methyl radical at quinoline position 3 reduces activity and additional replacement by methylene position 8 completely eliminates activity. The details of the relationship between structure and activity of chloroquine and its collaborators were discussed by Berliner et al., 1948.

**Pharmacological Effects**

Although chloroquine has been developed primarily as an antimalarial drug, it has several other pharmacological properties. Its use in the treatment of amoebiasis was satisfactory (POWELL, 1971). Due to its anti-inflammatory properties it has also been used in the treatment of rheumatoid arthritis (BAGNAL, 1957) and, more frequently, in discoid and systemic lupus erythematosus (RAINSFORD, 2015); its effectiveness however in the last indication is controversial (DUBOIS, 1978).

Chloroquine has also been used with oxyto in the treatment of photo allergic reactions, such as late cutaneous porphyria, solar urticaria and polymorphic eruption; whereas in these conditions much higher doses are necessary than in malaria, which requires weighting and caution when calculating the risk/benefit ratio in relation to its toxicity (ISAACSON, 1982).

As for what regards antimalarial properties, chloroquine, even in massive doses, has no significant activity against the exoerythrocyte phases of plasmodiums in tissues. The substance is therefore not a causal prophylactic agent and does not prevent the establishment of infection. However, it is highly effective against the asexual erythrocyte forms of P. vivax and P. falciparum and P. vivax gametocytes. In acute attack of malaria, chloroquine quickly controls clinical activity in human malaria have a chlorine atom at position 7 of quinoline. Substitution by methyl radical at quinoline position 3 reduces activity and additional replacement by methylene position 8 completely eliminates activity. The details of the relationship between structure and activity of chloroquine and its collaborators were discussed by Berliner et al., 1948.

**Antimalarial Mechanism of Action**

Although chloroquine causes several effects that, individually or combined, may be related to its primary mechanism of plasmodicidal action, this process is still unclear. Initially it was thought that at least in part, through an interaction with the DNA of the cell. Schellemberg and Coatney (1960) found that chloroquine inhibited the incorporation of P32-labeled phosphate into RNA and DNA by P. gallinaceum in vitro and in vivo. Later it was demonstrated that chloroquine strongly combined with duplicate DNA. It had also been reported that the substance strongly inhibited DNA polymerase and, to a lesser extent, RNA polymerase (COHEN, 1965), in both cases in combination with model DNA (Allison et al., 1965; Cohen and Yielding, 1965). Changes in several physical parameters were consistent with the intercalation of chloroquine with double DNA containing guanine (Allison et al., 1966). This
intercalation also occurred with primaquine and quinine, but not with mefloquine, an antimalarial structurally belonging to the quinone family (Davidson et al., 1977).

When exposed to chloroquine, plasmocyte-infected erythrocytes rapidly concentrate the drug and also present granulation of the malaria pigment that forms while the parasite digests hemoglobin from host erythrocytes. The two processes may be related to each other, since both are energy dependent, saturable and competitively inhibited by antimalarials such as amodiaquine, quinine and mefloquine (Chou et al., 1980).

**Absorption, Destination and Excretion**

Chloroquine is absorbed by the gastrointestinal tract rapidly and almost completely, since less than 10% of the ingested dose is found in feces (CORTEGIANI, 2020). About 55% of the plasma substance is bound to non-diffuser and unidentified plasma constituents (PLOWE, 2005). The elimination of chloroquine is very slow, but increases with the acidification of urine. It is also deposited in tissues in considerable amounts, and in animals a concentration of 200 to 700 times higher than plasma may have been found in the liver, spleen, kidneys, lungs and tissues containing melanin. The substance also focuses on leukocytes. The opposite happens in the brain and spinal cord, containing only 10 to 30 times the concentration present in plasma (National Center for Biotechnology Information, 2019).

As time goes by, chloroquine undergoes appreciable transformation in the body. The main metabolite is desethylchloroquine, which represents a quarter of the total material that appears in the urine; bidesethylchloroquine, a carboxylic acid derivative and other uncharacterized metabolic products are found in small ones. Just over half of the products of the substance found in urine consist of unchanged chloroquine (National Center for Biotechnology Information, 2019).

**RNA viruses**

RNA genomes were initially discovered in plant viruses, most of them composed only by RNA and protein. These viruses encode a specific enzyme that could catalyze the synthesis of RNA from an RNA template (RNA-direct RNA synthesis), interestingly using the same mechanism of base pairing between complementary strands as is employed during DNA replication or transcription of RNA from DNA. Although they have genomic RNA in their viral particles, trials conducted by Howard Temin in the early 1960s indicated that their replication requires DNA synthesis in infected cells, leading to the hypothesis that DNA viruses replicate via synthesis of a DNA intermediate, denominated DNA provirus. Already in 1975, Temin and David Baltimore independently discovered that RNA tumor viruses contained an enzyme that catalyzed the synthesis of DNA from an RNA template. In short; the synthesis of DNA from RNA, now called reverse transcription, was thus established as a mode of information transfer in biological systems (TEMIN, 1975).

Reverse transcription is important not only in the replication of RNA viruses, but also in at least two other broad aspects of molecular and cellular biology. First, reverse transcription is not restricted to viruses. It happens to occur in the cells as well, in the transposition of DNA sequences from one chromosomal location to another. Second, enzymes that catalyze RNA-directed DNA synthesis (reverse transcriptases) can be used experimentally to generate DNA copies from any RNA molecule. One adequate example is the physiology of virus that contain RNA genomes in their viral particles. When it infects a host cell, however, a DNA copy of the viral RNA is synthesized via reverse transcription. This viral DNA is then integrated into chromosomal DNA of the host to form a DNA provirus, which is described to yield progeny RNA virus. This is the base of RNA virus pathology.

**Cellular Alterations Caused By Chloroquine and Hydroxychloroquine**

The search for new derivates from chloroquine has been used in order to lessen its toxic effects, and so one of the best discovered was hydroxychloroquine. There is also a phosphate version added to chloroquine to be used in animals. What makes hydroxychloroquine interesting, particularly when it involves virotoxic infections, is the fact that it acts in the “cell powerhouse”, and changes the cell itself, jeopardizing virus entrance, replication and the secretion of virotoxic infective particles.

Proteins are needed for a number of the cell functions, such as repairing damages or directing chemical processes. By understanding the bases of virotoxic physiopathology, it is easy to see that these microorganisms use the very host cell structures in order to replicate, and infect other cells. Inevitably for such need, the have to enter the cells and use have its DNA or RNA replicated, which means that any drug mechanism directed to halt the virus pathology should alter directly the ribosomes, structures whose main function is protein production. Ribosomes can be found floating in the cytoplasm, or attached to the endoplasmatic reticulum where they come from. As for the main functions of ribosomes, they assume the role of bringing together amino acids to form particular proteins, which are important for completing the cell's activities. Proteins are essential for numerous cell functions such as directing chemical processes or repairing processes. Ribosomes are usually found floating inside the cytoplasm or joined to the endoplasmic reticulum. Therefore,
for the accomplishment of the virus infection, the role of ribosomes is essential. They are responsible for synthesizing proteins, and this is accomplished by translating the genetic code transcribed into mRNA into an amino acid sequence. They use cellular accessory proteins, soluble transfer RNAs, and lots of metabolic energy in order to accomplish the initiation, elongation, and termination of peptide synthesis.

Hydroxychloroquine alters cellular capacity to produce protein by altering the normal functions of the ribosomes. In order to enter the cytoplasm, the virus has to be englobed, and have their genoma decoded into proteins for replication. When the ribosomic activity is decreased, the cells show low protein production capacity, and this very fact implies in at least three barriers for virus survival. The first one is reduced cell capacity to accomplish endocytosis, which jeopardizes virus entrance for the fundamental fact that it alters endocytosis. Under the hydroxychloroquine influence, ribosomes are working insufficiently. However, in the overall infection, some virus manage to penetrate the cytoplasms because the process differs from cell to cell. Once within, viral particles will be packed in the endosome, and the genetic information will be read by the ribosomes to produce non structural viral proteins. The second barrier: from the many non structural proteins existent, the most important is replicase, an enzyme that catalyzes the synthesis of a complementary RNA molecule using an RNA template. It will help replicating the virus genetic material, whether DNA or RNA. From this point of view, Hydroxychloroquine also jeopardizes replication, since it inhibits the enzymes that will replicate the virus. Finally, the third barrier: with the cellular mechanism all altered, the secretory via is also affected for the virus to liberate infective particles into the blood stream.

One of the best characteristics of chloroquine and its congeners is that they are cheap drugs with more than 70 years of clinical use, whose adverse effects have been studied for all these period, due to their indications as antimalarial.

**Antiviral Potential of Chloroquine**

Many of the recent epidemies that affected modern societies were originated in China, more typically respiratory syndromes, able to spread quickly caused by mutations on virus that originally infected animals. Severe acute respiratory syndrome (SARS-CoV-1) was one of these diseases, which was initially reported in Guangdome Province of China, in 2002, and then transmitted to 30 countries in few months after its initial report. This former disease was caused by SARS coronavirus 1. Recently, on December 31\textsuperscript{st} 2019, a new and much more powerful disease, COVID-19, has been ongoing and causing a pandemic that halted the economy of the world, implying in serious damages so much in deaths as also on the way of living of millions of people, all over the continents. In the first 2002 breakout, chloroquine had been initially also used, but did not get too much attention since the vaccine was reached short after, impeding the propagation, and controlling the disease.

This new emerging virus, therefore, was named SARS coronavirus 2. A second disease, much more powerful in infective power as in aggressiveness, but with similarities with SARS coronavirus 1 in physiopathology (REF). Up to the moment of the construction of this paper, no specific therapy has been indicated for COVID-19 yet. There are a number of agents under clinical trials, but the fact is that the efficacy for any drug has not been stablished yet. Nevertheless, chloroquine, in the form of hydroxychloroquine, in patients under intensive care therapy. The French were the first official researchers to use it as a treatment for COVID-19, associated with azithromycin with a reduced number of patients (26 only), but with excellent results.

The reason for the rediscovery of chloroquine reemerged during the epidemic of SARS-CoV-1. When chloroquine was administered in that time, a dramatic dose-dependent decrease in the number of virus antigen-positive was observed (REF). So significant was the result, that 0.1-1\textmu M chloroquine reduced the infection by nearly 50%; and up to 90-94% inhibition was observed with 33-100 \mu M concentrations. With these results in hands, some authors hypothesized that, as chloroquine was a lysosomotropic agent, another common lysosomotropic agent, NH\textsubscript{4}Cl, also known as ammonium chloride, when associated with it might lead to better results. NH\textsubscript{4}Cl has been reported as being able to reduce pseudotypes viruses decorated with SARS-CoV spike protein.

Up to the moment of the construction of this paper, no specific therapy has been indicated for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19. There are a number of agents under clinical trials, but the fact is that the efficacy for any drug has not been stablished yet. Nevertheless, chloroquine, in the form of hydroxychloroquine, has shown promising results when applied in patients under intensive care therapy.

The reason for the rediscovery of chloroquine reemerged during the epidemic of severe acute respiratory syndrome (SARS) caused by SARS coronavirus 1, the previous member of the vast family Coronoviridae. Some countries, due to the rise of the pandemy and the thousands of dead petrols, especially in Italy, have authorized its prescription in clinical trials, such as Brazil and USA. More recently yet, in the south-east of Brazil, São Paulo, epicenter of the COVID-19 pandemic, studies are being carried out with a larger number of patients with the intention of
establishing a protocol for the usage of hydroxychloroquine in the beginning of the symptoms, associated with azithromycin. Researchers claim that the ability of hydroxychloroquine in jeopardizing virotic entrance into the cytoplasm, by decreasing and disarranging ribosome activity to cleave the genetic material of the virus, should be better thought to be used while the systemic and more serious symptoms are not present, allowing patients to begin the treatment at home.

The fact is that some drugs are being tested, alone or in combinations with other drugs. The main ones are the following (SMITH, 2020):

- **Chloroquine** – Limited in vitro clinical data and trials suggest a potential benefit when used alone.
- **Hydroxychloroquine** – In vitro and limited clinical data accomplished with low numbers of patients do suggest potential benefit.
- **Azithromycin** – Has been associated with hydroxychloroquine and are now being tested in COVID-19 therapy with positive results. Its use as adjunct therapy has brought hope for the treatment.
- **NH₄Cl** (ammonium chloride).

In December 2019, a novel pneumonia caused by a previously unknown pathogen emerged in Wuhan, a city of 11 million people in central China. The initial cases were linked to exposures in a seafood market in Wuhan. As of January 27, 2020, the Chinese authorities reported 2835 confirmed cases in mainland China, including 81 deaths. Additionally, 19 confirmed cases were identified in Hong Kong, Macao and Taiwan, and 39 imported cases were identified in Thailand, Japan, South Korea, United States, Vietnam, Singapore, Nepal, France, Australia and Canada. The pathogen was soon identified as a novel coronavirus (2019-nCoV), which is closely related to severe acute respiratory syndrome CoV (SARS-CoV). 2 Currently, there is no specific treatment against the new virus. Therefore, identifying effective antiviral agents to combat the disease is urgently needed.

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Chloroquine and hydroxychloroquine have shown antiviral effects. Their mechanism of action is based on increased pH of lysosomes and cellular endorsements, resulting in the impairment of virus release from within them. Since the vast majority of viruses require a low pH to be unleashed into the cellular cytoplasm, all clinical evidence suggest that this is the mechanism by which chloroquine may play this important role in the therapy (SAVARINO, 2003). In this way, the virus is unable to release its genetic material inside the host cell and replicate (AL-BARI, 2017; FREDERICKSON, 2002). The association with azithromycin has been indicated for the capacity of this antibiotic to treat many different types of infections caused by bacteria, such as respiratory infections, skin infections, ear infections, eye infections, and sexually transmitted diseases.

**Chloroquine and QT interval of the Electrocardiogram**

Over the years with clinical use of chloroquine, some cardiac changes related to the dosage of the drug have been detected, and then researched. The normal heart beats regularly and well coordinated, because the electrical impulses generated and transmitted by myocytes with unique electrical properties trigger a sequence of organized myocardial contractions, sufficient for adequate blood pumping. Chloroquine has been reported as able to induce prolonged QT intervals in ECG.

The long QT interval responsible for *torsades de pointes* may be congenital or drug-induced. The QT interval, however, predisposes to arrhythmias prolonging the repolarization of myocytes, a fact that induces early post-
depolarization and spatial dispersion of refractory. Arrhythmias and conduction changes are caused by abnormalities in the generation or conduction of these electrical impulses, or both. It is important to highlight that the increase the QT interval is in fact able to cause fatal arrhythmias in 10% of patients (HAEUSSLER, 2018). Therefore, it is important, if not fundamental, that ECG monitoring be systematically incorporated in case these drugs are implemented in the conventional treatment. The risk exists, and, since the mortality rate of coronavirus is around 3% in the majority of the countries that it infected, the treatment offered must never be worse in rates than the illness itself. The panic cause by the rise of the pandemy does not justify hurried medical conducts taken based on weak evidence, like some studies that have been published with low number of patients.

Another study aimed to verify the influence of chloroquine and hydroxychloroquine on the QT interval of the electrocardiogram. The authors studied 46 rheumatic patients (42 using chloroquine and 4 using hydroxychloroquine); in both groups the dosage was 7mg/kg/day of hydroxychloroquine and 4mg/kg/day of chloroquine). Their results showed that prolongation of the QTc interval was observed in 17.39% of patients. All patients with abnormal results, except 1, repeated the ECG with return to normal values. The authors concluded that patients using chloroquine may indeed have prolongation of the QT interval as an adverse effect of the drug (REY, 2003).

One of the most dangerous things concerning the use of chloroquine is undoubtfully the fact that excessive QT prolonged interval implies in inherent risk of sudden cardiac death (SCD). The reason is that polymorphic tachycardia, or simply TdP, causes the prolongation of ventricular repolarization, leading to an oscillation in the membrane potential denominated early after depolarization (EAD), which, on the other hand, if reaches a critical limit in a relatively large area of the myocardium, may lead to ectopic beat. Death risk may then become imminent (January and Riddle, 1989).

**CONCLUSIONS**

Chloroquine, used as an antimalarial agent since 1939 and nearly forgotten in the medical arsenal, seems to have potential antivirotic properties that may be useful in the treatment of the grave acute forms of COVID-19 infections, when used associated with Azithromycin. Its indication, however; must be accomplished with due care and attention, due to the risk of cardiac QT prolongation able to cause sudden deaths. Periodic ECGs must be included in the protocols for the patients under the prescription of this drug.

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