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IMPACT OF HYDROXYCHLOROQUINE IN COVID-19 AND ITS CLINICAL CONSIDERATIONS IN DRUG USAGE

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ABSTRACT

Background: Current CoVID-19 is a threatening across the Globe. Till now, there is no specific treatment has been proven to be effective for SARS-CoV-2 infection. Patients were managed with supportive care, such as oxygen supply in mild cases and extracorporeal membrane oxygenation for the critically ill patients, specific drugs for this disease are still being researched. In this scenario Hydroxychloroquine is Effective for anti-inflammatory agent and also Anti-Viral properties, has been used in COVID-19 Patients. It is showing better clinical outcomes in combination with Azithromycin. But Clinical Monitoring is required for this drug which has been discussed in this article. Objective: To know the mechanism of action of hydroxychloroquine in COVID-19. To assess the risk and benefits of hydroxychloroquine therapy in terms of contraindication and adverse effects. Conclusion: Hydroxychloroquine have Anti-Viral Properties that has been used extensively in CoVID-19 and can significantly inhibits the binding of Virion with ACE and decrease the production of cytokines in COVID-19 patients. Although Hydroxychloroquine providing Positive Clinical Outcomes, we must still consider its Contraindications and Adverse effects.

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INTRODUCTION

The outbreak of COVID-19 due to SARS-Cov-2 virus has spread from China, since the first case of CoVID-19 was reported in Wuhan, China in December 2019 from patients with pneumonia⁽⁹⁾. Coronavirus is one of the major pathogens that primarily targets the human respiratory system. Current virus which is threatening the world is COVID-19, which belongs to order *Coronaviridae*. The WHO described the global COVID-19 situation as a pandemic. As of Now, no treatment has demonstrated clinical efficacy against COVID-19. However, several treatment strategies are being considered and evaluated in numerous clinical trials. Among these strategies, the use of Hydroxychloroquine (HCQ) appears to be a promising option, although only limited evidence is available at the present time. HCQ has the advantage of being widely available to a large number of patients. But very little information is available concerning the drug action and individualized dosage regimen especially in the context of CoVID-19, as HCQ is responsible for adverse events among them the most serious adverse event is cardiotoxicity characterized by prolongation of the QT interval which may lead to Arrhythmias. Since SARS-CoV-2 utilizes the similar surface receptor ACE2, it is believed that chloroquine can also interfere with ACE2 receptor glycosylation thus preventing SARS-CoV-2 attachment to the target cells^(10,11). Angiotensin-converting enzyme 2 (ACE2) expressed in lung, heart, kidney and intestine⁽¹²⁾.

HYDROXYCHLOROQUINE:

Chloroquine (CQ) [N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4-pentanediamine] has been used to treat malaria and amebiasis since many years. However, *Plasmodium falciparum* developed widespread resistance to it, and with the development of new antimalarials, it has become a choice for the pro-phylaxis of malaria.

Hydroxychloroquine (HCQ) sulfate, a derivative of Chloroquine, it was first synthesized in 1946 by introducing a hydroxyl group into Chloroquine and was demonstrated to be much less toxic than Chloroquine as shown in animal studies. Now a days more importantly, HCQ is still widely available to treat auto-immune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Since CQ and HCQ were similar chemical structures and mechanisms of acting as a weak base and immunomodulator.⁽¹⁾

MECHANISM OF ACTION:

Hydroxychloroquine can effectively inhibit COVID-19 entry, by changing the glycosylation of ACE2 receptor and spike protein, it is also effective on the post-entry stages of COVID-19^(1,7).

[NOTE: Glycosylation is one of the most important post-translational modifications (chemical changes proteins-After translation) of proteins, which plays an essential role in various biological processes]

Detail Mechanism Of Action Effect Of Hydroxychloroquine On Covid-19:-

Hydroxychloroquine is a weak base and it has a potential Broad spectrum antiviral activity to increase the pH of acidic intracellular cells, such as endosomes/lysosomes.⁽¹⁾⁽²⁾

Hydroxychloroquine inhibits the entry of virus and co-localization of virions (virus particles) with early endosomes or endolysosomes. It was analyzed by immune-fluorescence analysis (IFA) and confocal microscopy.

In the presence of Hydroxychloroquine, Significantly more virus particles were detected in the early endosomes and very few virus particles were found to be co-localized with endolysosomes. This mechanism suggests that Hydroxychloroquine blocks the transport of COVID-19 from early endosomes or endolysosomes.

Immune-fluorescence analysis (IFA) and confocal microscopy analysis Observed that, at the time of 90 min in untreated cells, 16.2% of internalized Virus particles were observed in early endosomes antigen1-Positive. More than 30% of virus particles were transported into the late endosomal-lysosomal protein.⁽²⁾

PHARMACOKINETICS:

HCQ-Bioavailability has Complete and Rapid Absorption and 1-3 hours of peak plasma time, its half life is 32-50 days, Protein bound-55%, Excretion- urine 60%⁽²⁾. It exhibits strong tissue tropism, particularly for the kidney and liver, with a long half-life (several weeks). The risk of overdose is higher in Patients with impaired renal and/or hepatic function.

CONTRAINDICATIONS⁽²⁾:-

When we assess the risk and benefit ratio of losing life with COVID-19 patients to that of contraindication of HCQ, one must still consider the factors such as Retinopathy, Myocardial toxicity or myocardial dysfunction, QT interval prolongation, ventricular arrhythmia, Atrioventricular block, G6PD deficiency, Pulmonary hypertension, Hypersensitivity reaction to hydroxychloroquine or chloroquine, Breastfeeding, Pregnant, Not recommended in individuals below 15 yrs of Age.

Recommended Dose For Empiric Use Of Hydroxychloroquine For Prophylaxis Of Sars-Cov-2 Infection:-

- ✓ Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals.
- ✓ Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals.(ICMR)⁽³⁾.

CLINICAL PARAMETERS TO BE MONITORED:-

Hypoglycemia, QT interval prolongation when it is coadministered with drugs that have the potential to induce cardiac arrhythmias, LFT's to be monitored.

TREATMENT:-**Effect of Hydroxychloroquine during CoVID-19 :-**

Hydroxychloroquine primary effects the changes in number, size and morphology of early endosomes or endolysosomes. In the untreated cells, most early endosomes were much smaller than endolysosomes ⁽²⁾.

Hydroxychloroquine treated cells, were abnormally enlarged early endosomes vesicles and which are larger than endolysosomes in the untreated cells. Virus particles were localized around the membrane of the early endosomes vesicle. Hydroxychloroquine also treated cells, the size and number of ELs increased significantly⁽²⁾.

Hydroxychloroquine plays a crucial role in acidification of endosome maturation and function. We conclude that endosome maturation might be blocked at time of intermediate stages of endocytosis, so resulting in failure of further transport of virus particles to the ultimate releasing site⁽²⁾.

Recent studies found that high concentration of cytokines were detected in the plasma of critically ill patients infected with Covid-19. Hydroxychloroquine is a safe and Effective for anti-inflammatory agent that has been used extensively in autoimmune diseases and can significantly decrease the production of cytokines in COVID-19 patients. Hydroxychloroquine safe dosage (6–6.5 mg/kg per day) as per few studies .

DISCUSSION

In a recent trial with patients on COVID-19 treatment 100% of patients treated with Hydroxychloroquine in combination with azithromycin (macrolide antibiotic) were virologically cured comparing with 57.1% in subjects(test dose) treated with single molecule of Hydroxychloroquine, and 12.5% in the subjects(control group). Presently Chloroquine and Hydroxychloroquine will be tested in subjects with pneumonia caused by COVID-19⁽⁴⁾. Most Recent work, an *in vitro* antiviral effect has been demonstrated on SARS-Cov-2 conducted by Wang et al. showed that a chloroquine concentration of 0.36 mg/L decreased viral load by 50% in a cell model⁽⁸⁾

A recent paper reported an inhibitor effect of remdesivir (a new antiviral drug) and chloroquine (antimalarial drug) on the growth of SARS-CoV-2 in vitro ⁽¹⁾ and an early clinical trial conducted in COVID-19 Chinese patients, showed that chloroquine had a significant effect, both in terms of clinical outcome and viral clearance, when comparing to controls groups. Chinese experts recommend that patients diagnosed as mild, moderate and severe cases of COVID-19 pneumonia and without contraindications to chloroquine, be treated with 500 mg chloroquine twice a day for ten days ⁽⁶⁾.

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