

MECHANISM OF ACTION OF HYDROXYCHLOROQUINE ON SARS-CoV2

K.KRISHNA, M.MEGHANA

Department of pharmacy, A.MReddymemorialcollegeofpharmacy,
petturivaripalem, narasaraopet.

Abstract

Recently, a novel corona virus which officially called as severe acute respiratory syndrome coronavirus-2 of the genes Betacoronavirus and causative agent is COVID-19. according to world health organization declared that SARS-CoV2 is global pandemic(world wide spread of disease) on 12 march 2020.SARS-CoV2 which is first identified in the city of wuhan in china's hubei province in December 2019, which is characterized as pulmonary infection . Therefore as the research was carried by the international authorities is that the patients should be diagnosis and rapid isolation should be done due to the lack of effective drug therapy. But due public health emergency it is made the sense to 4investigate a drug that shows possible effect of hydroxychloroquine against SARS-CoV2 . but the drug hydroxychloroquine is consider as part of an investigational protocol for the patients who are with COVID19 . therefore FDA approved hydroxychloroquine drug distribute millions of doses to hospitals across the country. hydroxychloroquine is the most potent inhibitor of these coronavirus .which have strong antiviral activity, and therefore inhibits the infection and spread of coronavirus. The drug hydroxychloroquine mainly shows immunomodulatory effect that is it is used to control the pro-inflammatory mediators (cytokines and interleukins) at the late phase of SARS-CoV2

Introduction of hydroxychloroquine

Hydroxychloroquine is developed during world warII it is derivative of quinacrine, that is chemically and clinically similar to 4-aminoquinolines .this drug is used as anti-infective, anti-malarial, anti-parasitic, insecticidal activity, enzymatic inhibitors, immunosuppressive agent etc. but recent investigations that is according to u.s food and drug administration (FDA) and world health organization (WHO) states that the hydrochloroquine has invitroactivity against SARS-CoV2

Hydrochloroquine sulfate(200mg)-film coated tablet

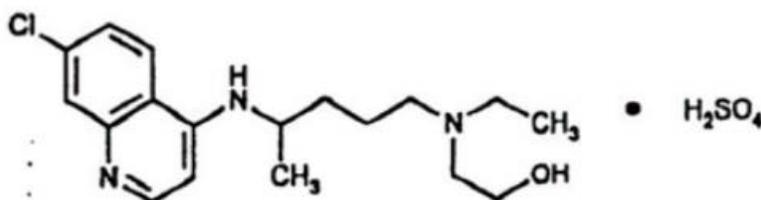
Brand name-plaquenil

It is white crystalline powder which freely soluble in water and it is insoluble in alcohol, chloroform and in ether

Molecular weight is 433.95

Molecular formula is C₁₈H₂₆ClN₃O₂S₄

IUPAC NAME-2[[4-[7-chloro-4-quinolylamino]pentyl]ethylamino]ethanolsulfate



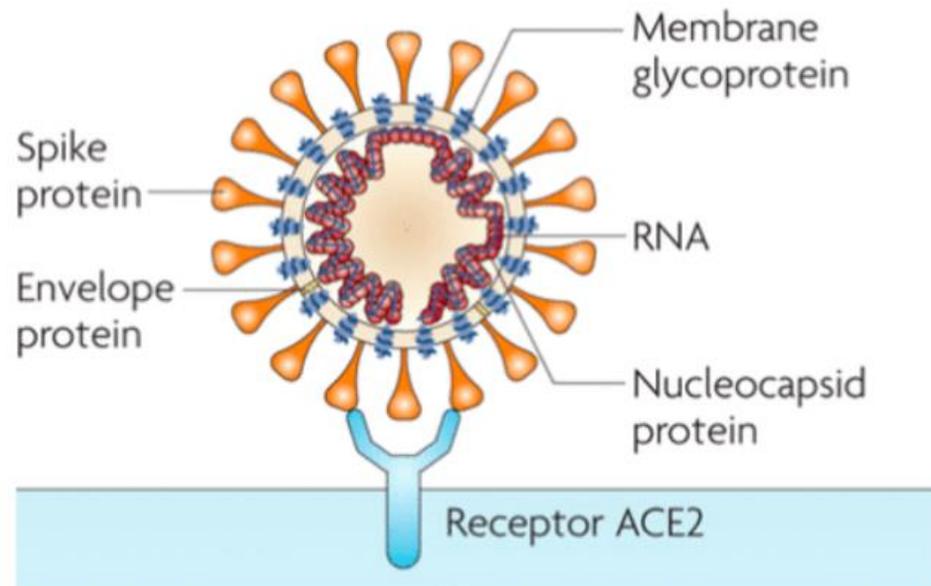
Pharmacokinetics

- It is absorbed oral and iv route i.e., 200mg-oral route, 155mg and 310mg iv route absorption
- Bioavailability is 67-74%
- The drug has R and S enantiomers
- It has large volume of distribution in blood and plasma
- It is highly bound to proteins i.e., R enantiomer (37% protein bound), S enantiomer (64% protein bound)
- Absorption Half life is about 3 to 4 hours and due to large volume of distribution the half life is about 40-50 days
- It is metabolized in liver by CYP3A4 enzyme
- It is excreted through renally (40-50%), urine (16-21%), sloughed skin (5%), feces (24-25%)

Pharmacodynamics

Mechanism of action of hydroxychloroquine

According to virology the SARS-CoV-2 which is a large virus containing a single strand positive sense RNA genome encapsulated with a membrane envelope and the viral membrane is made up of crown-like appearance called glycoprotein spikes. and the spike glycoprotein is a type-I membrane protein that facilitates viral infection.



Generally virus enters by binding to cell surface (lungs) called angiotensin-converting enzyme2(ACE-2). Here the drug hydroxychloroquine reduces glycosylation of ACE-2 there by preventing the COVID-19 infection and stops binding to host cell. The drug hydroxychloroquine blocks the pro inflammatory mediators like interleukins-6 and cytokines. Therefore it blocks acute respiratory distress syndrome(ARD'S).

Glycosated spikes facilitate host cell produce serine proteases and hence viral genome encodes several non-structural proteins including RNA dependent RNA polymerase and therefore the viral genome released single strand RNA translated into viral poly proteins. The drug hydrochloroquine inhibits viral DNA and RNA polymerase

Later the virus enters into host cell through endocytosis and the virus is transported in vesicle called endosome within which the virus replicate .and the endosome fuses with the intra cellular lysosome which lead to replicate of endosome and then it leads to release of viral content. The drug hydroxychloroquine accumulate on lysosomes and it interfere with this process therefore the drug increases the PH level of endosome which may interfere with viral entry/ exist from the host cell

Invitro studies- it states that 50% maximal effective concentration at which viral RNA increase is inhibited

Invivo clinicaltrials – PCR technique of SARS-CoV2 RNA from nasopharyngeal swab

Adverse effect of hydroxychloroquine

- Risks of cardiac arrhythmia (Q-Tinterval prolongation)
- Risk of retinal damage,especially in the case of long term use
- Caution in diabetic patient because of the drug hydrochloroquine leads to severe hypoglycemia so the glucose levels should be monitored

- Caution in patients with glucose6phosphate deficiency because it leads to blood disorders like aplastic anemia
- Drug interaction should be checked

Conclusion

Due to lack of drugs capable of pan-corona virus a anti viral activity will increase the vulnerability of public health systems to a highly pathogenic coronavirus which globally pandemia so, hydroxychloroquine which is potent antiviral drug. It is used as a preventive therapy SARSCOV2. But there is no evidence that hydroxychloroquine is only correct therapy.

References

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