Status of hydroxychloroquine: COVID disease management protocol

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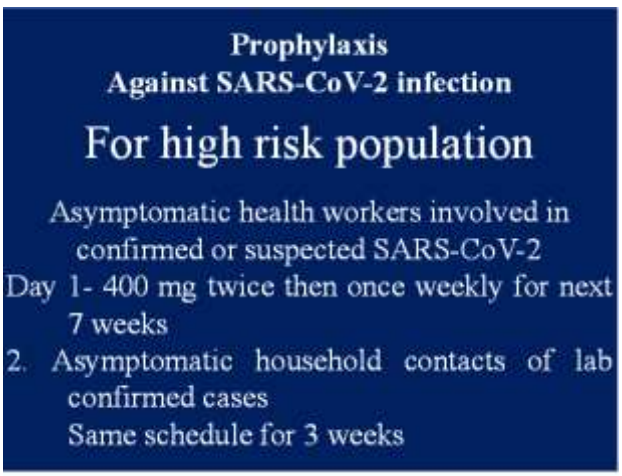
Abstract
Hydroxychloroquine, a safe derivative of chloroquine has been in practice since 1950. This drug has been used successfully as anti-viral agent previously. Its role in COVID-2 has been authenticated in the management protocol. The sudden death assigned to hydroxychloroquine is misplaced though it can be a very uncommon complication in cardiac patients with arrhythmia. Its prophylactic and therapeutic dose schedule needs to be streamlined at a lower dose schedule and is recommended to be used in early part of the disease and not during the stage of later complication.

Keywords: Hydroxychloroquine, Arrhythmia, Pathogen, Host target cell, ACE-2, Intracellular.

Hydroxychloroquine, the pronounced "Game Changer" drug has been claimed to be effective in the treatment of SARS-COVID-2 disease. The anti-malarial drugs,[7] apart from rheumatoid arthritis it is also licensed to treat connective tissue disorder (CTD).[1] Hydroxychloroquine including the original chloroquine have also worked as broad anti-viral agent.

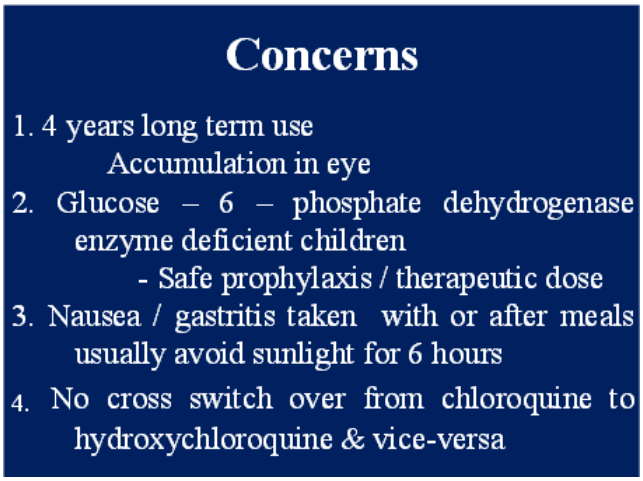
National Task Force for COVID-19 was constituted by ICMR. This task force released an advisory on hydroxychloroquine, which was approved by Drug Controller General of India.

The dose schedule recommendation for high risk population has been put forward with the caution that this regimen should not instill a sense of false security and should not be used in children below 15 years.



Christian Perronne, Head, Infectious Disease, Universal Hospital Raymond Poincare, Garches, Paris proclaimed in the wake of COVID-19 which is worth quoting "I really believe in hydroxychloroquine. It is a drug, I find rather fascinating that has been used for decades. There have been positive results in an in vitro study and a preliminary Chinese study in 100 patients which showed that hydroxychloroquine reduced the viral load, the symptoms lasted for less time, and they are not as severe. This could reduce the number of carriers, which I find, interesting from an epidemiological perspective."

Concerns were expressed regarding use of hydroxychloroquine in the management protocol for COVID-19.

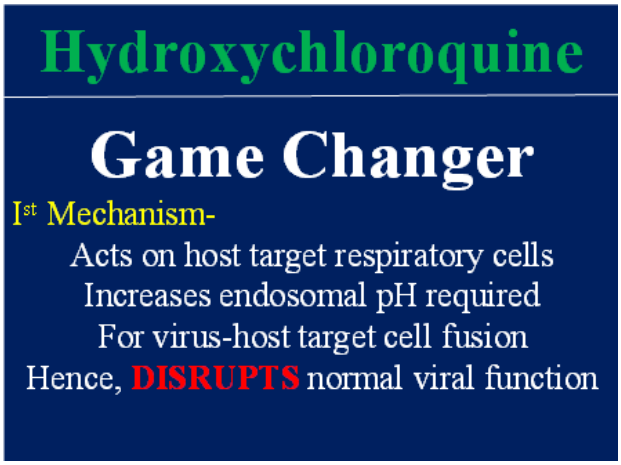


Therapeutic resistance does never develop with HCQ since all the mechanisms are involved on target host cells only. Importantly the sum total effect does not even allow mutation of the virus, hence arrests the progression of the disease. This therapeutic resistance is enforced by

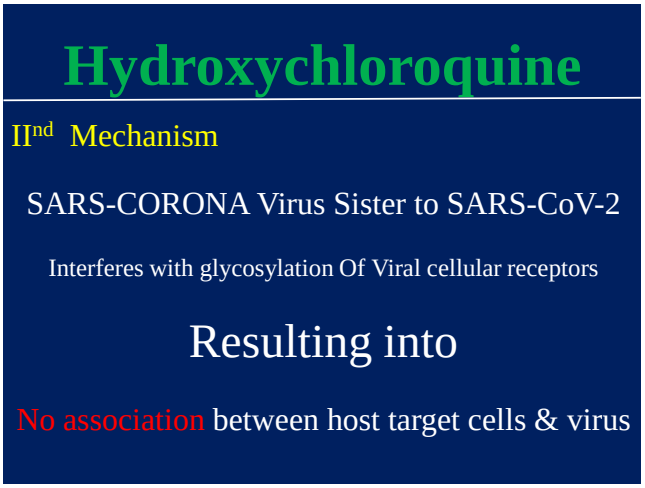
various mechanisms inhibiting the virus-target host cell union.

The Mechanisms Involved

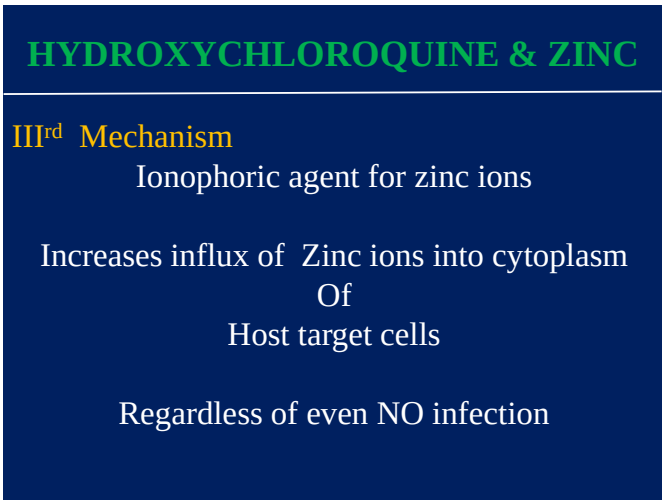
HCQ acts on host target respiratory (alveolar) cells. It increases endosomal pH, thereby denies the required lower pH favoring the virus-host target cell fusion. Thus, disrupting the progression of normal viral function.



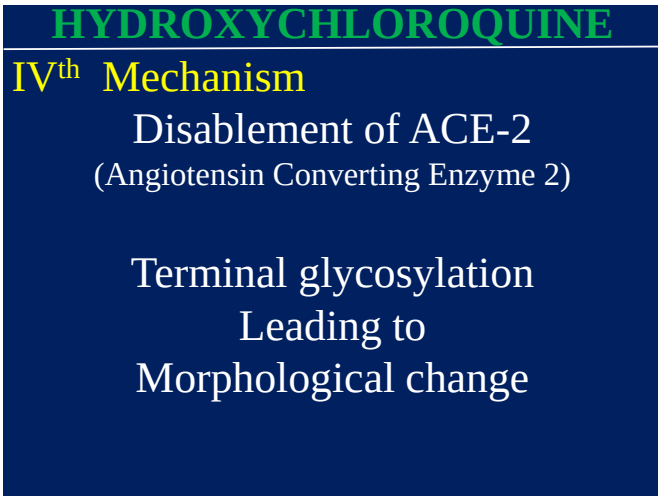
SARS-Corona Virus (2003) is a predecessor / sister to the recent SARS-COVID-2. It had shown an effective interference with glycosylation of viral cellular receptor inhibiting any association between host target cells and the virus. This terminal glycosylation brings about a morphological change in the virus, too.



During routine times, even in absence of any infection, HCQ works as iontophoreic agent for zinc ions increasing influx of zinc ions into the cytoplasm of host target cells.



Most importantly, ACE-2 (Angiotensin Convering Enzyme 2) is a surface receptor present on target host cell. COVID-2 virus require ACE-2 receptor for getting attached to target host cell. HCQ disrupts this virus-target host cell association by effecting disablement of ACE-2.



Theoretical discussion of various probable situations arising after the host gets inoculate, further dissects the various advantages offered in each situation by HCQ. Invariably, the attempt made by the virus to get attach to the target host cell and subsequent pathological sequences leading to evolution of the diseases are limited or aborted.

Situation 1

After the virus remaining dormant for upto initial three weeks, some viruses in an attempt to infect the host cell.

Various Probable Situations
Situation 1

No initial exposure / dormant for 3 weeks
Then
Attempted entry of virus
Initiation of infecting host cells

"Ist and IInd mechanism"
Prevents union of virus-target host cell

Situation 2

Even if some viruses are successful in entering the target host cells, the virus encounters the normally prevalent intra-cellular zinc ions, which is waiting to adhere to the RNA dependent -RNA polymerase enzyme of virus. This stops intracellular polymerisation of COVID-2.

Various Probable Situations
Situation 2

Even if some viruses succeed
to enter target host cells
Virus encounters-Zinc ions
waiting to adhere
to the RNA dependent
-RNA polymerase enzyme of virus
Stops intracellular polymerisation of CoV-2

In the life cycle of some intracellular pathogens including viruses implicates the cytoskeleton in recent advances. The basis for intracellular movements responsible for transporting the pathogen to and from the cell surface to the nuclear region. Apart from this, the cytoskeleton also produces cortical protrusions, projecting the pathogen from the cell surface towards another adjacent cell. Intracellular motility is driven by pathogen-mediated actin polymerisation. Inhibition of intracellular movements provides a potential strategy to limit pathogenicity. Potential targets for novel antimicrobial therapy are linked with interaction between host cell motors and pathogenic factors. Hence, stoppage of intracellular polymerisation leads to loss of intracellular mobility.

Situation 3

The virus mutates several times inside the cell where it encounters the zinc ions which stops the viral multiplication inside the respiratory alveolar cells irrespective of strain of the virus.

Various Probable Situations
Situation 3

Several intracellular virus-mutation
Zinc ions actively
inhibit viral multiplication
inside host respiratory cells
Irrespective of viral strain

Situation 4

The virus if still can manage to escape the intracellular zinc-ion trap, gets released from the host target cell cytoplasm into the interstitial cell matrix in the surrounding intercellular space in an attempt to re-infect the neighbouring healthy cell.

Various Probable Situations
Situation 4
If virus manages to escape
From zinc-ion trap
Releases from host target cell cytoplasm
Into
Interstitial cell matrix
Intercellular space
Tries to re-infect healthy cells

Even at this stage, Hydroxychloroquine prevents re-union viral genome with the host cell with the help of first and second mechanism. Finally, infection gets halted in its preliminary stage and development of "Covid pneumonia" gets aborted.

Prevents re-union of
Viral genome with host cell
Via
Ist & IInd mechanism, thus
Halts infection in preliminary stage
COVID-pneumonia aborts
Hydroxychloroquine-no loss of effectivity
Pre and post infection

Hydroxychloroquine has been in use to treat rheumatic diseases since 1980s. Apart from rheumatic arthritis, it is also used for other chronic inflammatory diseases like systemic lupus erythematosus (SLE) and occasionally in Sarcoidosis.

Though it has anti-inflammatory property[1] but is not used as anti-inflammatory alone. It is orally administered[3] as DMARD but mechanism of this effect is not well explained except for its impaired phagocytic and lysosomal functions thus inhibiting the toll like receptors.[6]

HCQ has a long half life (approx 22 - 40 days).[2] Minimum six months is required to achieve a steady concentration in the system. Hence, for being effective, it requires a latent period of 3-6 months, which is longer than any other DMARDs.[2,8]

Dosage

200-400 mg daily is a typical dose in rheumatology.[3] It should not exceed 6.50 mg / kg / per day. Adjustment of dosage favourably relieves the neurological side effects like headache, dizziness and tinnitus.

Prophylactic dose recommended by ICMR is 400 mg morning and evening on day one followed by 400 mg once weekly for seven days for frontline workers and for three weeks in people remaining indoors. In my personal opinion, 800 mg is a higher dose on day one. I recommend 200 mg as initial test dose on day one followed by 400 mg on day two and is then to be repeated 400 mg every week. A preliminary occasional ECG and routine cardiological evaluation must be undergone in suspected cases to minimise any HCQ complication.

Similarly, the higher therapeutic dose of 400 mg thrice should be modified to 400 mg B.D. for one week and the patient should be admitted and monitored.

Toxicity

It is contraindicated in pre-existent maculopathy.[3] It exacerbates psoriasis and in epilepsy.[3] It reduces seizure threshold. It is safe in pregnancy and even during breast feeding.[5]

Unlike other DMARDs, it does not have any increased risk of infection. Skin rashes, though rare responds to stoppage of the drug if severe.

For avoiding gastrointestinal features like nausea, vomiting and abdominal pain, it should preferably be taken with meals.

The drug is prone for photosensitive reaction, which may not be so uncommon, it is better prevented by prescribing the drug to be taken during night, minimum six hours prior to exposure to sun.

Slow heart beat, symptoms of heart failure, unusual tiredness, unusual weight gain, anxiety, depression, hearing changes can take place.

Hypoglycaemia in a diabetic patients warrants dose adjustment.

Major toxic concern is the ocular toxicity and can progress to blindness even after drug withdrawal but fortunately, is rare in the dose used for rheumatological conditions.[4] Earliest feature of blurring can be reversed following withdrawal of the drug.[2] Prolonged QT interval in rheumatoid patients is not so frequently recognised.

Torsades de Pointes (TdP) is the condition of sudden death from fatal cardiac arrhythmia with initial verntricular tachycardia with heart rate greater than 100 beats per minute.

The cardiovascular risk factors are:

1. Hypertension
2. Obesity
3. Ischemic heart disease
4. Deep vein thrombosis
5. Cerebro vascular accident

The various arrhythemias usually recognized in above conditions are:

1. Atrial fibrillation
2. Supraventricular tachycardia
3. Unspecified arrhythmia

Expectations due to the hype created by the international demand of this drug, I still feel is justified but it will have

to be clearly understood that this drug alone can not treat patients in late stage when oxygen saturation becomes very low and when there are features are secondary involvement of heart, kidney, liver and brain. It can keep its promises of being effective in the earlier part of the disease and definitely not when second cytokine storm has taken place.

Summary

COVID-2 pandemic has changed the world but what came out brilliantly as the shining star in the management protocol was hydroxychloroquine. The initial media reporting of complications associated with this drug has largely been due to not excluding patients of obesity and cardiological diseases including arrhythmia. Hydroxychloroquine has various mechanisms of action preventing virus host target cell attachment and mutation and multiplication of the virus. HCQ still maintains its lead in the management of early part of the disease when complications affecting vital organs have not taken place.

Source of Funding

None.

Conflict of Interest

None.

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