Indian Pacing and Electrophysiology Journal 20 (2020) 117–120

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Cardiovascular risks of hydroxychloroquine in treatment and prophylaxis of COVID-19 patients: A scientific statement from the Indian Heart Rhythm Society

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ARTICLE INFO

Article history:
Received 3 April 2020
Accepted 3 April 2020
Available online 8 April 2020

Keywords:
Hydroxychloroquine
COVID-19
QTc interval
Torsade de pointes
Heart disease

Coronavirus disease 2019 (COVID-19) is now a pandemic as recognized by the World Health Organization (WHO) on March 11, 2020. The disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2/2019-nCoV). At the time of release of this statement, as per the available global statistics, more than 1.5 million had infection and around 87000 had died [1]. The corresponding figures in India are 4714 and 149 respectively [2]. There is a distinct possibility of COVID-19 overwhelming the healthcare capacity of India. The measures to contain the spread of COVID-19 such as social-distancing, hand hygiene, surveillance, and isolation of persons suspected or confirmed to have infection have been considered to be largely effective. In this regard, Government authorities have issued guidelines to health care workers and to the public at large, uniformly advising strict adherence to above measures and acknowledge the limited role of drugs in the treatment and prophylaxis of COVID-19 infection.

This statement from Indian Heart Rhythm Society (IHRS) addresses specifically the drug hydroxychloroquine (HCQ) mentioned in these guidelines. This includes a brief review of its cardiovascular effects, with respect to its propensity to cause QT interval prolongation and potentially lethal cardiac arrhythmia in certain patients. Identification of high-risk population and monitoring for prevention of such adverse events of sudden cardiac death are also discussed.

1. Cardiovascular effects of hydroxychloroquine

The drug, HCQ, is a 4-amino-quinoline that is widely used to treat certain autoimmune disorders, and related inflammatory and dermatological conditions. It is a hydroxylated version of chloroquine – an antimalarial that has been in use for decades, with a similar mechanism of action. HCQ is considered to be safer than chloroquine based on clinical studies [3,4]. This drug has now found place in management of COVID-19 infection [3–10]. It has been observed to inhibit ACE2 receptor-mediated entry of the SARS-CoV2 virus through various actions such as raising of intravesicular pH, inhibiting lysosomal activity, affecting antigen processing, etc. [3–7]. In addition, it has anti-inflammatory and immunomodulator actions which could be relevant in the crisis

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Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2020.04.003

generated by cytokines storm during COVID-19 infection [8–10].

HCQ can lead to QT interval prolongation and torsades de pointes (TdP) in susceptible individuals. The risk of TdP is not a linear function of basal QTc or drug-induced prolongation in QTc interval. Moreover, not all patients with drug-induced QTc prolongation will develop TdP. This side effect is rare, but co-prescription of other drugs such as azithromycin (which is also being recommended for the treatment of COVID-19) could amplify this risk. Many other drugs such as quinolones, antihistamines etc. which are often used may also add to the risk of TdP (refer to https://www.crediblemeds.org/drugsearch for list of drugs associated with QT prolongation). HCQ also interacts with other cardiac drugs such as beta blockers and digoxin and increases the blood levels of these drugs.

2. Recording ECG to measure QTc interval

It is recommended to have a baseline ECG to estimate the QTc interval in individuals receiving HCQ treatment. The QTc interval is calculated by measuring the QT interval on 12-lead ECG and using Bazett's formula. The normal upper limit for QTc interval is 460 ms for women and 450 ms for men [11].

In a situation where 12-lead ECG is not available, one can simply measure the QT interval on a rhythm strip and compare it with RR interval. As a simple 'rule of thumb' QT interval should be less than half of RR interval. In case of doubt or borderline situation, perform a 12-lead ECG and calculate QTc interval. One can also use smartphone app, or an online calculator https://www.qtcalculator.org for calculating QTc interval.

In patients with wide QRS due to underlying intraventricular conduction defects or paced rhythm, use the following formula to estimate QTc interval: wide QRS adjusted QTc = QTc − (QRS duration−100 ms) [11].

3. Alternatives to standard 12-lead ECG in current COVID-19 pandemic

While an ECG is a relatively simple screening tool, it still poses challenges in the current pandemic as screening people by performing multiple ECGs in COVID-19 positive patients is associated with need of personal protective equipment, the risk of contamination of equipment as well as risk to healthcare workers. Accurate measurement also demands a specialist physician's expertise adding further burden on the strained resources. The alternative approaches in these settings could be the following.

1. Standard telemetry systems which are also equipped with real time QTc monitoring is an option. This is especially true for sick, hospitalized COVID-19 patients who may be on continuous rhythm monitoring. The presence of associated dyselectrolytemia, which can further increase the risk of QTc prolongation in these sick patients, makes telemetry a good alternative to 12-lead ECG for this subset.
2. Using a smartphone-enabled mobile QTc app or the FDA-approved mobile ECG devicesuch as AliveCor (Kardia Mobile-6L device), if available, obviates the need of personnel resources to obtain an ECG. The AliveCor was granted emergency approval by the US FDA on March 20, 2020 for this purpose and is currently available in India. If a smartphone or AliveCor app is used, the QTc could be recorded every 12 h.

4. Patients at high risk of hydroxychloroquine-induced QT prolongation and TdP

When HCQ administration is considered for a COVID-19 patient or suspect, efforts should be made to identify all potentially high-risk individuals who should have a baseline ECG recording. In general, ECG is recommended for measurement of QTc interval in all hospitalized COVID-19 patients, before starting HCQ.

Patients can be categorized into a low-risk group with a normal QTc interval (group A), a moderate-risk group with slightly prolonged (up to 500 ms; group B) and a high-risk group with a prolonged QTc interval ≥500 ms (group C) (see Fig. 1).

Besides prolonged QTc interval, certain clinical factors which predispose a person to HCQ toxicity should be noted (Table 1).

5. Recommendations for use of hydroxychloroquine in COVID-19 therapy

The Government of India, Ministry of Health and Family Welfare Guidelines on Clinical Management of COVID-19 (dated March 31, 2020) [12], recommend that following drugs may be considered as an off–label indication in patients with severe disease and

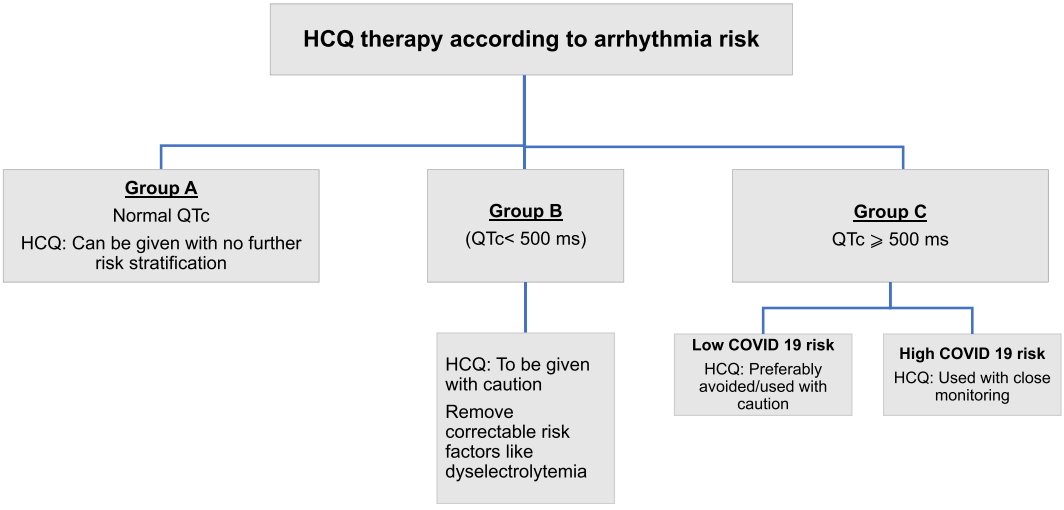

Fig. 1. Hydroxychloroquine therapy according to cardiovascular risk.
Abbreviations: HCQ – Hydroxychloroquine, QTc-corrected QT interval.

Table 1
Risk factors for hydroxychloroquine-induced arrhythmia.

1. Structural heart diseases especially ventricular hypertrophy or left ventricular dysfunction
2. Previous history of ventricular arrhythmia or syncope
3. History of implantable heart rhythm devices
4. Co-administration of other QT prolonging drugs (macrolides, quinolones, anti-histaminics, antiviral, anti-arrhythmic, or anti-fungal drugs, etc.). (Refer https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf for a detailed list)

requiring ICU management:

- HCQ: 400 mg BD for one day followed by 200 mg BD for 4 days, in combination with
- Azithromycin: 500 mg OD for 5 days.

These drugs should be administered under close medical supervision, with monitoring for side effects including QTc interval. The above regimen is presently not recommended for children less than 12 years, and pregnant or lactating women. These guidelines are based on currently available information (uncontrolled clinical trials) and will be reviewed as new evidence emerges.

5.1. Recommendations for hydroxychloroquine therapy according to arrhythmic risk

a) Those with normal QTc interval (Group A): HCQ can be administered without further risk stratification.
b) Those with slightly prolonged QTc interval (<500 ms; Group B): HCQ should be used with caution with attempts to resolve correctable risk factors.
c) Those with baseline QTc ≥500 ms (Group C): These patients should have clinical evaluation as per Table 1, and can be further subdivided into two categories on basis of COVID-19 risk.
   - Low COVID-19 risk: In patients having lower risk of COVID-19 complications, HCQ should preferably be avoided or used with caution.
   - High COVID-19 risk: In patients having higher risk of COVID-19 complications, HCQ may be used with close monitoring.

5.2. Frequency of ECG monitoring

1. In patients with QTc ≥500 ms at baseline, it is recommended to perform an ECG at 2–4 h after the first dose to measure any change in QTc, and then at 48 and 96 h [13].
2. If there is prolongation in QTc interval by more than 60 ms from baseline, reassess benefit versus risk of continuing HCQ therapy.

6. Recommendations for use of hydroxychloroquine in COVID-19 prophylaxis

The National Task Force for COVID-19 constituted by Indian Council of Medical Research (ICMR) on March 22, 2020 recommended HCQ for prophylactic use [14]. The recommended dosage is as follows.

1. 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
2. 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.

The drug is not recommended for prophylaxis in children under 15 years of age. In addition, the drug is contraindicated in persons with retinopathy, known hypersensitivity to HCQ and 4-aminoquinoline compounds, and pregnant patients.

These recommendations, according to the task force, are based on the evidence of benefit supported by pre-clinical data and under 'exceptional' circumstances. The prophylactic use of HCQ should be coupled with pharmacovigilance for adverse events through self-reporting using the Pharmacovigilance Program of India (PvPI) helpline/App.

When HCQ is used for prophylaxis, although it is preferable to have a baseline ECG to measure the QTc interval, it may not be logistically possible in everyone. However, efforts should be made to identify all potentially high-risk individuals (Table 1) and they should undergo ECG monitoring for QTc interval.

7. Conclusions

Hydroxychloroquine is being used globally for treatment and prophylaxis of COVID-19. Various countries have issued recommendations on its use based on in-vitro, or small clinical studies. In absence of randomized trial data, these recommendations reflect the extraordinary situation of a rapidly evolving pandemic of a highly contagious disease. The guidelines are likely to change as more data from randomized clinical trials is available. The decision to use HCQ for COVID-19 should take into account the occasional possibility of cardiac arrhythmia.

Indian Heart Rhythm Society recommends the use of HCQ as per the ICMR task force recommendations and strongly discourages its use for the general public without medical supervision and prescription. Even though a 12-lead ECG is a widely available tool, obtaining ECG of every suspected or confirmed patient of COVID-19 may be impractical and strain healthcare resources in a pandemic situation. Hence, using smartphone-based pocket ECG devices can potentially save healthcare resources in the current situation. The measures of restrained advocacy for potentially beneficial effects of HCQ and advice against self-medication can help prevent adverse events related to this drug.

Declaration of competing interest

None of the authors has anything to disclose.

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