



International Journal of Hospital Pharmacy (ISSN:2574-0318)



Guidelines for Safe and Effective Use of Hydroxychloroquine in COVID-19 Patients

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ABSTRACT

The emergent need to treat COVID-19 patient must be tempered with safe use of drugs. The guideline set forth provides parameters for dosing and monitoring hydroxychloroquine in this population, reducing the occurrence of adverse effects and improving overall pharmacotherapy.


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How to cite this article:

Hannah Ariel. Guidelines for Safe and Effective Use of Hydroxychloroquine in COVID-19 Patients. International Journal of Hospital Pharmacy, 2020, 5:38

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Hydroxychloroquine is rapidly emerging as a first-line contender in the armamentarium against COVID-19. Several completed small studies demonstrate the efficacy of hydroxychloroquine in moderate doses (200mg twice daily or three times daily, for 5-10 days). At these doses, virological clearance and improvements in clinical and radiologic parameters are reported¹ Observations from these preliminary studies, along with theoretical knowledge of hydroxychloroquine structure-activity relationship provide the impetus to treat COVID-19 with hydroxychloroquine +/- azithromycin. Initiation of larger trials using higher doses of hydroxychloroquine +/- azithromycin are currently being planned.

The immediacy of need for rapid and effective treatment of acute COVID-19 must be balanced with safe medication usage. The readily accessible FDA labelling does not include recommendations at this time for safe use of hydroxychloroquine in the setting of renal dysfunction, polytherapy, or concomitant cardiac conditions in the COVID-19 patient. However, early pharmacokinetic and pharmacodynamic studies characterizing hydroxychloroquine in humans reveals important considerations in this regard. These important findings follow.

Hydroxychloroquine is 60-70 percent bioavailable after oral administration. Bioavailability is minimally affected by food intake. Patients receiving hydroxychloroquine should take it with food or avoid taking it on an empty stomach to decrease gastric irritation and gastrointestinal side effects. Prior to administration baseline electrocardiogram is warranted, and QTc calculation advised. Considering peak levels of hydroxychloroquine are seen 3-5 hours after ingestion of the medication, particular attention should be given to the electrocardiogram around this time. Furthermore, considering well documented variation in QTc, establishment of a QTc "patient range" is recommended, with critical time points for QTc widening predicted in the early morning hours and early evening hours.^{2,3} This range,

combined with observed QTc at time of peak absorption of medication into the bloodstream will aid in determine any subsequent dosage adjustments. At time of peak hydroxychloroquine ingestion (average of 4 hours status post dose), an observed QTc widening up to 25-35% baseline is expected. No change in subsequent doses is warranted. For QTc peak widening of 35-50%, decrease hydroxychloroquine dose approximately 25 percent. For QTc peak measurements of 50 percent widening compared to baseline, hold next dose of hydroxychloroquine, and reinstitute subsequent doses at 25-50% original dose. Since hydroxychloroquine shares antiarrhythmic effects similar to those of Class IA antiarrhythmic quinidine, proarrhythmic is an inherent risk with excessive QTc widening. Any signs of QTc widening exceeding 50% warrant holding of subsequent doses, and re-evaluation of further treatment with hydroxychloroquine, with the assistance of cardiology consultation.

The proarrhythmic adverse effects of hydroxychloroquine are dose-related. Therefore, in average sized patients, the average dose of 600-800mg daily divided into 2-3 doses is acceptable. For those patients presenting with decreased actual body weight, a weight-based dosing strategy is recommended. This includes pediatric patients and those adult patients with decreased body weight and visibly thin appearance. Weight based dosing recommended for hydroxychloroquine is 6.5 mg of hydroxychloroquine salt (5 mg of the base) per kg daily. This dose is divided into two to three daily doses. Considering that the hydroxychloroquine is available in 200 mg tablets (Watson manufacturer's hydroxychloroquine is scored, making more accurate dosing possible), dosing should be round to the nearest 100mg. For example, a 50 kg adult patient would receive 6.5mg x 50kg or 335 mg daily. This is most closely met with 1.5 tablets of 200mg scored hydroxychloroquine. Check with the pharmacy to ensure that scored

tablets are available. If not, the second choice is to round the nearest 200mg.

This dosing strategy is based on moderate dosing recommendations, which have been shown to be effective and relatively well tolerated. Higher dosing strategies increase the risk for untoward cardiovascular proarrhythmic effects. Higher dosing strategies should be carefully considered.

Hydroxychloroquine is metabolized in the liver to active metabolites, and undergoes up to 50 percent renal excretion. Although FDA recommendation do not include recommendations dosing in renally compromised patients, the patient population afflicted with COVID-19 typically has significant changes in renal clearance. Dosage adjustment for creatine clearance less than 30mL/min is warranted. Furthermore, other concomitant medications which are renally cleared will compete for clearance of hydroxychloroquine.

Clinically significant drug interactions exist between hydroxychloroquine and drugs which are bound to alpha-1 acid glycoprotein, such as digoxin. Patients receiving concomitant digoxin therapy should be closely monitored and dosage adjustments in digoxin made according to clinical presentation and trough digoxin levels. Hydroxychloroquine is metabolized through the CYP 2D system. Therefore, any drugs sharing this metabolic pathway will compete for hydroxychloroquine metabolism, and should be adjusted according to QTc changes and clinical impression.

What follows is an algorithm for safe hydroxychloroquine therapy:

GUIDELINES FOR SAFE AND EFFECTIVE USE OF HYDROXYCHLOROQUINE IN COVID-19 PATIENTS

I. Prior To Hydroxychloroquine Administration

- A. Actual Body Weight
- B. Baseline ECG; QTc
- C. Baseline Renal Function (BUN and SerCr; ClCr)

II. ECG Acceptable: Initiate Hydroxychloroquine ECG Abnormal: Consult Cardiology

III. Dosage Selection

A. Average actual body weight: Standard Dosing not to exceed 800mg daily

B. Decreased actual body weight: Weight-based dosing

* For ClCr \leq 30 mL/min, consider decreased maintenance dose

**Patients receiving Digoxin therapy may require reduction in Digoxin dose: Monitor trough Digoxin levels and clinical presentation

*** Patients receiving CYP2D inhibitors: monitor closely for signs of toxicity (increased QTc) and dose adjust accordingly

IV. Subsequent Monitoring of ECG with attention QTc and clinical presentation

A. Baseline ECG with attention to QTc

B. Establish QTc range for patient

C. Expect increased QTc at 3-5 hours status-post oral dose of hydroxychloroquine

D. Use observed QTc range and maximum QTc prolongation as context for subsequent dosing adjustments and therapeutic decisions

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