PHARMACEUTICAL SOCIETY OF KENYA

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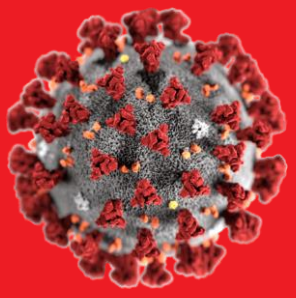

POSITION STATEMENT ON USE OF HYDROXYCHLOROQUINE IN COVID - 19

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There has been a lot of attention recently in social media circles on the use of Hydroxychloroquine in the management of COVID 19. This has raised a lot of curiosity among medical colleagues with some prescribing this medicine for patients who test positive in their health facilities. We fully understand that the public is anxious and is desperately looking for a cure, but this desperation should not be exploited. All COVID-19 positive patients need to be fully informed on the benefits vis-à-vis the risks of using this drug,

Based on anecdotal reports, hydroxychloroquine has been suggested as a potential drug that can be used for the management of COVID-19; however, data is still limited. Results from a single, small, open-label, non-randomized study of a limited number of hospitalized adult patients suggest hydroxychloroquine may be beneficial in reducing the duration of viral carriage (Gautret 2020).

There are no currently available data from Randomized Clinical Trials (RCTs) to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection. Although optimal dosing and duration of hydroxychloroquine for treatment of COVID-19 are unknown, some U.S. clinicians have reported anecdotally different hydroxychloroquine dosing such as: 400mg BID on day one, then daily for 5 days; 400 mg BID on day one, then 200mg BID for 4 days; 600 mg BID on day one, then 400mg daily on days 2-5

However, based on WHO guidelines, there is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19. There are many ongoing clinical trials testing various potential antivirals and investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials.

WHO further recommends that if conducting an RCT is not possible, then investigational therapeutics should be used under **Monitored Emergency Use of Unregistered Interventions Framework (MEURI)**, until an RCT can be initiated.

In view of the above, the Pharmaceutical Society of Kenya, taking into consideration the safety, efficacy and potential for abuse of HCQ, recommends the following:

1. Health care providers use the WHO recommendations for management of COVID-19 patients.
2. We discourage over the counter dispensing of HCQ by community pharmacists.
3. In the scenario where a health care provider wishes to prescribe HCQ for off-label use, full disclosure should be made to the patient and consent be taken prior to use.
4. The following recommendations be taken into account:
    a. Patient's allergy history be documented in the patient's file.
    b. Patient's drug history be documented and a drug interaction check be done by a qualified pharmacist.
    c. Adverse effects of this drug may alter the disease state of patient's with co-morbidities such as diabetes, cardiac arrhythmias and retinopathy.
    d. A pregnancy test be conducted for women of child bearing age prior to using this drug.

We further recommend that health care providers take the time to read the monograph below and empower the patients with this information.

HYDROXYCHLOROQUINE : DRUG INFORMATION

DOSING: ADULT

Note: Dosage forms; All doses below are expressed as hydroxychloroquine sulfate salt. Hydroxychloroquine sulfate salt 200 mg is equivalent to hydroxychloroquine base 155 mg.

Safety: To avoid retinopathy and permanent vision loss, do not exceed recommended maximum doses.

Tolerability: GI upset (nausea, vomiting, diarrhea) is a common adverse effect. Dividing doses, taking with food, and, if appropriate, gradual dose escalation may improve tolerability.

Coronavirus disease 2019 (COVID-19) (off-label use): Note: Limited data available. Dose based on one small, open-label, nonrandomized study in hospitalized patients with coronavirus disease 2019; currently, there are no data to support use for prophylaxis.

Oral Dose: 200 mg 3 times daily for 10 days (Gautret 2020).

Alternative dosing: 400 mg twice daily on day 1 followed by 200 mg twice daily for 4 days (CDC 2020; Yao 2020) **OR** 400 mg twice daily on day 1 followed by 400 mg once daily for 5 days or 600 mg twice daily on day 1 followed by 400 mg once daily for 4 days (CDC 2020).

DOSING: RENAL IMPAIRMENT: ADULT

There are no dosage adjustments provided in the manufacturer's labeling; dosage reduction may be needed; use with caution.

DOSING: HEPATIC IMPAIRMENT: ADULT

There are no dosage adjustments provided in the manufacturer's labeling; use with caution

DOSING: PEDIATRIC

Data is not yet available in pediatric patients. The impact of hydroxychloroquine on the course of disease is unknown. As data and experience in pediatric patients continue to rapidly evolve, dosing will be updated as appropriate.

ADMINISTRATION: ADULT

Administer with food or milk. Do not crush or divide film-coated tablets

MEDICATION SAFETY ISSUES (SOUND-ALIKE/LOOK-ALIKE ISSUES):

Hydroxychloroquine may be confused with hydrocortisone, hydroxyurea

CONTRA-INDICATIONS

i. Patients who are hypersensitive to 4-aminoquinoline compounds eg Quinine, Mefloquine.

ii. Patients with retinopathy and pre-existing maculopathy of the eye.

iii. Patients with retinal or visual field changes attributable to any 4-aminoquinoline compound

iv. Pregnancy.

PREGNANCY WARNING

Pregnancy category: D

Animal studies have revealed evidence of fetal harm. Use of hydroxychloroquine and other 4-aminoquinolines in high doses and for prolonged durations has been associated with neurological disturbances and interference with hearing, balance, and vision in the fetus. There are no controlled data in human pregnancy.

Risk Summary: Animal studies show that this drug passes rapidly across the placenta. It accumulated selectively in the melanin structures of the fetal eyes and was retained in the ocular tissues for 5 months after the drug had been eliminated from the rest of the body.

ADVERSE REACTIONS

1% to 10%: Ophthalmic: Retinopathy (4%; serum concentration dependent [Petri 2019]; early changes reversible [may progress despite discontinuation if advanced])

Frequency not defined:

Dermatologic: Acute generalized exanthematous pustulosis, alopecia, bullous rash, dyschromia (skin and mucosal), erythema multiforme, exacerbation of psoriasis, exfoliative dermatitis, hair discoloration, pruritus, skin photosensitivity, skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Exacerbation of porphyria, severe hypoglycemia, weight loss

Gastrointestinal: Abdominal pain, decreased appetite, diarrhea, nausea, vomiting

Hematologic & oncologic: Agranulocytosis, anemia, aplastic anemia, bone marrow failure, hemolysis (in patients with glucose-6-phosphate deficiency), leukopenia, thrombocytopenia

Hepatic: Abnormal hepatic function tests, acute hepatic failure

Hypersensitivity: Angioedema

Immunologic: Drug reaction with eosinophilia and systemic symptoms

Nervous system: Ataxia, dizziness, emotional lability, fatigue, headache, irritability, nervousness, nightmares, psychosis, seizure, sensorineural hearing loss, suicidal tendencies, vertigo

Neuromuscular & skeletal: Myopathy (including palsy or neuromyopathy, leading to progressive weakness and atrophy of proximal muscle groups; may be associated with mild sensory changes and loss of deep tendon reflexes)

Ophthalmic: Corneal changes (corneal edema, corneal opacity, corneal sensitivity, corneal deposits, visual disturbance, blurred vision, photophobia), decreased visual acuity, macular degeneration, maculopathy, nystagmus disorder, retinal pigment changes, retinitis pigmentosa, scotoma, vision color changes, visual field defect

Otic: Deafness, tinnitus

Respiratory: Bronchospasm

Cardiovascular: Cardiomyopathy, prolonged QT interval on ECG, torsades de pointes, ventricular arrhythmia

Endocrine & metabolic: Hypoglycemia

Ophthalmic: Epithelial keratopathy

WARNINGS/PRECAUTIONS

CONCERNS RELATED TO ADVERSE EFFECTS:

• Cardiovascular effects: Cardiomyopathy resulting in cardiac failure, sometimes fatal, has been reported (symptoms may present as atrioventricular block, pulmonary hypertension, sick sinus syndrome, or as cardiac complications), and may appear during acute or chronic therapy. Monitor for signs/symptoms of cardiac compromise; discontinue treatment promptly if signs and symptoms of cardiomyopathy occur. In a scientific statement from the American Heart Association, hydroxychloroquine has been determined to be an agent that may either cause direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: major) (AHA [Page 2016]). Consider chronic toxicity if conduction disorders (eg, bundle branch block, atrioventricular heart block) as well as biventricular hypertrophy are diagnosed. May also be associated with QT interval prolongation; ventricular arrhythmia and torsades de pointes have been reported (avoid concurrent use of other medications which may prolong the QT interval).

• Dermatologic effects: Skin reactions to hydroxychloroquine may occur; use with caution in patients on concomitant medications with a propensity to cause dermatitis.

• Hematologic effects: Bone marrow suppression (eg, agranulocytosis, anemia, aplastic anemia, leukopenia, thrombocytopenia) have been reported; periodically monitor CBC during prolonged therapy. Discontinue treatment if signs/symptoms of severe blood disorder not attributable to the underlying disease occur.

• Hypoglycemia: Severe hypoglycemia, including life-threatening loss of consciousness, has been reported in patients with and without concomitant use of antidiabetic agents. Advise patients of risk of hypoglycemia and associated signs/symptoms; discontinue use in patients who develop severe hypoglycemia.

• Neuromuscular effects: Proximal myopathy or neuromyopathy, leading to progressive weakness, proximal muscle atrophy, depressed tendon reflexes, and abnormal nerve conduction may occur, especially with long-term therapy. Curvilinear bodies and muscle fiber atrophy with vacuolar changes have been noted on muscle or nerve biopsy. Muscle strength (especially proximal muscles) and reflexes should be assessed periodically during long term therapy.

• Psychiatric effects: Suicidal behavior has been reported rarely.

• Retinal toxicity: Retinal toxicity, potentially causing irreversible retinopathy, is predominantly associated with high daily doses and a duration of >5 years of use of chloroquine or hydroxychloroquine in the treatment of rheumatic diseases. One study suggested a correlation of higher serum concentrations of hydroxychloroquine with ocular toxicity (Petri 2019). Other major risk factors include concurrent tamoxifen use, renal impairment, lower body weight, and the presence of macular disease. Daily hydroxychloroquine (base) doses >5 mg/kg actual body weight were associated with an ~10% risk of retinal toxicity within 10 years of treatment and an almost 40% risk after 20 years of therapy. Risk is most accurately assessed on the basis of duration of use relative to daily dose/body weight (Marmor [AAO 2016]; Melles 2014). Based on these risks, the American Academy of Ophthalmology (AAO) recommends not exceeding a daily hydroxychloroquine dosage of 5 mg/kg using actual body weight in most patients. Previous recommendations to use ideal body weight are no longer advised; very thin patients in particular were at increased risk for retinal toxicity using this practice. Current AAO guidelines do not specifically address dosing in obese patients. AAO also recommends baseline screening for retinal toxicity and annual screening beginning after 5 years of use (or sooner if major risk factors are present) (Marmor [AAO 2016]). If ocular toxicity is suspected, discontinue and monitor closely; retinal changes and visual disturbances may progress after discontinuation. A baseline ocular exam is recommended within the first year of initiating hydroxychloroquine treatment.

MONITORING PARAMETERS

CBC at baseline and periodically;

Liver function;

Renal function (in patients at risk for ocular toxicity);

Blood glucose (if symptoms of hypoglycemia occur);

Ophthalmologic exam at baseline (fundus examination within the first year plus visual fields and spectral-domain optical coherence tomography [SD OCT] if maculopathy is present) to screen for retinal toxicity.

Pharmacodynamics and Pharmacokinetics

Onset of action: still under investigation

Absorption: Incomplete and variable (~70% [range: 25 to 100%])

Protein binding: ~40%, primarily albumin

Metabolism: Hepatic; metabolites include bidesethylchloroquine, desethylhydroxychloroquine, and desethylchloroquine

Half-life elimination: ~40 days

Excretion: Urine (15% to 25% as metabolites and unchanged drug up to 60%); may be enhanced by urinary acidification.

REFERENCES

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