Instituto de Salud Pública
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GUIDELINES FOR MONITORING ADVERSE EFFECTS IN COVID-19 PATIENTS TREATED WITH CHLOROQUINE OR HYDROXYCHLOROQUINE.

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I. INTRODUCTION:

The pharmacological treatment of COVID-19 continues to be the focus of research and controversy due to the lack of a globally accepted standard treatment. Some of the most frequently used drugs in COVID-19 patients include the quinine derivatives chloroquine and hydroxychloroquine, although evidence on efficacy is not conclusive.

As yet, available publications on the usefulness of chloroquine and hydroxychloroquine in this disease include a reduced number of studies, with a limited number of patients and moderate benefits, if any, expressed in variables that do not necessarily reflect a clinically relevant effect in patients; several recent review articles suggest that currently available information does not provide enough evidence to support the use of this drug for this indication nor does it allow to define the best dosing schedule.[1-6]

In March 2020, upon a specific request from the Biomedical Advanced Research and Development Authority (BARDA), the Food and Drug Administration (FDA) issued an emergency use authorization to allow the use of chloroquine and hydroxychloroquine on the grounds that these medicines would be included in clinical recommendations for hospitalized patients in different countries based on in vitro and anecdotal clinical data from case series.[7]

The FDA indicated that these drugs, which are not authorized to treat COVID-19, should preferably be used within the context of randomized controlled clinical trials that may produce evidence on their effectiveness in this disease. Nevertheless, understanding that some patients cannot have access to a study or their participation in a clinical trial is not feasible, the FDA agreed to issue this emergency authorization, limiting the scope as follows:

- It applies to hydroxychloroquine (approved by FDA for other uses) and chloroquine (not previously authorized), with the relevant labelling and inserts, provided that they are supplied by the US Strategic National Stockpile.
- These drugs should be given in a healthcare facility, according to a valid prescription issued by an authorized professional.
- These drugs should only be used to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation in a study is not feasible.[7]

The Ministry of Health of Chile (MINSAL) does not recommend the routine use of chloroquine or hydroxychloroquine in COVID-19 patients (conditional recommendation, with a very low level of certainty). The panel of experts consulted by the MINSAL recommends that although in most COVID-19 patients it is advisable not to use chloroquine or hydroxychloroquine, this is a therapeutic alternative to be considered in patients admitted to critical care units, particularly if they are older than 65 years, suffer comorbidities, have severe pneumonia or progressive respiratory infection. Nevertheless, there is no evidence, to date, that the use of chloroquine or hydroxychloroquine improves the prognosis of COVID-19 patients. Only isolated reports suggest that these drugs have in vitro activity against the SASR-CoV-2 virus and could shorten viral shedding during treatment.8
On April 3rd 2020, the MINSAL distributed circular B21/Nº59 with guidelines on the clinical management of infections caused by COVID-19 indicating that chloroquine or hydroxychloroquine

can be used in patients older than 65 years and/or with comorbidities, presenting with severe pneumonia or progressive respiratory infection who are admitted to Critical Care Units (CCU).
In this scenario, it is important to consider that both drugs are related to significant adverse effects and, therefore, deciding their use in a particular patient should go in line with a proper follow-up and subsequent report of potential adverse effects.

II. OBJECTIVES:

This document is intended to:

1. Provide health professionals with information on the potential risks of treating COVID-19 patients with chloroquine or hydroxychloroquine.
2. Recommend to the health team the parameters that should be monitored before and after the treatment with these drugs.
3. Remind on the obligation of notifying suspected ADRs detected during off-label use of chloroquine and hydroxychloroquine for COVID-19 treatment, and provide the guidelines for this end.

III. BACKGROUND ON CHLOROQUINE AND HYDROXYCHLOROQUINE

1. Sanitary Registrations:

In Chile, both chloroquine and hydroxychloroquine are currently registered and approved by the Public Health Institute (ISP, for its Spanish acronym). Oral chloroquine has been registered for two indications: treatment and prophylaxis of malaria and, combined with an amebicide, for the treatment of extraintestinal amebiasis (Table 1). On the other hand, oral hydroxychloroquine has been registered for six indications: treatment of several diseases such as malaria, amebiasis, lupus, rheumatoid arthritis and some skin conditions (Table 2).[10]

Table 1. Chloroquine Sanitary Registries in force

ISP REGISTRATION NBR.	NAME OF PHARMACEUTICAL PRODUCT	REGISTRATION DATE	COMPANY	ACTIVE PRINCIPLE
F-2258/19	CHLOROQUINE DIPHOSPHATE, TABLETS 250 mg	03-12- 1971	LABORATORIO CHILE S.A.	CHLOROQUINE
F-2135/19	CHLOROQUINE PHOSPHATE, COATED TABLETS 250 mg	11-12-1999	BPH S.A.	CHLOROQUINE

Table 2. Hydroxychloroquine Sanitary Registries in force

ISP REGISTRATION NBR.	NAME OF PHARMACEUTICAL PRODUCT	REGISTRATION DATE	COMPANY	ACTIVE PRINCIPLE
F-22467/16	DROLSAN COATED TABLETS 200 mg (HYDROXYCHLOROQUINE SULFATE)	02-18- 2016	MINTLAB Co S.A.	HYDROXYCHLOROQUINE
F-22406/16	HYDROXYCHLOROQUINE SULFATE, COATED TABLETS 200 mg	01-19-2016	EXELTIS CHILE S.p.A	HYDROXYCHLOROQUINE
F-23869/18	HYDROXYCHLOROQUINE SULFATE, COATED TABLETS 200 mg	07-09-2018	DIFEM LABORATORIOS S.A	HYDROXYCHLOROQUINE
F-17359/19	ILINOL COATED TABLETS 200 mg (HYDROXYCHLOROQUINE)	01-30-2009	PHARMA INVESTI DE CHILE S.A	HYDROXYCHLOROQUINE
F-24346/18	PLAQUINOL COATED TABLETS 200 mg (HYDROXYCHLOROQUINE SULFATE)	11-21-2018	SANOFI-AVENTIS DE CHILE S.A	HYDROXYCHLOROQUINE
F-18705/16	REUMAZINE COATED TABLETS 200 mg (HYDROXYCHLOROQUINE)	06-24-2011	INSTITUTO SANITAS S.A.	HYDROXYCHLOROQUINE

2. Contraindications:[10,11]

Hydroxychloroquine:

- Known hypersensitivity to 4-aminoquinoline derivatives
- Pre-existing maculopathy
- Children < 6 years of age (since the 200-mg dosage form not adapted for weight< 35 kg)

Chloroquine:

- Known hypersensitivity to 4-aminoquinoline derivatives
- Current retinal or visual field damage
- Psoriasis
- Porphyria
- Baseline prolonged QT interval and increased risk of arrhythmia (chloroquine)

3. Precautions and warnings on main adverse reactions by affected system or organ:[10-13]

Warnings and precautions to be considered with the use of either chloroquine or hydroxychloroquine are presented below in order to prevent or minimize adverse reactions associated to this therapeutic class.

a. <u>Cardiovascular System</u>

Cardiomyopathy: cases of cardiomyopathy that may result in cardiac failure, sometimes with a fatal outcome, have been reported with long-term and high-dose use of hydroxychloroquine or chloroquine. Patients may present atrioventricular block, pulmonary hypertension, sinus node disease, or electrocardiographic (ECG) abnormalities both with acute and chronic treatment. If cardiotoxicity is suspected, treatment should be immediately discontinued.

Prolonged QT interval: both chloroquine and hydroxychloroquine have the potential to prolong the QTc interval in some patients. These drugs should be used with caution in the presence of risks factors, namely: history of prolonged QT interval, heart diseases (including cardiomyopathy, pericarditis and myocarditis) history of ventricular arrhythmias, bradycardia, potassium or magnesium imbalance, and concomitant use of drugs that prolong the QT interval. When administered, they should be used with extreme caution and patients should be closely monitored.

The magnitude of QT interval prolongation may be higher when drug concentrations are increased. QT interval prolongation may be associated with Torsades de Pointes (TdP) ventricular tachycardia as well as with syncope and sudden death due to TdP degeneration into ventricular fibrillation, which is a risk marker both in patients with different heart diseases and in those without structural heart disease.

b. Endocrine-Metabolic System

Hypoglycemia: Patients with or without antidiabetic treatment may have severe or life-threatening hypoglycemia including loss of consciousness. Patients with symptoms suggesting hypoglycemia during chloroquine or hydroxychloroquine treatment should be monitored for their blood sugar levels and treatment should be reevaluated.

c. Hematological System

The use of chloroquine or hydroxychloroquine may lead to severe blood disorders, including pancytopenia, neutropenia, aplastic anemia, agranulocytosis, leukopenia and thrombocytopenia. In addition, both drugs should be used with caution in patients with glucose 6-phosphate dehydrogenase deficiency since hemolysis cases have been reported.

The use of hydroxychloroquine is not recommended in patients with porphyria unless the benefits outweigh the risks, since the disease may be exacerbated.

d. Musculoskeletal System

Myopathies, neuromyopathies and muscle weakness (particularly in proximal muscles) have been described and they can be associated with mild sensorial changes, absent or hypoactive tendon reflex (hyporreflexia) and abnormal nerve conduction.

e. Central Nervous System

In addition to neuromyopathies, isolated cases of extrapyramidal symptoms, nystagmus and seizures have been reported.

f. Eye Disorders

Irreversible retinal damage has been reported. Patients receiving daily doses above 6.5 mg/kg (5 mg/kg hydroxychloroquine base) or 2.3 mg/kg of chloroquine, presenting subnormal glomerular filtration, concomitant use of tamoxifen citrate, or concurrent macular disease and treated for more than 5 years are at a higher risk. It is advisable to monitor, even after treatment discontinuation, and discontinue the drug if potential damage is suspected.

g. Ear Disorders

Irreversible hearing loss may appear, although it is rare or very rare. In case of hearing impairment, treatment should be immediately discontinued and the patient should be evaluated. Use with caution in patients with preexisting hearing impairment.

h. Immune System

Anaphylaxis, including angioedema, has been reported. Drug reaction syndrome with eosinophilia and systemic symptoms (DRESS) has also been reported during post-marketing use of both drugs.

i. Liver Disorders

Use with caution in patients with hepatitis, liver disease, alcoholism, or receiving concomitant hepatotoxic medication; dose adjustment may be necessary. Abnormal liver function tests, hepatitis and fulminant hepatic failure have been reported with the use of chloroquine and hydroxychloroquine. It is recommended to test patients before starting treatment.

j. Skin Disorders

Severe exacerbation of psoriasis may be observed. Chloroquine or hydroxychloroquine is not recommended in patients with this pathology unless the benefits outweigh the risks.

Skin reactions may occur, particularly with the use of drugs with the potential to induce dermatitis. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis have also been reported.

k. Psychiatric Disorders

Delirium, hallucinations and suicidal behavior have been reported with the use of chloroquine or hydroxychloroquine.

4. **Special Populations:**[10,11,13]

- Use with caution in patients with renal disease; dose should be adjusted if necessary.
- There is no need to adjust the dose in patients with a glomerular filtration rate ≥ 10 mL/min.
- Consider reducing the dose by 50% in patients with a glomerular filtration rate ≤ 10 mL/min.
- Avoid use during pregnancy, unless the benefits outweigh the potential risks. Although there is no evidence of damage to the fetus, both chloroquine and hydroxychloroquine accumulate and are retained in fetal ocular tissues for months, even after the drug has been eliminated from the body.
- Chloroquine and hydroxychloroquine are excreted in breast milk, although effects are not expected at therapeutic doses in breastfed children. Nevertheless, potential risks should be weighed against the benefits for the patient.
- A 50% dose reduction should be considered for patients on hemodialysis or peritoneal dialysis.
- Children appear particularly susceptible to the effects of these drugs and their adverse reactions, and they should therefore be used with special caution in these patients.

5. **Interactions:**[10-16]

Chloroquine is a substrate of CYP2C8, 2D6, and 3A4 and a moderate inhibitor of CYP2D6. Due to the similar structures of chloroquine and hydroxychloroquine and because both drugs are metabolized to the active metabolite desethylhydroxychloroquine, we suggest considering the same profile of interactions mediated by cytochrome P450.[14] The interactions with these drugs are available at: http://www.covid19-druginteractions.org/.

Major interactions are detailed below:

- Digoxin: Concomitant use may result in increased serum levels of digoxin; digoxin levels should therefore be closely monitored.
- Antacids and Kaolin: they can reduce the absorption of chloroquine or hydroxychloroquine. An interval of at least 4 hours should be observed with concomitant administration.
- Insulin and other antidiabetic drugs: a decrease in doses of these drugs may be required since both chloroquine and hydroxychloroquine may enhance their hypoglycemic effects.
- Drugs producing arrhythmias or prolonging QT interval: chloroquine and hydroxychloroquine should be used with caution when administered concomitantly with this type of drugs since there may be an increased risk of inducing ventricular arrhythmias. Some of these drugs are: class IA y III antiarrhythmic agents (amiodarone), tricyclic antidepressants, antipsychotic agents, some anti-infective agents (azithromycin, moxifloxacin).
- Ampicillin: chloroquine and hydroxychloroquine may significantly reduce the bioavailability of ampicillin. An interval of at least two hours between intake of both drugs is required.

- Cyclosporine: chloroquine and hydroxychloroquine increase the risk of cyclosporine toxicity. Close monitoring of serum cyclosporine levels is recommended and, if necessary, consider discontinuation of chloroquine or hydroxychloroquine treatment.
- Mefloquine: It increases serum concentrations of chloroquine and hydroxychloroquine and thus the risk of convulsions and QTc interval prolongation. If concomitant use cannot be avoided, consider delaying mefloquine administration for at least 12 hours after the last dose of chloroquine or hydroxychloroquine.
- Tamoxifen: Concomitant use should be avoided since it can increase the risk of ocular toxicity.
- Antiepileptics: The activity of antiepileptic drugs might be affected if co-administered with chloroquine or hydroxychloroquine.
- Antipsychotics (phenothiazines): Chloroquine or hydroxychloroquine may increase serum levels of phenothiazine.
- Beta-blockers: Hydroxychloroquine may reduce the metabolism of some beta-blockers, except for atenolol.
- Dapsone: Simultaneous use may increase the risk of hemolytic reactions. Any sign or symptom of hemolysis should be closely monitored, particularly in patients with Glucose-6-Phosphate-Dehydrogenase, methemoglobin reductase or hemoglobin M deficiency.
- Trastuzumab: Simultaneous use may increase the risk of neutropenia.
- Aminoglycoside antibiotics: Concomitant use may increase the risk of neuromuscular blockade.

IV. CARDIAC MONITORING OF COVID-19 PATIENTS TREATED WITH CHLOROQUINE OR HYDROXYCHLOROQUINE:

Several organizations and institutions in Chile and at international level have recently published recommendations, guidelines and protocols on the use of chloroquine or hydroxychloroquine in COVID-19 patients in order to prevent or reduce life-threatening arrhythmia events associated with prolonged QT interval. Of particular interest and concern is the concomitant use with azithromycin, a drug that may produce the same adverse effects and, therefore, its concomitant use has a higher risk potential. All publications agree on the fact that the QT interval should be strictly monitored after beginning treatment and a thorough evaluation of the conditions or factors that may cause QT prolongation should be performed prior to the start of treatment.

Recommendations for follow-up and potential discontinuation of chloroquine or hydroxychloroquine therapy, based on currently available evidence, are listed below.[17-20]

1. Prior to the start of treatment

Identify and evaluate the presence of (both non-modifiable and modifiable) risk factors or conditions for QT prolongation and their correction or treatment, whenever possible:

- History of long QT syndrome
- Female gender
- Cardiovascular disease (acute myocardial infarction, heart failure)
- Electrolyte imbalance (hypokalemia, hypomagnesemia, hypocalcemia)

- Renal/liver failure
- Sepsis
- Hypothermia
- Bradycardia (<50 bpm)
- Concomitant use of drugs causing QT prolongation, in which case drugs not considered essential should be discontinued (further information at www.crediblemeds.org).

2. **QT interval measurement**

Manual measurement is recommended. ECG leads suggested for this purpose are mainly D II, as well as V3, V5, V6. QT measurement should be adjusted for heart rate thus obtaining the corrected QT (QTc). Bazzett's formula is the most frequently used for this measurement and it is still universally accepted in spite of its limitations.

The upper limit of normal in prepubertal children of both sexes is 460 ms. In post pubertal males and females, these values are 470 and 480 ms, respectively.

3. **Treatment initiation and monitoring**

a. Daily monitoring of K serum concentrations, which should be within the normal range (average: 4.5 mEq/L).

b. Perform a baseline ECG; consider the following in the ECG reading:

- A baseline QTc ≥ 500 ms, or ≥ 550 ms if QRS is ≥ 120 ms (a "red light" according to Giudicessi et al. characterization) represents a relative contraindication for use. If it is nevertheless decided to start treatment (benefit/risk assessment), the QTc should be measured 2-3 hours after the second dose. If a 30 ms increase is detected, discontinuation of drug should be considered.
- In patients with normal QTc values (a "green light" according to Giudicessi et al. characterization) or above normal but lower than 500 ms (a "yellow light" according to Giudicessi et al. characterization) treatment may be started and its continuation will be assessed based on QTc values during the follow-up.
- If the QTc interval increases 60 ms or more from baseline ECG, or the QTc is 500 ms or more (or ≥ 550 ms if QRS is ≥ 120 ms) discontinuation of the drug or dose reduction should be considered.
- If, in despite of dose adjustment the QTc remains increased 60 ms or more from baseline ECG, or the QT is higher than or equal to 500 ms (or ≥ 550 ms if QRS is ≥ 120 ms) discontinuation of drug should be considered or a new assessment of the risk/benefit ratio should be done in order to decide on the continuation of treatment.
- If the QTc interval is not prolonged 60 ms or more or is not ≥ 500 ms (or ≥ 550 ms if QRS is ≥ 120 ms), treatment may be continued with the option of measuring the QT in a tracing from the monitor, and repeat measurements after 48 and 96 hours.

V. NOTIFICACIÓN DE SOSPECHAS DE REACCIONES ADVERSAS:

Remember that, pursuant to current standards, all suspected adverse drug reactions (ADRs) to chloroquine or hydroxychloroquine should be reported to the National Pharmacovigilance Centre within the set deadlines. The following recommendations should be taken into account when reporting is made:

- Specify age and sex of patient.
- Record clinical history of patients including, for example, chronic diseases or underlying pathology.
- If the ADR affects the cardiovascular system, indicate the baseline QT interval if it was measured before starting chloroquine or hydroxychloroquine treatment, as well as current value.
- For all agents used in the treatment of COVID-19, either suspected or concomitant, specify this indication in the field "reason for prescription"
- Do not forget to notify the treatment start date for the suspected drug and the date of the reported event.
- Record the doses of chloroquine or hydroxychloroquine used and the concomitant agents used by the patient, particularly those that prolong the QT interval.
- The description of the adverse reaction should include the event, signs and/or symptoms experienced by the patient, and the evolution of the adverse reaction. You may attach useful files to better explain the event observed.

Details on the notification process, as well as notification forms are available at: http://www.ispch.cl/anamed/farmacovigilancia_1/nram.

Remember to keep a documentary record of the patients treated with chloroquine under your care, whether they have originated an ADR report or not; later on, you may be asked for information in this regard.

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