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Hydroxychloroquine and azithromycin: cardiovascular risk, QTc prolongation and sudden death in the new COVID-19 outbreak

Hidroxicloroquina y azitromicina: riesgo cardiovascular, prolongación de QTc y muerte súbita en el nuevo escenario de la pandemia por COVID-19

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Abreviaturas
QTc: corrected QT interval

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To date, huge efforts are being made to find a treatment for COVID-19. Chloroquine or hydroxychloroquine, whether or not combined with antibiotics such as azithromycin or antivirals (lopinavir/ritonavir) are among the drugs that may eventually be used[1,2].

These drugs are extensively implemented in the treatment of collagen diseases such as systemic lupus erythematosus, and other autoimmune or rheumatic diseases. They are also used in the case of parasitic (even for long-lasting treatments) and bacterial (in the case of azithromycin) infections; yet its adverse effects are by now well known[3,4]. However, hydroxychloroquine, derived from chloroquine, has been largely deployed in malaria cases proving way more effective than the former[5].

The need for urgent action in the face of the growing pandemic coupled with the experience gained in the use of such drugs for the treatment of other viral diseases such as SARS-CoV-2 are compelling many countries such as France, China, Italy[6,7], among others to start a race of clinical trials with these drugs based on some scientific insight. At times, given the circumstances and limited time available, they are implemented early and without any kind of randomized study; something that, within the current scenario, would take up a bit of time. In fact, at this point, the appropriate doses are being considered.

A recent (March/2020) non-randomized and small research by a medical group in Marseille, France[6], has found that chloroquine lowers viral load in patients with VIDOC-19; however, there are online reports of sudden death events in these patients over the course of the pandemic mostly due to complex –torsades de pointes (TdP) ventricular arrhythmias– type[5],

triggered by the presence of prolonged QT. Furthermore, a number of recent reports are indicating a high prevalence of cardiac complications associated with the virus (myocardial injury/infarction, cardiogenic shock) as well as multi-organ dysfunction.

Hydroxochloroquine has two basic mechanisms of action: 1) it prevents viral replication and release of viral RNA by being able to change lysosomal pH and 2) has an anti-inflammatory effect mainly by impairing the tumor necrosis factor, cytokines, lymphokines, among others[8].

Why would this happen?

Each of these drugs alone may be responsible for prolonging the QT interval, especially chloroquine, hydroxychloroquine, and azithromycin. The first two belong to the group-A drugs list which are those that may produce long QT and TdP; whereas azithromycin is framed in group-B, with isolated reports of TdP and less substantial prolongation of corrected QT (QTc)[9,10], when compared to erythromycin or clarithromycin[11]. Although there is evidence of sudden death in some publications, these events are associated with factors such as age, sex and deterioration of the internal environment[5,12].

Both hydroxychloroquine and chloroquine directly affect the QT by modifying potassium ion channels (If) and calcium ion streams (IcaL). While azithromycin would react upon the fast sodium stream and L-calcium stream, according to laboratory animal tests and human cell preparations[13-15].

Hydroxychloroquine has the ability to inhibit the potassium channel KCNH2, encoded in the gene HERG4[16]; a gene mutation that is also found in type 2 long QT syndrome. There are subclinical cases of long QT (10%, according to some series) where the use of these drugs could actually unmask severe long QT.

Predisposing factors

History, comorbidities, and any association with other potentially malignant drugs should be thoroughly assessed before using both hydroxychloroquine and azithromycin as they may cause QT prolongation.

What should be evaluated?

- Pre-existing long QT
- Subclinical long QT (if unmasked at follow-up)
- Sinus bradycardia
- Female sex
- Adulthood
- Underlying cardiomyopathy
- History of myocardial infarction
- Alterations in the internal environment (hypocalcemia, hypokalemia, hypomagnesemia)
- Association with other drugs (some of them, as for instance, antihistamines are freely dispensed in Argentina), but even more so antiarrhythmics such as amiodarone, quinidine, flecainide, sotalol, propafenone, and so forth[17].

The FDA (Food and Drug Administration) has issued an alert for monitoring the QT interval in patients receiving hydroxychloroquine treatment; especially those taking it in combination with another drug known to prolong the QT interval.

QT interval

Under normal conditions, the QT interval will not show dispersion when measured on the electrocardiogram and therefore not many differences will be observed in the measurements of the different leads; but since such dispersions have been found in some diseases, the D_{II} lead is usually preferred for measurements.

The QT interval value should normally neither exceed nor fall below 10% of its corresponding heart rate value. This value is called corrected QT (QTc) and is precisely what we are referring to in this article. The absolute value of the QT interval is not generally used, but it is important to know that its

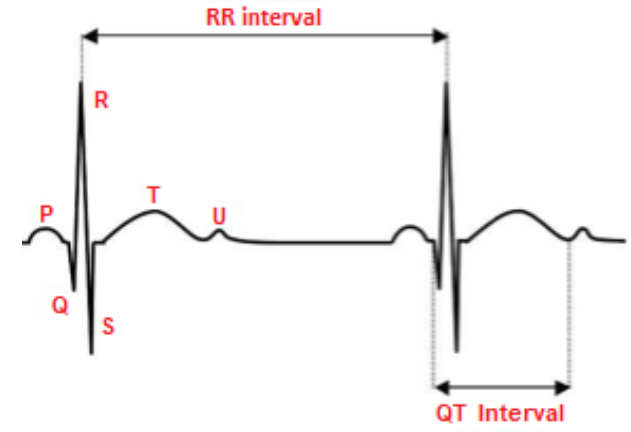

Figure 1. QT and RR interval measurement diagram.

value in normal individuals should not be more than 440 ms.

Clinically, the meaning of a long QT interval is variable. A long QTc –in this specific case– may be produced by the effect of certain type of pharmacological molecules that could also be the cause of severe ventricular arrhythmias in some cases.

Table 1. Formulas used to correct the QT interval.

Method	Fórmula
Bazett's method	**QTc = QT / (√RR) o QTc= QT/RR$^{1/2}$**
Fridericia's method	QTc = QT / (^{3}√RR) o QTc= QT/RR$^{1/3}$
Framingham's method	QTc = QT + 0,154 (1/RR)

When and how is QT measured?

1. Whenever these drugs (hydroxychloroquine and azithromycin) are used.
2. Preferably on a long D_{II} trace at admission and on a daily basis with corrected internal environment: potassium (>4 mEq/L) and magnesium (>2 mEq/L).
3. In the presence of general arrhythmogenic conditions such as hypoxia, hypovolaemia, myocardial ischemia, acidosis, hypothermia, hypokalemia, hypomagnesemia, hypocalcaemia, or association of QT-prolonging drugs (www.qtdrugs.org)[18].

QT measurement

The QT interval and RR distance are measured in milliseconds (ms) on an electrocardiogram or monitor rhythm calibrated at 25 or 50 mm/second. The RR distance is the interval between two successive R waves (**Figure 1**) and the QT, the interval between the beginning of the QRS and the end of the T wave (not including the U wave).

The **table 1** shows the formulas used to correct the QT interval according to heart rate. The normal range of the QTc is between 350-450ms.

Algorithm attempt according to QT mobilization during treatment

The following recommendations (summarized in **figure 2**) should be followed during treatment with these medications depending on the result of the QT interval measurement. To this end, patients should be divided into two groups according to the width of the QRS at the start of treatment.

Narrow QRS group < 120ms

1. **QTc < 460 ms:** Assess during the second dose of the drug, whether or not the QT increases by more than 50 ms. If it does not increase, proceed to continue treatment; if it increases, then re-evaluate after the fourth dose of hydroxychloroquine. If the QTc increases <50 ms, no further QT monitoring is required; but if it increases more than 50 ms, discontinuation should be considered.
2. **QTc 460-500 mg:** Same as above, and at 4th dose if QTc <550ms continue, and if it increases

Table 2. Most common drugs associated with prolongation of the QT interval. Se www.crediblemeds.org and www.qtdrugs.org[9,17,18].

Antiarrítmicos	Antidepresivos	Antipsicóticos	Antibióticos	Antihistamínicos	Otros
Disopyramide	Amitriptyline	Haloperidol	Ery- & azithromycin	Loratadine	Methadone
Procainamide	Desipramine	Phenothiazines	Pentamidine	Astemizole	Probucol
Quinidine	Imipramine	Citalopram	Chloroquine	Diphenhydramine	Droperidol
Dofetilide	Doxepin		Ciprofloxacin	Hidroxycine	Ondansetron
Dronedarone	Fluoxetine		Fluconazole		
Ibutilide	Sertraline		Levofloxacin		
Sotalol	Venlafaxine		Moxifloxacin		
Amiodarone			Clarithromycin		
			Itra- & ketoconazole		

to >550ms, suspend.

3. **QTc > 500 mg:** Do not administer.

Wide QRS group > 120ms

1. **QTc < 500ms:** Assess after the second dose of the drug, whether or not the QT increases by more than 50 ms. If it does not increase, proceed to continue treatment. If it increases, then re-evaluate after the fourth dose of hydroxychloroquine: if the QTc is <50 ms, no further QT monitoring is

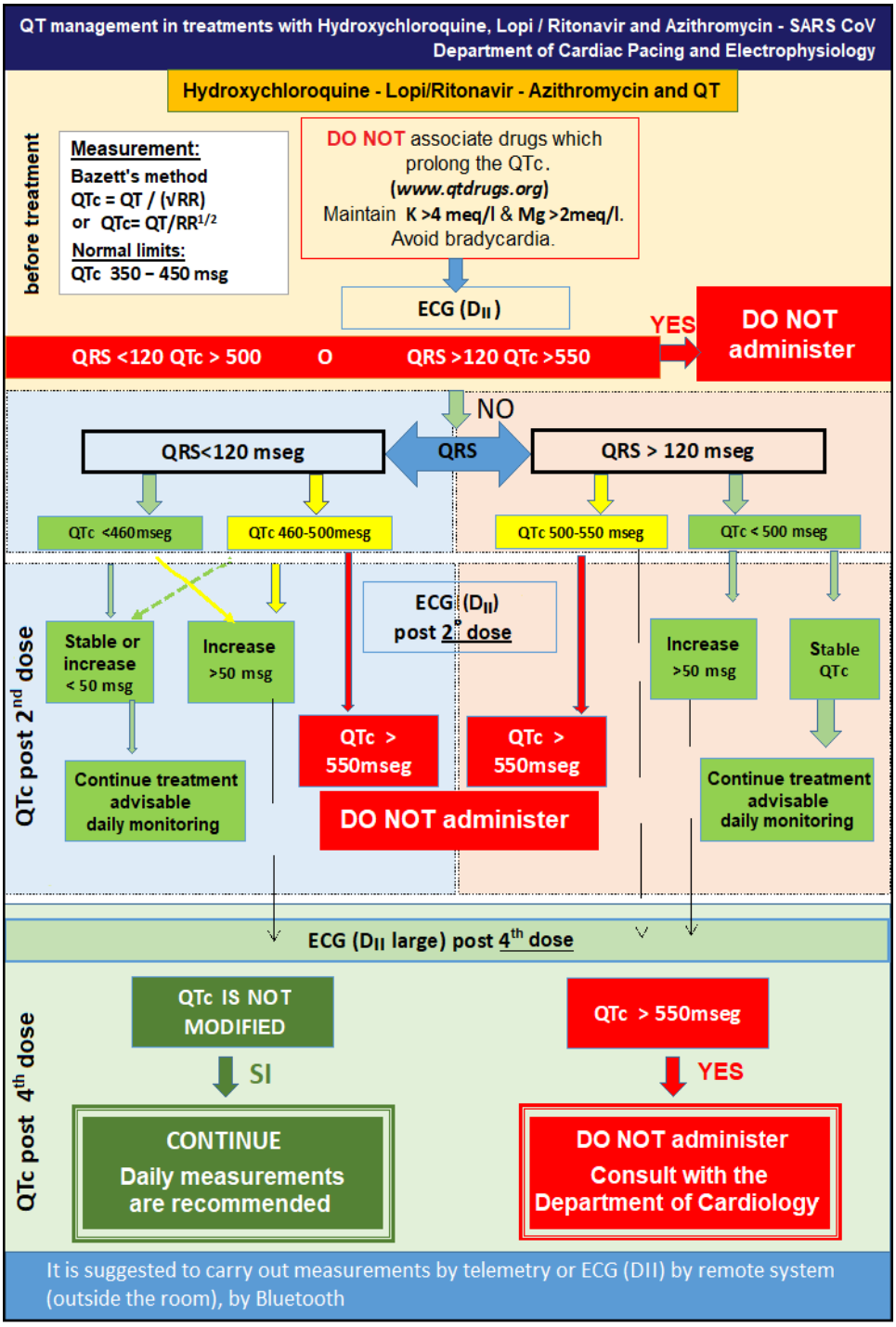

Figure 2. QT follow-up algorithm with the administration of hydroxychloroquine or other associated drugs.

required; but if it increases more than 50 ms, discontinuation should be considered.
2. **QTc 500-550 ms**: Same as above, and at 4th dose if QTc <550 ms continue, and if it increases to >550 ms, suspend.
3. **QTc>550 ms**: Do not administer.

Recommendations

In summary, our recommendations are as follows:

- Do not administer hydroxychloroquine for an initial QTc > 550ms.
- If QTc < 500 ms, with narrow QRS, re-evaluate at the second and fourth dose of the drugs. If QTc < 550 ms: stop and consult with Cardiology (either in the second or fourth dose).
- If the QTc is not prolonged (value <550 ms), treatment may be continued with daily QTc monitoring.
- Another simple option is that if the QTc is prolonged with any dose between 20-25%, starting from a normal basal, treatment should be suspended and proceed to consult with Cardiology. This should be defined by his/her practitioners.
- Discontinue other drugs that prolong (**Table 2**)[9, 17,18].
- Maintain serum potassium and magnesium levels above 4.0 mEq/L and 2.0 mEq/L, respectively.
- Avoid bradycardia.
- Consider the possibility of transient pacemakers with very low heart rates.

REFERENCES

1. Ministerios de Sanidad. Documento técnico: Manejo clínico del COVID-19: tratamiento médico [Internet]. Madrid: Gobierno de España [cited 19 Mar 2020]; 2020. Available at: http://www.aeemt.com/web/wp-content/uploads/2020/03/4_6026300193912129107.pdf
2. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, *et al.* Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. J Am Coll Cardiol [Internet]. 2020 [cited 19 Mar 2020]: In Press. Available at: https://doi.org/10.1016/j.jacc.2020.03.031
3. Morgan ND, Patel SV, Dvorkina O. Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. J Clin Rheumatol. 2013;19(5):286-8.
4. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila). 2006;44(2):173-5.
5. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. Mayo Clin Proc [Internet]. 2020 [cited 20 Mar 2020];95: In Press. Available at: https://mayoclinicproceedings.org/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_covid19.pdf
6. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care [Internet]. 2020 [cited 19 Mar 2020]: In Press. Available at: https://doi.org/10.1016/j.jcrc.2020.03.005
7. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3(11):722-7.
8. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M,*et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents [Internet]. 2020 [cited 20 Mar 2020]: In Press. Available at: https://doi.org/10.1016/j.ijantimicag.2020.105949
9. CredibleMeds.COVID-19 experimental therapies and TdP Risk [Internet]. Online 20 Marzo 2020 [cited 20 Mar 20]. Available at: https://crediblemeds.org/blog/covid-19-experimental-therapies-and-tdp-risk/
10. Choi Y, Lim HS, Chung D, Choi JG, Yoon D. Risk Evaluation of Azithromycin-Induced QT Prolongation in Real-World Practice. Biomed Res Int [Internet]. 2018 [cited 20 Mar 2020];2018:1574806. In Press. Available at: https://doi.org/10.1155/2018/1574806
11. Guo D, Cai Y, Chai D, Liang B, Bai N, Wang R. The cardiotoxicity of macrolides: a systematic review. Pharmazie. 2010;65(9):631-40.
12. Howard PA. Azithromycin-induced proarrhythmia and cardiovascular death. Ann Pharmacother. 2013;47(11):1547-51.
13. Galán Martínez L, Calderín Pulido AD, Fleites-Vázquez A. Acción inotrópico negativa y prolongación del intervalo QT por azitromicina. Rev

Cuban Cardiol [Internet]. 2017 [cited 20 Mar 2020];23(4). Available at: http://www.revcardiologia.sld.cu/index.php/revcardiologia/article/view/720/pdf_108

14. Yang Z, Prinsen JK, Bersell KR, Shen W, Yermalitskaya L, Sidorova T, *et al*. Azithromycin causes a novel proarrhythmic syndrome. Circ Arrhythm Electrophysiol [Internet]. 2017 [cited 20 Mar 2020];10(4):e003560. Available at: https://doi.org/10.1161/CIRCEP.115.003560
15. Zhang M, Xie M, Li S, Gao Y, Xue S, Huang H, *et al*. Electrophysiologic studies on the risks and potential mechanism underlying the proarrhythmic nature of azithromycin. Cardiovasc Toxicol. 2017; 17(4):434-40.
16. Miranda-Aquino T, Pérez-Topete SE, Ortega-Pantoja W, Gómez-Vázquez CA, Meneses-Pérez LG, González-Padilla C, *et al*. Síndrome de QT largo secundario a la interacción entre hidroxicloroquina y amiodarona. Rev Mex Cardiol. 2018;29(2): 98-101.
17. Taira CA, Opezzo JA, Mayer MA, Höcht C. Cardiovascular drugs inducing QT prolongation: facts and evidence. Curr Drug Saf. 2010;5(1):65-72.
18. CredibleMeds. Risk Categories for Drugs that Prolong QT & induce Torsades de Pointes (TdP) [Internet]. Last update 19 Marzo 2020 [cited 20 Mar 2020]. Available at: https://crediblemeds.org/new-drug-list/