Call for Retraction – Potential drug poisoning by chloroquine in Borba et al COVID-19 assay

Dear Editor,

We read the article titled "Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial", by Borba et al, published by JAMA in April 2020[1].

In introduction, 4th paragraph, authors state that The Health Commission of Guangdong Province recommended the use of phosphate chloroquine tablets at a dose of 500mg twice daily for 10 days (total dose, 10 g) for the treatment of patients aged 18 to 65 years with mild, moderate, or severe pneumonia secondary to COVID-19", citing the Chinese consensus of specialists[2]. That clearly indicates that Brazilians meant to follow the Chinese protocol accordingly.

In Brazil, a department of Oswaldo Cruz Foundation, FarManguinhos, manufactures chloroquine diphosphate for the Ministry of Health. The tablets available contain 150 mg of chloroquine base, converted to 241 mg of chloroquine diphosphate. However, the label at the tablet package can mislead the reader to understand that it contains 150 mg of chloroquine diphosphate, since it is written "150 mg" close to "chloroquine diphosphate". The package insert, however, states that it contains "150 mg of chloroquine", "equivalent to 241,91 mg of chloroquine diphosphate"[3].

In "Procedures", item (4), authors state that only 150 mg chloroquine base tablets are available in Brazil and state that they tried to avoid tablet partition, what would explain why in line 16 they used 4 tablets x 150 mg twice a day, 600 mg of chloroquine base, in an attempt to mimic the Chinese 500 mg twice a day chloroquine diphosphate regimen.

However, Chinese chloroquine tablets are described in salt, not in base, meaning that 500 mg of chloroquine diphosphate contains approximately 310 mg of chloroquine base. Each Chinese administration of 500 mg chloroquine diphosphate should therefore be replaced by 2 Brazilian tablets of 150 mg, but Brazilians used 4 tablets instead. So, Chinese administered twice daily 1 tablet of 500 mg chloroquine diphosphate (620 mg chloroquine base daily) and Brazilians administered twice daily 4 tablets of 150 mg chloroquine base (1200 mg chloroquine base daily).

The result is that Borba et al almost doubled the daily dose used in Chinese studies.

Chloroquine is a drug with a small safety margin between therapeutic and toxic doses in long-term treatment, but still allowing high loading doses. In clinics it has been replaced by hydroxychloroquine, a drug with a larger safety margin. In the package insert[3], the fundamental parameters are half-life from 72 to 120 h (according to plasma levels) and volume of distribution >100L/ Kg, justifying the use of a loading dose to immediately elevate the drug concentration in the plasma. In hepatic amebiasis, 600 mg of chloroquine base are recommended as a loading dose in the 1st and 2nd days, followed by 300 mg during 2-3 weeks.

In "Procedures", the authors defend their chosen chloroquine dose, stating that "effects of high doses, such as hydroxychloroquine 600mg twice daily for 28 days, were already studied in patients with cancer, showing good safety even in phase I trials". However, the three references cited by them in favor of this statement [4-6] all refer to hydroxychloroquine, not chloroquine. No simple relation can be established between the two drugs on a gram-per-gram basis, as they have different tissue distributions, different toxicities, and different therapeutic/toxic dose safety margins. Therefore, these hydroxychloroquine studies cannot be taken as a support to the use of high chloroquine doses.

Toxic or lethal effects have been found to range from ingestion of 1 to 26.7 g of chloroquine base[7]. Most authors consider that an average adult suffers toxic chloroquine effects with a 1.5 g dose. The clinical series of chloroquine shows that a chloroquinemia of 25μmol/L is fatal in general if not readily treated for chloroquine poisoning, and the prognosis is worse when more than 4 g are ingested at once [7] To avoid toxic effects, WHO is clear to recommend a safety margin: a single dose should not exceed 600 mg chloroquine base or 10 mg/kg[7]. A single dose of 30 mg/kg may be fatal[3].

The Brazilian package insert[3] (drug described as chloroquine base) states that: "Chloroquine poisoning is extremely dangerous, and ingestion of a single 1500 mg dose or 30 mg/kg can be fatal within hours. The main effect of overdose is cardiovascular toxicity, with hypotension, cardiac arrhythmia and irreversible cardiac arrest". Nevertheless, the authors used a daily dose of 1200 mg in the "high dosage" group, for 10 days. The package insert still states "Even for adults over 60 kg, the total dose of chloroquine given over three days should be a maximum of 1500 mg."[3]. Yet in 3 days, the authors administered 3600 mg. The warnings in package insert should have been enough to avoid any attempts to surpass those limits.

Patients with cardiovascular disease, who should have been excluded from the trial due to known cardiovascular drug toxicity, were all (5 patients) randomized to the high-dosage drug group, which might have caused cardiac arrhythmias (table I). In fact, in another study of hospitalized COVID-19 patients treated with chloroquine, an ECG was performed prior to treatment and patients with a prolonged QT interval were excluded from the assay as a reasonable safety measure, since chloroquine has known cardiotoxic properties, and still authors used far smaller doses, 400-450 mg for 5 days[8]. In eTable 1, it becomes clear that the high dosage group had 7 patients at cardiovascular risk from the beginning who presented a > 500 ms QTc after 1-3 days of treatment. Only 1/8 patients, a female, survived after presenting a QTc >500 ms in the high-dosage group, while all (4/4) low-dosage patients who had a QTc >500 ms survived.

In "Population Characteristics", the authors state that a preliminary analysis was performed on April 5th by a committee, when mortality was 11 (7 in the high and 4 in the low dosage group). Nevertheless, it is not clear how many patients in high-dosage group completed the 10-day treatment planned by authors. At the end of the results section, the authors state that "the DSMB recommended the *immediate* interruption of the high-dosage group for all ages and that all patients be unmasked and reverted to the low-dosage group". It is not clear whether the authors refer to the interim analysis by DSMB in 5th April when they found 11 deaths (7 in the high dosage versus 4 in the low dosage group) or to the 13th day of treatment (before the 28th day chosen as primary endpoint) at the end of the time axis in Figure 2 (when there were 16 deaths in the high dosage versus 6 in the low dosage group). If Figure 2 has mixed regimen patients (who were assigned to the high-dosage but reverted to the low-dosage group) it should have been clearly stated in figure legend and text.

In "Lethality Outcomes" the text states that 16/41 were dead in the high-dosage and 6/40 in low-dosage group, a significant difference (p=0.03, log-rank test, as informed by the article), indicating that the high dosage caused more deaths. The authors also state that the difference is no longer present when controlled by age but admit that the sample is not big enough to allow this kind of analysis (odds ratio, 2.8; 95%CI, 0.9-8.5). As stated by the authors on page 8: "The high-dosage group was associated with lethality (odds ratio, 3.6; 95%CI, 1.2-10.6)". So, it is clear that compared to the low-dosage, the high-dosage group presented a significantly increased mortality, compatible with drug poisoning. These results are also compatible with greater survival in low-dosage group, a possibility dismissed by the authors. Considering the history of chloroquine drug poisoning and the cardiac effects experienced by

the patients in high-dosage group, this possibility seems less likely to explain the results than overdosage.

The article by Borba et al was used to support NIH policy[9] concerning COVID-19 treatment, emphasizing that chloroquine treatment during COVID-19 caused deaths. Still, authors argue that the doses chosen by them are not toxic. Would that mean that the drug is safe to be used even at high dosages by fragile patients?

Drug poisoning during a clinical trial is a very touchy issue, particularly at the light of the mistake identified by us due to different forms of drug description in tablets, and the dangerous, potentially lethal design of the assay. Therefore, we ask JAMA editors to retract Borba et al, sparing further deaths that might occur when researchers attempt to mimic doses found in this study in new studies.

References

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Yours sincerely,

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