Erratum Short Communication

Shunt due to Hydroxychloroquine Sub-lethal Dosage Resulted in Excess Transfer to Mechanical Ventilation and Death in Hospitalized Patients with Covid-19

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Introduction

We have recently published, on February 11, 2021, a letter of concern in the NEJM, regarding hydroxychloroquine overdosing in Recovery, the British mutli-center randomized clinical trial [1,2]. Our letter indicates also that at lower dose (around 400 mg/day) HCQ may be active due to its extremely high concentration in phagolysosomes, the organelles mediating SARS-Cov2 entry in the cell. We mention as well that too a high dose of HCQ may suppress anti-inflammatory cytokines production. In their reply to our letter the principal investigators of Recovery have argued that their HCQ maintenance dosage was well below (half) that of the trial of Borba et al. that was prematurely stopped due to toxic deaths [1]. They persist that they have established proper dosage, based on their own pharmacokinetics (PK) investigations, with a loading dose of 2.4 g on day 1, whereas PK of HCQ in the context of Covid-19 was already published online (March 09, 2020) in a peer reviewed international journal. This study indicated, for European patients, a loading dose of 800 mg (400 mg twice daily) on day 1, followed by

a maintenance dose of 400 mg (200 mg twice daily) the next 4 days [3]. These published PK data show that after 5 days this dosage reaches 3 times the potency (ratio concentration in the lungs/EC_{50}; EC_{50} being in vitro measurement of anti-viral activity) of chloroquine phosphate when given 500 mg twice daily. Hydroxychloroquine (EC50 = 0.72 µM) was found to be more potent than chloroquine (EC50 = 5.47 µM) in vitro.

Keywords: Hydroxychloroquine; Overdosing; Intoxication; Pulmonary shunt; Covid-19

HCQ overdosage

Reacting to their reply, we would like to point out some facts. It is true that the HCQ sulfate maintenance dose (800 mg/day) in the Recovery trial protocol is equivalent to half the dose of 1200 mg chloroquine base per day (Borba et al. Brazilian trial) [4,5]. In the trial of Borba et al. 4 tablets of 150 mg chloroquine (equivalent to 241.91 mg of chloroquine diphosphate) from Farmanguinhos, Fiocruz (Brazil) were administered twice daily 800 mg of HCQ sulfate is equivalent to 620 mg of HCQ in the base form [3]. This means that the maintenance dose of Recovery was actually 51.7% of the daily dose of Borba et al. in term of active base form (HCQ and CQ are basically the same molecule with only 5% difference in their molecular weights). Thus, the 2.4 g of HCQ salt administered the first day in Recovery is 1.55 times de dose of Borba et al. the first day. The cumulative HCQ base form over the first 3 days is 3.1 g in Recovery which is 86% of the 3.6 g CQ cumulative dose in Borba et al. This loading dose and sustained daily dosage on weakened and aged hospitalized patients was certainly toxic at about the same level as in the Borba et al. during the first three days of treatment. That trial was stopped in April 2020 after 16 over 41 patients (39%) had died within 13 days from trial initiation [4, 5]. Borba et al. did not want to impute the excessive death ratio directly to CQ because all patients received also azithromycin (500 mg/day for 5 days). Although, azithromycin alone could not be the cause of such an increase of toxic death, it could have exacerbated CQ overdosing toxicity [6]. The trial demonstrated that one must be very careful to accurately determine the tablet dosage in terms of base form [5]. The Indian council of medical research (ICMR) had alerted WHO about the overdosing situation in Recovery [7].

According to the summary of product characteristics (SPC) of Plaquenil, HCQ overdosing starts à 25 mg/kg in healthy adults [8]. According to the World Health Organization, the lethal dose of chloroquine in the sulfate form (per os) starts at 65 mg/kg, this means 4.5 g for a healthy adult of 70 kg [9]. As for hydroxychloroquine (oral) the lethal dose starts at around 4 g [10]. Obviously, for a frail and aged patient < 70 kg, or a patient suffering from pulmonary disorder in relation with Covid-19, the lethal dose may be substantially lower. Additionally, the WHO document specifies that overdosing of this drug leads to cardiac dysrhythmia and breathlessness due a pulmonary oedema.

Analysis of Recovery published survival data shows incoherence and excess mortality

From the Recovery survival curves data it can be inferred that the median time to death and first quartile in the HCQ arm are 6.6 days, interquartile range (IQR) [3.7 – 12.7] days, and 6.9 IQR [3.7 – 12.5] days in SOC [11]. Therefore, no difference can be deduced from the curves about the first quartile Q1 = 3.7 days. If this information was exact, why not giving it quantitatively directly instead of providing it in a cryptic way whereas it is a question of real importance. In the French AP-HP study [12] the median times to death are 8.52

IQR [4.52 – 14.26] days for HCQ and 7.54 IQR [3.94 – 13.0] for the standard of care (SOC). Therefore, figures from Recovery are consistent with those from AP-HP regarding SOC but fundamentally differ regarding HCQ, with a shortening of the median time to death and of the first quartile Q1 by 2 days and 1 day, respectively.

The authors of Recovery affirm that their trial shows HCQ is neither toxic nor active. However, this is a consequence of the convention on the interpretation of the p-value whose threshold is arbitrarily set to 0.05. In Recovery, the value of p = 0.18, between the HCQ and SOC arms, tells that objectively there are 18% of chances to be wrong, and thus 82% of chances to be right, in affirming that HCQ has resulted in more deaths than SOC.

We think that Recovery authors must be more transparent regarding the fact that 276 patients (357 – 81 patients from cumulated deaths at D3) in the HCQ arm have stopped treatment between D1 and D3 [11]. What are the reasons for these treatment stops that are certainly not hospital discharges? It would have been a more directly relevant information to produce accurate data on the reasons of treatment stops (toxicities, deaths and transfers to ICU) in this time interval. The fact that 276 patients have stopped treatment within 3 days from treatment randomization is a strong indication, if not an evidence, of an excess toxicity.

In their discussion the authors of Recovery state: "we did not observe excess mortality in the first 2 days of treatment with hydroxychloroquine, the time when early effects of dose-dependent toxicity might be expected." However, ad hoc mathematical modelling of their published survival curves [11] show inconsistencies indicating that an excess mortality (compared to the AP-HP modelled HCQ survival curve) of as much as 85 deaths may have occurred between D1 and D7 with as much as 35 deaths in excess at D3. Sub-lethal dosage on weakened or frail patients may have considerably aggravated their disease toward an irreversible condition.

The mechanism of "pseudo-Covid-19" pulmonary shunt

In Recovery, cardiac monitoring was not proceeded with nor reported accurately. More importantly, sub-acute HCQ intoxication may have caused polypnea, even in the absence of other symptoms. Hypoxemia with hypocapnia, compatible with an intra-pulmonary shunt has been reported [13-17]. We therefore understand that HCQ overdosing, or near-overdosing, may present a symptomatic respiratory deterioration similar to Covid-19 with similar life-threatening implications.

In Covid-19 deceased patients, autopsies show diffuse alveolar damage, similar to that observed with acute respiratory distress syndrome (ARDS), with hypoxemia arising from shunt, where the pulmonary parenchyma is perfused but not ventilated, followed by an hypercoagulable state with microthrombi in larger numbers than in other types of ARDS.

"At present, the pathophysiology underlying the hypercoagulable state is poorly understood. However, a growing body of data suggests that the initial events occur in the lungs. A severe inflammatory response, originating in the alveoli, triggers a dysfunctional cascade of inflammatory thrombosis in the pulmonary vasculature, leading to a state of local coagulopathy" [18].

The shunt effect starts with the "happy" hypoxemia oberved in patients who can remain with low O_2 partial pressure, for quite a long time, without presenting obvious symptoms of dyspnea. Indeed, the respiratory need is less severely related to a depletion of oxygen than a CO_2 increase

(hypercapnia detected by chemoreceptors). Since the shunt effect actually induces a depletion of CO_2 in blood (hypocapnia), the patient experiences obvious clinical symptoms of pulmonary impairment only lately at the stage of micro-thrombi and larger oedema.

A lot is known about acute HCQ/CQ intoxication with an unambiguously characterized diagnosis via cardiac disorders. However, much less is known about sub-acute intoxication (just below the lethal dose). Hospital laboratories investigations may be needed to measure physiological signs of poisoning gravity such as hypokalemia and oligonauric renal injury which is of poor prognosis, especially in frail Covid-19 patient where the viral disease may have spread as well in the kidneys.

Thus, overdose of this drug may lead to the symptoms that cannot be distinguished at first sight from Covid-19 disease progression requiring mechanical ventilation. Sub-lethal dosage may have aggravated the weakened health condition of the Recovery hospitalized patients, culminating with a cumulated dose of 4 g over 3 days which represents 86% of the dose delivered to the patient during the first 3 days of the Borba et al trial. Being considered, the long elimination half-time of HCQ (30-50 days) and the often aged poly-pathological patients, these HCQ doses must be regarded as extremely high and certainly toxic, if not potentially lethal, even-though azithromycin was not associated.

Conclusion

Thus, in the Recovery randomized trial, fragile patients with a moderate form of Covid-19 with chances to recover may have had their medical condition irreversibly worsened due to very toxic HCQ overdosing resulting in a pulmonary shunt, with ICU transfer masking the potential benefit of HCQ [10].

We don't see how an excess toxicity could not have happened in the first 3 days of treatment and beyond in the Recovery trial, with many treatment stops and a number of toxic deaths still to be elucidated. Identifying them may be a complicated task since HCQ overdosing result in acute respiratory failure just like Covid-19. The authors of Recovery are very elusive about this reality. However, they admit that : "...those (patients) not on invasive mechanical ventilation at baseline were more likely to reach the composite endpoint of invasive mechanical ventilation or death (29.8% vs. 26.5%; risk 44 ratio 1.12; 95% CI 1.01-1.25)".

In western countries, public health recommendations were issued based on the results of Recovery, a large phase 3 multi-center randomized trial. Being considered the issue raised, a thorough analysis of all Recovery patients files, available electro-cardiogrammes and laboratory tests (hypokaliemia, creatinine) is advocated although many parameters such as renal tubulopathies related to Covid-19 may overlap with the signature of HCQ intoxication.

Conflict of interest: None

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