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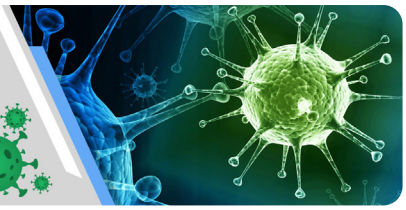

Erroneous Assessment of The Effect of Hospital Treatment – The Misleading Creation of 17000 Deaths and its Consequences for Good Medical Practice

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Abstract

Despite a peer review process prior to being published in Biomedicine & Pharmacotherapy, Pradelle et al, "Deaths induced by compassionate use of hydroxychloroquine (HCQ) during the first COVID-19 wave: an estimate" is cluttered with several scientific integrity issues, one of them being the lack of validation against real life data. Mathematical model-based research should be dealt with an even greater care by reviewers and call upon mathematicians for a review of the logic and appropriateness of the model used. This is illustrated here by the use of an odds ratio (OR) taken as the corner stone of a circular reasoning based on a simple mathematical extrapolation without cross validation against reality and without appraisal regarding the corpus of knowledge amply developed and published on the topic addressed. This resulted in a blind and oversimplistic mathematical treatment of an issue of the foremost importance.

A flawed model by design has yield results that can be viewed as a pure fabrication. The OR used is not an accurate representation of the true OR associated with the treatment involved. It was based on the result of a meta-analysis that included only RCT trials with OR exceeding 1. with the two trials with an over-dominating weight having used excessively high doses of HCQ: the Recovery and Who Solidarity trials with weight of 73.7 % and 15.2%, respectively. Recovery was conducted on frail patients hospitalized at a very late disease stage and having received sub-lethal doses of HCQ, very close to the lethal dose, dramatically higher than the safe dosage established by the pharmacokinetics properties of HCQ.

Keywords: hydroxychloroquine, toxicity, mathematical extrapolation, Circular reasoning, integrity in science

Introduction

We read with interest the article by Pradelle et al, "Deaths induced by compassionate use of hydroxychloroquine during the first COVID-19 wave: an estimate", published in Biomedicine & Pharmacotherapy [1]. Even though the authors stated that the level of evidence was low, this paper presents findings that are unreliable as there are some clear issues of data mishandling (Belgium data) and results fabrication: Belgium hospitalisation and hydroxychloroquine (HCQ) intervention data, Spanish HCQ intervention data. Several aspects raise significant concerns over data veracity and scientific integrity. Within three days of publication, it has received significant press coverage in France and many countries, hence yielding a significant issue of trust in medical science.

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Data integrity – data mishandling/miscalculation and results fabrication:

This study includes data miscalculation and results fabrication. They fall into two categories (1) issues on hospitalisation data at a nationwide level and (2) issues on HCQ usage in the target countries for both prescription timing and differences in drug dosages.

The Belgian data were miscalculated, yielding a results fabrication for Belgium

- Pradelle et al wrongly calculated that 10 018 hospitalised patients would have been treated with HCQ during the first Covid-19 wave. A 51% HCQ prescription rate was artificially generalised and applied to aa data base of 19 644 hospitalized patients.
- In fact, the national Belgium study conducted until 24 May 2020 provided the basis for the 51% HCQ prescription rate, with 4542 patients of 8910 patients receiving HCQ (Dauby et al International Journal of Antimicrobial Agents Oct 2020) [6].
- Therefore, there is a huge discrepancy between the 4542 patients who received HCQ according to the national data and the Pradelle et al., calculation of 10 018. It does not correspond to real life data. Two external data sources validate this (1) Sciensano (Belgium Health Institute) confirmed in August 2020 that 4500 patients have received HCQ [7]; (2) On 16 June 2020, the Belgium health minister stated, in a public session of the Chamber of Representatives, that 5000 patients had received HCQ in Belgium [8].
- Pradelle et al did not validate the Belgium hospitalised patients data on the cut-off date. On 17 July 2020, Pradelle et al stated that 19 644 patients had been hospitalised whereas, Sciensano shows that the number of 19 652 hospitalised patients was only reached on 31 August 2020 [7].
- Pradelle et al calculated that 10 018 patients would have received HCQ. This is impossible.
  (1) Sciensano shows that 17 357 patients had been hospitalised in Belgium and only 4542 had received HCQ on 24 May 2020.
  (2) The difference shows that 2287 (19 644 –17 357) additional patients would have been hospitalised between 24 May 2020 and 17 July 2020.
  (3) The difference of patients receiving HCQ, 10 018 (from Pradelle et al on 17 July) minus 4542 (from Dauby et al on 24 May 2020) is 5476 patients [1, 6].
  (4) it is impossible that 5476 hospitalised patients would have received HCQ in the period with only 2287 additional hospitalised patients in the same period.
- The over-mortality attributed to HCQ in Belgium, resulting in 240 deaths as stated by Pradelle et al is in complete contradiction with the national Belgium study that concluded that there is a reduced mortality rate for patients receiving HCQ [6].
- Finally, the relative HCQ effect on death (OR=1.11) used in the model to estimate the over-mortality was issued from Axfors et al, that used HCQ over-dosages (2400 mg the first day) [3, 9, 19]. This dosage, 4 times higher than the maximum authorized dosage, is potentially lethal [5]. It is well known that an overdose of HCQ may be used for suicide.
- Considering the errors quantum identified for Belgium, it is very likely that the data estimated for the other countries will also be erroneous, hence leading to results fabrication.

A flawed model yielding results fabrication

- The model used is mathematically speaking an extrapolation where $N_{death} = N_{hospitalised\ patients} \times$ mortality rate $\times$ HCQ exposure$_{median,\ min,\ max} \times OR_{HCQ\text{-}mortality}$ is by design constructed to model an overestimation of death as it uses a constant ($OR_{HCQ\text{-}mortality}$ =1.11) as the relative HCQ effect on death. It is therefore unsurprising that the authors find an over-mortality as this is their ingoing hypothesis. This is the well-known fallacy of the circular reasoning often compared with a serpent biting its tail, equivalent to assert that the reason why the sky is blue is that we can observe its blue color.
- The $OR_{HCQ\text{-}mortality}$ =1.11 is issued from Axfors et al, [5] that uses HCQ dosages that are highly superior to the ones used and recommended in various countries (Belgium above, IHU Mediterranée 600mg but also Spain and Turkey).
- It is not representative of the dosage used in hospitals in the various countries.
- The Recovery study weights 73.7% in the OR calculation in the meta-analysis of Axfors et al., [5]. It has a regimen of 2400 mg of HCQ on day 1 and 9600 mg over 10 days. 10% of the patients had a negative SARS CoV-2 test, 27% had a cardiac underlying condition and patients received HCQ at a very late stage of the disease (median 9 days after symptoms, and 3 days after hospitalisation), at a time where antiviral drugs are not effective anymore. We point out that meta-analysis must be conducted with a lot of cautions to avoid selection bias as we have discussed in depth previously, showing that a rigorous selection of trials leads to a favourable OR for HCQ [11].
- It is neither scientific, nor medical good practices, nor ethical to use the death rate of an overdosed drug to

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prove the harmfulness of a drug used in normal doses and known for decades to be safe in the treatment of numerous pathologies.

- As the authorities of many countries dissuaded general practitioners and clinicians from prescribing HCQ, HCQ exposure levels used in the model are thus questionable, either for Belgium (51%) or for Spain (84%).
- Even if Pradelle et al., removed the data from Belgium, the other data should be removed due to miscalculation. Indeed, as demonstrated above the model itself based on a circular reasoning itself based on a biased meta-analysis allows the fabrication of the results. The model is flawed by design as it can only find this result.

There are significant medical errors that are not considered in this study.

Antiviral treatment should have been prescribed to outpatients early in the viral phase of the disease to decrease the viral load and prevent the aggravation of the disease and the probability of requiring oxygen and/or hospitalisation. This condition was realized methodically and coherently by the IHU Méditerranée in Marseille where more than 30 000 Covid-19 patients were treated successfully with the HCQ-azithromycin association with an adjusted OR= 0.419; 95%CI= [0.327; 0.539], $p < 0.001$) [2]. General practitioners were prevented from prescribing HCQ, leading to a loss of chance for patients and a risk of aggravation and then hospitalization. This resulted in HCQ being prescribed far too late at a stage when its efficacy had greatly diminished or even disappeared. So prescribing HCQ to impaired hospitalised patients is a flawed medical reasoning. By comparison, oseltamivir is effective to decrease influenza severity, only if prescribed early, especially during the first 48h of the symptomatic phase.

1. It's also astonishing that the sole effect of HCQ could be identified as lethal in an environment where the patient is monitored, particularly for potassium plasmatic level and ECG (to prevent cardiac rhythm disorders). Several other factors could have been taken into consideration such as the patients characteristics of age, comorbidities as can be identified in some of the underlying studies for example in Bartoletti et al, that concludes the lack of efficacy of corticosteroids [12]. From that same study, Pradelle et al., infer that since 85.5% of patients had received HCQ, it had a lethal consequence without taking into consideration other factors. In Fummagali et al., the authors retain the partial information that among the deceased patients, 35% had received HCQ and were 79-year-old on average, but they did not take into consideration the fact that among survivors 57% had taken HCQ and were 64-year-old on average [13].
2. Neither the dosage of HCQ nor the duration of treatment is taken as a parameter or mentioned. Some studies, such as Recovery, have dramatically overdosed hydroxychloroquine, and it can induce a paradoxical deleterious effect by shunt effect (which explains the happy hypoxia and can, moreover, mimic a severe Covid) [3].

Pradelle et al., refer to various studies carried out in the countries concerned.

Among these studies, only a few assessed the mortality rate associated with HCQ, either alone or in combination with azithromycin and most conclude that there is a reduction in mortality. When a model reaches the opposite conclusion to that of the referenced studies, the methodology should be questioned as the results are not validated by real life observations.

- For Spain, the only study mentioning the mortality rate linked to HCQ concludes 'Half of the COVID-19 patients were treated with the combination hydroxychloroquine + azithromycin, which is associated with a significant decrease in mortality'. [14].
- An Italian study concluded: 'HCQ use was associated with a 30% lower risk of death in COVID-19 hospitalized patients.' [15].

For the USA, one study concluded 'According to a protocol-based treatment algorithm, among hospitalized patients, use of hydroxychloroquine alone and in combination with azithromycin was associated with a significant reduction in-hospital mortality compared to not receiving hydroxychloroquine'. [16].

A serious question of concern – why Pradelle et al., did not use UK data in their model?

Hospitalised data is available for the UK, which was an inclusion criteria. As UK data contributed to 74% of the OR calculation (1.11), why did the authors not use the UK data to support their case and address the issue that they were using an OR calculated mainly from UK data, without applying it to the UK country data to prove their case? The ONS (UK office of national statistics) reports that between 20 March 2020 and 10 July 2020, 235 863 persons have died in the UK of which 50 946 would have been from Covid-19. In the same period 95 574 patients have died in hospital of which 32393 (34%) with Covid-19 [17]. In Recovery study, only 14% of patients (1561 in the HCQ arms out of the 11 197 patients enrolled) received HCQ. That is probably the reason why Pradelle et al would not want to include this study as if they generalise a prescription rate of 14% to all hospitalised patients in the UK that would lead to questioning their argument for other countries. Choosing not to take UK data into account makes it

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possible to artificially obtain (false) results in favour of HCQ toxicity. This is cherry-picking, a method used a priori to reach the conclusion one expects at the outset.

Reality is always more reliable than a model.

Calibration to real world data is necessary

- Pharmacovigilance committees of countries cited by Pradelle et al, transmit their data to the WHO Vigibase. Vigibase collects data from more than 120 countries since 1968, due to the Thalidomide disaster. Over a 50-year period, in these 120 countries, WHO shows only 114 deaths attributable to HCQ for tens of billions of doses of HCQ administered over this period of time. That, in itself, demonstrates strikingly the gross inconsistency in the 17 000 deaths calculated by Pradelle et al., In France, over a three-year period, a very strict pharmacovigilance showed 8 deaths possibly due to HCQ, while the cause of death could be the cardiac complications linked to SARS-CoV-2 infection.
- For calibration of their model, Pradelle et al could have cited Emmerich. Emmerich showed in Brazil that the state of Para (296 deaths per million) had 5.5 times less deaths than the state of Amazonas (1645 deaths per million) during the same period [18]. Therefore, it is impossible that HCQ alone could have yielded such a number of deaths.
- Pradelle et al did not refer to the 30 423 patients treated at the Marseille IHU in France.[2] The data are accessible online, complete and undisputable, as verified by a bailiff. The published study (Outcomes after early treatment with hydroxychloroquine and azithromycin: An analysis of a database of 30,423 COVID-19 patients concludes to an adjusted OR of 0.55 in favour of HCQ plus azithromycin [19].

Conclusion

Thus, the calculations of Pradelle et al., misleadingly based on the result of a meta-analysis where two questionable trials determined the overall OR, receives press coverage yielding a significant issue on how much the peer review system should be trusted and its implication for the disinformation of the general public. The official report of Recovery did not specifically conclude to a treatment toxic effect, but implicitly suggests it, dissimulating the deleterious effect of HCQ overdosing the effect of which cannot be distinguished from the worsening induced in the latter stage of the Covid-19 disease.

The Pradelle et al. study has already received significant media attention in the first 3 days of publication from mainstream media in France and many countries anchoring the wrong fact that some 16 000 patients have died from HCQ usage. This is creating an issue of public trust and confidence in science as journalists in general are not qualified to appraise scientific methodologies and the possible presence of biases in the study. The media have broken their impartiality pledge, systematically giving audience to results that provide untoward credit and justification to the public health policy implemented by the western countries governments during the Covid-19 pandemic. The article from the Pradelle et al. study does not meet the required standards of a healthy scientific community. It leads to an erroneous and dishonest evaluation of the treatment effect of HCQ in the general population.

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