WHO "Solidarity" and UK "Recovery" clinical trials of Hydroxychloroquine using potentially fatal doses, according to WHO consultant

Meryl Nass, MD
207-522-5229
merylnass@gmail.com

The Solidarity Trial is a WHO-led conglomeration of many national trials of treatments for Covid-19. Per the WHO:

> *As of 3 June 2020, more than 3500 patients have been recruited in 35 countries, with over 400 hospitals actively recruiting patients. Overall, over 100 countries have joined or expressed an interest in joining the trial, and WHO is actively supporting 60 of them...*

The hydroxychloroquine arm of the Solidarity trials restarted enrolling patients June 3, after being halted May 25 by WHO Director-General Dr. Tedros Adhanom Ghebreyesus and the Executive Group of the Solidarity Trial. (The hydroxychloroquine (HCQ) arm of the trials was stopped after publication of the Lancet *Surgisphere* study, which claimed 35% higher death rates in patients who received hydroxychloroquine, but the Lancet study was retracted 13 days after publication, as its data had been fabricated.

Below are the drugs being tested in Solidarity:

- Remdesivir
- Hydroxychloroquine
- Lopinavir with Ritonavir
- Lopinavir with Ritonavir plus Interferon beta-1a.

However, the **doses** were not specified on WHO's list of the drugs to be trialed, nor were they specified, surprisingly, in WHO's 4 person consultation on chloroquine (CQ) dosing, dated April 8. Instead, the Introduction of the Report of that meeting notes,

> *"The chloroquine or hydroxychloroquine schedule selected for the trial includes two oral loading doses (250 mg per tablet CQ or 200 mg per tablet HCQ), then oral twice-daily maintenance doses for ten days. This meeting convened to discuss the appropriateness of the selected doses for the trial."*

Last week, I was alerted to the fact that India's ICMR, its official medical research agency, had written to the WHO, telling WHO that the hydroxychloroquine doses being used in the Solidarity trial were **4 times higher** than the doses being used in India. Then I learned that

Singapore had been hesitant to participate in the WHO trial due to the hydroxychloroquine dose.

The UK "Recovery" trial was very similar to, but not part of, the international Solidarity conglomeration of clinical trials. The Recovery trial ended its HCQ arm on June 4, reporting no benefit. In-hospital mortality of the 1542 patients receiving hydroxychloroquine was 25.7%, or 396 deaths, about 10% higher than those receiving standard care, a non-significant difference.

The Recovery trial Study Protocol notes it is funded in part by the Wellcome Trust and the Bill and Melinda Gates Foundation, and by UK government agencies. The Protocol provides the doses of hydroxychloroquine used, on page 22. Twitter users began to notice a dosing problem, with hashtag #Recoverygate.

The HCQ dosing regimen used in the Recovery trial was 12 tablets during the first 24 hours (800mg initial dose, 800 mg six hours later, 400 mg 6 hrs later, 400 mg 6 hours later), then 400 mg every 12 hours for 9 more days. This is **2.4 grams** during the first 24 hours, and a cumulative dose of 9.2 grams over 10 days.

The quote from the WHO report on dosing, provided 4 paragraphs ago, seems to be deliberately vague regarding the dose used in the Solidarity trial, stating the number of milligrams per tablet, but not the number of tablets to be used. The trial is registered but the registration fails to specify dosages.

The registration of the Canadian portion of the Solidarity trial informs us of its HCQ dose: Ten 200 mg tablets during the first 24 hours (800 mg initial dose, 800 mg 12 hours later) then 400 mg every 12 hours for 9 more days). This is 2.0 grams during the first 24 hours, and a cumulative dose of 8.8 grams over 10 days, or only 0.4 grams less than what Recovery used. The Norwegian Solidarity trial uses dosing identical to Canada.

Co-Principal Investigators of the Recovery trial, Drs. Peter Horby and Martin Landray, said they followed the WHO dosing. Landray also claimed in an interview with *Paris Soir* that the maximum allowed HCQ dose was "6 or 10 times" the dose used in Recovery, and that he was using the hydroxychloroquine dose that is used for amebic dysentery. However, the accepted use for HCQ in amebiasis is only for a liver abscess and only then in pregnancy, when other drugs cannot be used. That dose is 600 mg per day for 2 days, then 300 mg per day, considerably less than half the Recovery dose. Co-Principal Investigator Peter Horby said that *Paris*

Soir misinterpreted Landray's comments, but *Paris Soir* said Landray had confirmed what he told them in an email prior to publication. Landray is a very busy man, too busy, apparently, to look up the proper dose of a drug he gave to over 1500 subjects, who were randomized to the treatment and had no say in the matter.

We know that in Brazil, both a high HCQ dose and a low HCQ dose were trialed, and by April 17 the high dose arm was stopped prematurely due to an excess of deaths. The low dose trial continues in Brazil.

How is the drug hydroxychloroquine normally used? For chronic daily use in systemic lupus erythematosus or rheumatoid arthritis, patients receive between 200 and 400 mg daily, or a maximum of 5 mg/kg. In acute Q fever, 600 mg daily may be given at the start of treatment. For acute attacks of malaria, 2,000 mg should be given over 3 days. Professor Didier Raoult's group in Marseille used 600 mg daily for up to ten days in 1061 Covid-19 patients, and reported 8 deaths, a mortality rate of 0.75%, all over 74 years of age. The mortality rate reported by Landray and Horby in the Recovery trial is 34 times higher.

We know from WHO's March 13 Informal consultation on the potential role of chloroquine that the Gates Foundation had been studying the drug's pharmacokinetics, and of the 25 participants at this meeting, 5 were from the Gates Foundation.

The only treatment dose mentioned in the March 13 Informal consultation report was in a paragraph about preventive doses. It said, *"Higher doses would be considered for treatment, i.e., 10mg/kg base, followed by 5mg/kg twice daily for seven days."*

What is the "base"? A 200 mg dose of chloroquine or hydroxychloroquine contains 155 mg "base" drug.

The typical 70 kg person would, if this suggestion were followed, receive 700 mg base, or 900 mg total of hydroxychloroquine as a loading dose, then 450 mg twice daily. Generally, a loading dose refers only to a high first dose, not to several high additional doses.

What is a toxic dose? All experts agree. "... c*hloroquine has a small toxic to therapeutic margin,*" according to Goldfrank's Toxicologic Emergencies. The drug is very safe when used correctly, but not a lot more can potentially kill. Prof. Nicholas White, a Wellcome Trust Principal Research Fellow and expert in malaria treatment, who attended both WHO

consultations on the chloroquines, has confirmed this. Careful monitoring of electrolyte levels and an EKG can prevent most problems.

The WHO hired a consultant to explore the toxicity of hydroxychloroquine in 1979. The consultant, H. Weniger, looked at 335 episodes of adult poisoning by chloroquine drugs. Weniger on page 5 notes that a single dose of 1.5-2 grams of hydroxychloroquine base "may be fatal."

The Recovery trial used **1.86 grams** hydroxychloroquine base (equal to 2400 mg of hydroxychloroquine) in the first 24 hours for treatment of already very ill, hospitalized Covid-19 patients, a potentially lethal dose. The Canadian and Norwegian trials used 2,000 mg of HCQ, or **1.55 grams** of HCQ "base" in the first 24 hours. Each trial gave patients a cumulative dose during the first 24 hours that, when given as a single dose, has been documented to be lethal. (The drug's half-life is about a month, so the cumulative amount is important.)

The doses used in these trials are not recommended for therapy of any medical condition, which I confirmed with Goodman and Gilman's Pharmacology textbook, the drug's label, and the online subscription medical encyclopedia UptoDate.

Excessive, dangerous HCQ dosing continues to be used in WHO's Solidarity trials. These trials are not, in fact, testing the benefits of HCQ on Covid-19, but rather are testing whether patients survive toxic, non-therapeutic doses.

The WHO Solidarity trials, in order to rapidly enroll patients and spare clinicians a lot of paperwork, collect only limited information on side effects. No information has yet been provided regarding causes of death in the completed hydroxychloroquine arm of the Recovery trial, in which 396 patients died, and may never be.

The Solidarity trial design being employed by WHO obscures whether mortality is due to drug toxicity (in which case, one would expect cause of death to be due to an arrhythmia, neuropsychiatric effects, or hypoglycemia, as opposed to death due to Covid-19.

In fact, the lack of safety data being collected is downright scary. Here is a description of the data collected on patients enrolled in Solidarity, as reported in Science magazine:

> *The participant has to sign an informed consent form that is scanned and sent to WHO electronically. After the physician states which drugs are available at his or her hospital, the website will randomize the patient to one of the drugs available or to the local standard care for COVID-19.*
>
> *"After that, no more measurements or documentation are required," says Ana Maria Henao Restrepo, a medical officer at WHO's Emergencies Programme.* ***Physicians will record the day the patient left the hospital or died, the duration of the hospital stay, and whether the patient required oxygen or ventilation, she says. "That's all."***

The WHO report of its meeting on chloroquine dosing states,

> *"Although the preponderance of opinion tilted towards a reasonable benefit risk profile for the intervention, there was some scepticism about what was considered a 'minimalistic safety data collection' currently included in the protocol."*

The high dose regimen being used in these trials has no medical justification. The trial design, with its limited collection of safety data, makes it difficult or impossible to identify toxic drug effects, compared to a standard drug trial. This is completely unethical.

Excessive dosing makes it impossible to assess therapeutic benefit, if any, of HCQ.

Giving the drug only to hospitalized patients means that the window of time during which HCQ would be expected to provide the most benefit, when viral titers are rising, has passed.

Didier Raoult's group has recently published on the major differences in treatment and outcomes patients receive when placed in "big data" studies vs. receiving individualized care for Covid-19.

As I was completing this article on June 15, the FDA announced it was withdrawing its Emergency Use Authorization for hydroxychloroquine in Covid-19, because the "known and potential benefits" no longer outweigh the risks of the drug.

To sum up:

1. In the Recovery trial, and in WHO Solidarity trials, HCQ is used in a non-therapeutic, toxic and potentially lethal dose.

2. HCQ is being given too late in the disease course to determine its value against SARS-CoV-2.
3. Collection of limited safety data in the Solidarity trials serves to protect trial investigators and sponsors from disclosure of adverse drug effects, including death.
4. It appears that WHO has tried to hide information on hydroxychloroquine dosages used in its Solidarity trial. Fortunately, the information is discoverable from registries of its national trials.
5. The conclusions to be drawn are frightening:

a) WHO and other national health agencies, universities and charities have conducted large clinical trials that were designed so hydroxychloroquine would fail to show benefit in the treatment of Covid-19, perhaps to advantage much more expensive competitors and vaccines in development.

b) In so doing, these agencies and charities have *de facto* conspired to increase the number of deaths in these trials.

c) In so doing, they have conspired to deprive billions of people from potentially benefiting from a safe and inexpensive drug, when used properly, during a major pandemic. This might contribute to prolongation of the pandemic, massive economic losses and many increased cases and deaths.

Filename: Potentially lethal doses of HCQ used in WHO and Recovery clinical trials, according to WHO consultant.docx
Directory: /Users/dave/Desktop
Template: /Users/dave/Library/Group Containers/UBF8T346G9.Office/User Content.localized/Templates.localized/Normal.dotm
Title:
Subject:
Author: meryl nass
Keywords:
Comments:
Creation Date: 6/15/20 2:15:00 PM
Change Number: 2
Last Saved On: 6/15/20 2:15:00 PM
Last Saved By: meryl nass
Total Editing Time: 6 Minutes
Last Printed On: 6/17/20 1:45:00 PM
As of Last Complete Printing
Number of Pages: 6
Number of Words: 2,007
Number of Characters: 14,955 (approx.)