Hydroxychloroquine and coronavirus disease 2019

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Hydroxychloroquine sulfate (C18H28ClN3O5S) (HCQ) and sontoquine C (C19H28ClN3) were amongst the synthetic antimalarials created in the 1940s in response to a shortage created by the unavailability of mepacrine from Germany due to the outbreak of the Second World War.[1,2] The first published report of its use as an antimalarial was in 1952.[3] It was first used in 1956 for managing discoid lupus (DLE)[4,5] and systemic lupus erythematosus.[6] The United States' Food and Drug Administration approved its use for DLE in 1958. By 1960 *Plasmodium* resistance to HCQ was already being recognised.[7] But other indications were being discovered for its use viz. amoebiasis,[8] rheumatoid arthritis,[9] porphyria cutanea tarda[10] and Sjogren's syndrome.[11] That we understand the mechanism of action of this drug in any of its indications would be a vast overstatement. There is some evidence that it reduces the leucocyte motility,[12] may reduce antibody production, interfere with interleukin-1 production from monocytes,[13] and produce lysosomal dysfunction.[14]

Coronaviruses are enveloped positive-sense single-stranded RNA viruses belonging to the order *Nidovirales*, family *Coronaviridae*. Distinct viruses causing an infective bronchitis had been known about since the first half of the twentieth century.[15] Their typical electron microscopic appearance resembling the solar corona was recognised in the late 1960s.[16] At around the same time, it was also recognised that these hitherto zoonotic viruses could also affect humans causing respiratory symptoms like the common cold.[17] Within the coronavirus subfamily is the genus *Betacoronavirus*, members of which have been responsible for causing large-scale outbreaks in humans: the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the current pandemic with SARS-CoV-2.

HCQ has previously been considered as an adjunctive treatment in the management of RNA viruses because of its in vitro ability to reduce post-transcriptional modification and bolster the host defence mechanisms.[18,19] A randomised double-blind placebo-controlled trial of HCQ 800 mg/day in patients with asymptomatic Human Immunodeficiency Virus (HIV)-1 infection, confirmed this finding.[20] In these patients, it even appeared to have greater ability to suppress interleukin-6 and immunoglobulin G levels compared with zidovudine.[21] It was thought to be a good adjunctive drug for treating HIV-1 infection in countries where the newer expensive antiretroviral drugs were not affordable,[22] but this fell out of favour because of its inefficacy in individuals with a high viral load. It has been shown to be of value in conjunction with Interferon-α and ribavirin for hepatitis C.[23]

For SARS-CoV-2, in vitro physiologically based pharmacokinetic modelling suggests that HCQ 400 mg bd as a loading dose followed by 200 mg twice daily for four days may be an effective treatment.[24] A similar regimen (the loading dose was 600 mg bd) was used in patients admitted to a New York hospital.[25] This retrospective observational study of 1,376 patients admitted with SARS-CoV-2 was designed to look at the role of HCQ in reducing time to intubation or death (whichever was earlier), but stopped short of giving us that information. However, the study did report that in patients treated with HCQ, there was no benefit in preventing intubation or death on multivariate analysis (hazard ratio 1.0) (Table 1). They conducted a further analysis after propensity matching the HCQ-naïve cohort with the same result. In two further peer-reviewed studies from Marseille (with some case overlap) they used a different dose[26,27] (Table 1). They found a signal for increased virological clearance on day 6 in patients treated with HCQ 200 mg tds but there were significant

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Table 1 The characteristics of three studies of HCQ in SARS-CoV-2

Author	Patients	Intervention	Control	Primary Outcome	Result	Comment
Gautret et al. 2020	Hospitalised patients ≥12 years of age with PCR positivity for SARS-CoV-2 carriage n=42	HCQ 200mg tds for 10 days n=26	No treatment n=16	Virological clearance at day 6 post-inclusion	14/26 (53.8%) in Intervention arm vs. 2/16 (12.5%) in Control arm	Controls were patients who refused treatment, had an exclusion criteria in the active centre or were enrolled at centres where HCQ was not offered
Gautret et al. 2020	Hospitalised patients with PCR positivity for SARS-CoV-2 carriage n=80	HCQ 200 mg tds for 10 days + AZI 500 mg on day 1, 250 mg on day 2–5 + CEF for patients with NEWS ≥5 n=80	No control arm	Requirement for oxygen therapy or transfer to ICU on day 3	No information	The paper comments that 15% of patients required oxygen during their inpatient stay. There is no information on numbers needing oxygen on day 0 and day 3
Geleris J et al. 2020	Hospitalised patients with PCR positivity for SARS-CoV-2 carriage n=1376	HCQ 600mg bd on Day 1 + 400mg daily on Day 2-5 n=811	All patients without HCQ exposure n=565	Time to intubation or death (whichever was earlier)	No information on primary endpoint	There are no data on time to intubation or death between the intervention and control arms. However, there is information about number of events. 262/811 (32.3%) of patients in Intervention arm had an event; 84/565 (14.9%) of patients in Control arm had an event

PCR: polymerase chain reaction; AZI: azithromycin; CEF: ceftriaxone; ICU: intensive care unit

biases with the control arm consisting of patients who had refused treatment or were not offered it. The second larger uncontrolled observational study (n=80) did not analyse for their primary outcome of requirement for oxygen therapy or transfer to intensive care. Only 15% of the patients in that study required oxygen at any time, calling into question the need for hospital admission for the other 85%.

In a retrospective study of a large healthcare database from Israel (n=14,520), the 1,317 individuals that tested positive for SARS-CoV-2 were compared to those who were not suspected to have the infection. 0.23% of the positive sample were HCQ users, compared with 0.25% of the control group. They concluded that HCQ use was not associated with any prophylactic benefit in preventing the infection.[28]

In 2017, 2018 and 2019 there were 336, 401 and 432 publications respectively addressing some aspect of HCQ (data from PubMed). In 2020, there have already been 401 articles on HCQ (data from PubMed, 9 May 2020). Of that vast quantity of medical literature, there is not one randomised placebo-controlled trial, but the dearth of data has been filled by opinion, biased studies and speculation.

There is an opinion that we should 'think outside the box' and why shouldn't we try a drug when people are dying? The practice of medicine is guided by the principle *primum non nocere* (first do no harm), not *primum aliquid attentent* (first try something). Rheumatologists will attest that HCQ is a safe drug, but it is a mistake to assume that it is not capable of producing highly toxic adverse effects.[29] Its effect on cardiac conduction pathways, ocular toxicity and agranulocytosis have been recognised since the 1960s.[30-32] There appears to be a wide difference in blood concentrations of the drug[33] and in some individuals even small doses of the drug have been implicated in behavioural changes leading to accidental or intentional overdose and death.[34] In the absence of definitive evidence of efficacy, it would be medically negligent to offer a treatment with an adverse risk-benefit ratio. These are extraordinary times, and it is in these times that it is most important to keep our heads and use sound principles of medical practice.

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