Intervention

Hydroxychloroquine 2.4g (equivalent to 1.86g base) loading dose in four divided doses over 24 hours, followed by 800 mg (620mg base) daily for a further 9 days or until discharge.

In the RECOVERY Trial we are testing hydroxychloroquine (HCQ). HCQ, a derivative of chloroquine (CQ), has been used for many decades to treat malaria and rheumatological diseases. It has antiviral activity against SARS-CoV-2 in cell culture and preliminary reports from China and France report a beneficial antiviral and clinical effect in COVID-19.

WHO has prioritized the evaluation of chloroquine or hydroxychloroquine in COVID-19 in clinical trials to assess safety and efficacy (see here).

The dose being used in RECOVERY is the same dose as in the WHO-led international clinical trial in COVID-19 and is based on a careful review of the optimal dose in COVID-19, balancing potential risks and benefits (See below and appendix).

Summary of information on chloroquine and its derivatives in betacoronavirus infections.

CQ has significant antiviral activity against SARS-CoV-2 in cell culture (EC50 = 1.13 μM; CC50 > 100 μM, SI > 88.50), as it does for the related SARS-CoV-1 1-4. CQ blocks virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.5 In SARS-CoV-2 infected Vero cells, HCQ (EC50=0.72 μM) has been reported to be more potent than CQ (EC50=5.47 μM) 5, although Liu et al reported that CQ was more potent than HCQ.6 These are relatively high levels by comparison with therapeutic exposures in the treatment of malaria but could be achieved with daily oral dosing. Chloroquine has complex pharmacokinetic properties and although the relationship between plasma concentrations and concentrations in respiratory epithelium is not known precisely, in rats the concentration in lung is between 124 and 748-fold that in plasma 7. If active, HCQ concentrations in the human lung would be expected to exceed those required for the EC90 after an initial dose. There are preliminary reports emerging from China and France of clinical benefit in the treatment of COVID-19 infections 8,9.

Potential harm

CQ was discovered in 1934 and introduced generally in 1947. It has been used on a very large scale, with an annual global consumption of hundreds of metric tonnes for over 50 years. It is inexpensive, simple to administer, and, at the appropriate doses, has an excellent safety profile in all age groups and has been the prophylactic drug of choice in pregnancy 10. CQ and HCQ are very similar, with HCQ having a hydroxyl group on the alkyl side chain. In addition to antimalarial uses, CQ and HCQ are used in continuous daily dosing for rheumatoid arthritis, systemic and discoid lupus erythematosus and psoriatic arthritis. HCQ is reported to have better safety profile than CQ, better gastrointestinal tolerability and less retinal toxicity 11.
Chloroquine and hydroxychloroquine are generally well tolerated. Apart from the bitter taste the most common adverse effect is itching in dark skinned patients. Occasionally there may be transient headache, difficulty focusing, dysphoria, emotional lability decreased appetite; nausea; vomiting, abdominal pain; diarrhoea or skin rash. Chloroquine predictably prolongs the electrocardiograph QT interval but arrhythmias are rare; indeed chloroquine is generally anti-arrhythmic. Arrhythmias are more likely with co-existent hypokalaemia so this should be addressed. At high doses, hypotension may occur. Reported retinal and muscle toxicity with HCQ is associated with long term high dose use and it is very unlikely to be encountered in short course regimens. Because of the long terminal half-life after a course of HCQ is completed, care should be taken when introducing other drugs after the course of HCQ is finished.

**Choice of intervention and dose**

**HCQ versus CQ:** In animal toxicity assessments HCQ usually has a higher ED50 or LD50 than chloroquine. This toxicity difference in favour of HCQ is greatest in dogs. The elimination kinetics of the two drugs are very similar. In man the two advantages of HCQ most widely quoted are better gastrointestinal tolerability and less retinal toxicity, although the evidence for both is not strong. It is unclear whether the risk of adverse cardiovascular effects (hypotension and QT prolongation) differ in man between the two drugs. From a clinical standpoint there are no downsides to using hydroxychloroquine and there may be a small advantage in tolerability.

**Dose:** The recommended adult dosing of chloroquine for treatment of non-falciparum malaria (BNF) is 620 mg initially, then 310 mg after 6–8 hours, then 310 mg daily for 2 days. This is equivalent to 930mg base in first 24 hours. This is a loading dose to ensure the necessary blood concentrations are achieved rapidly.

Hydroxychloroquine is very similar to chloroquine. It is used mainly to treat rheumatoid arthritis and other related conditions. The adult dose is usually 400-600mg/ day (equivalent to 310 to 465 mg base). Sometimes 800mg/day is given.

The dose in RECOVERY is Hydroxychloroquine (155mg base per 200mg tablet):
- Initial dose: 4 tablets
- 6 hours later: 4 tablets
- 12 hours: 2 tablets
- 24 hours: 2 tablets
- Thereafter: 2 tablets every 12 hours for a total of 10 days

The first day loading dose in RECOVERY (1.86g base) is twice the first day loading dose for treating malaria. This dose has been selected based on the available data of the IC$_{50}$ for SARS-CoV-2. The objective is to reach plasma concentrations that are inhibitory to the virus as soon as safely possible. The plasma concentrations that will result are at the higher end of those encountered during steady state treatment of rheumatoid arthritis. Given the significant mortality in patients hospitalised with COVID-19, this dose is felt to be justified. This is the schedule that has been adopted by the World Health Organisation in their SOLIDARITY trial. No dose adjustment is required for weight or kidney function based on the doses defined in this protocol.
The pharmacokinetics of hydroxychloroquine are complex, but are largely determined by distribution rather than excretion. Further details are given in the appendix, but in brief hydroxychloroquine is rapidly absorbed after oral dosing but blood concentrations then fall rapidly due to tissue binding which creates an apparent volume of distribution of >100 L. The loading doses included in RECOVERY are intended to ‘fill’ this large volume of distribution rapidly so that blood concentrations can be maintained in the range sufficient to kill the virus. Renal excretion clears about 20-50% of hydroxychloroquine but does not become an important determinant of blood concentrations for some time, because of the overwhelming effect of distribution, which is why no adjustment for kidney function has been made given the short duration of treatment (compared to chronic administration in rheumatological conditions). In addition, non-GFR related mechanisms of clearance appear to increase as GFR falls, limiting the impact of reduced kidney function. The two loading doses are the same as the two loading doses in the WHO-recommended treatment regimen for amoebic liver abscess, but separated by 6 hours rather than 24, and the total dose over 10 days is the same as the standard treatment of amoebic liver abscess, when the same total dose is given over 20 days. The seriousness of COVID-19 (with approximately 20% in-hospital mortality in the UK) justifies testing these higher doses.

Any serious adverse reactions to hydroxychloroquine are to be reported and the independent Data Monitoring Committee will review them alongside other clinical outcome data. If clear evidence of benefit or harm emerge then they would advise the Steering Committee should the trial protocol need to be modified or stopped.

References

