**Name of Journal:** *World Journal of Clinical Infectious Diseases*

**Manuscript NO:** 57503

**Manuscript Type:** LETTER TO THE EDITOR

**Top ten tips for perfect corona-2 prophylaxis**

Abul-Ainine A *et al*. Top ten tips for perfect corona-2 prophylaxis

Ahmad Abul-Ainine, Ali A Sadek

**Ahmad Abul-Ainine,** Consultant Paediatrician, Paediatric Department, Jeddah 23955, Saudi Arabia

**Ali A Sadek,** Kuwait-Consultant Public Health and Medical Statistics, Jeddah 23955, Saudi Arabia

**Author contributions:** Abul-Ainine A wrote the manuscript, revised it, made the dosing software, and made the submission; Sadek AA discussed all items principles, reviewed and corrected the manuscript and tested the software.

**Corresponding author: Ahmad Abul-Ainine, CCST, FRCP, Director,** Consultant Paediatrician, Paediatric Department, Thuwal, Jeddah 23955, Saudi Arabia. ainine@doctors.net.uk

**Received:** June 11, 2020

**Revised:** August 2, 2020

**Accepted:** September 18, 2020

**Published online:**

**Abstract**

The current corona-2 pandemic has stimulated wide research for hydroxychloroquine (Quine) therapy and lately, prophylaxis. To optimize prophylaxis proper methods of use are explained. The focus is on tools of assessment and robust comparison; defining infection objectively; loading and maintenance dose designing based on pharmaco-viro-kinetics; confirming Quine threshold-levels and its sufficiency; and Quine side-effects vigilance/amelioration. Attention to statistics to study valid endpoints of goals in appropriately-sized population is essential. mass interactive quine dose auto designer software is built to simplify, optimize and help collaboration of complex Quine dosing system. A similar chloroquine software can be built.

**Key words:** Corona-2; COVID-19; Hydroxychloroquine; Prophylaxis; Dose; Mass interactive quine dose auto designer

Abul-Ainine A, Sadek AA. Top ten tips for perfect corona-2 prophylaxis. *World J Clin Infect Dis* 2020; In press

**Core tip:** Quine's role in corona-2 pandemic prophylaxis can be assured *via* designing correct loading doses (LD)/ maintenance doses (MD), therapy duration, and volumetric absorptive microsampling (VAMS) concentrations, assuring human IC50 and Liver and Heart safety thresholds of TCL10 and TCH10. Surly, good care will translate VeroE6 Viro-kinetics into human Viro-kinetics and help human-tailored dosing; not misguided by improper models, malaria, or rheumatology doses. mass interactive quine dose auto designer, viral count, and VAMS test help initial Quine LD/MD designing and human-tailored LD/MD dosing.

**TO THE EDITOR**

A good effort to study post-exposure hydroxychloroquine (Quine) prophylaxis was recently published[1]. Despite that it has decent statistical design, it has salient issues that need to be addressed to perfect the outcome of further Quine prophylaxis: (1) The primary outcome should involve viro-conversion from positive at entry to negative on exit (little testing in this study); (2) Primary outcome involves clinical symptoms reported by patients (was its percent reliability factored in sample-size calculations?) and was rated by 4 Infectious Disease doctors (without mention of inter-rater training or kappa of agreement reliability)[2]; (3) No data on further exposure to corona-2; other flu virus or having nasal allergy during the 2-wk study; (4) Using primary outcome as clinical symptoms is subjective, neither sensitive (as 80% are asymptomatic) nor specific to COVID19, (is it another flu virus or hay-fever?); (5) The Quine antimalarial dose is smaller than its antiviral loading doses (LD) calculated from the pharmaco-kinetics data held by FDA[3] (table 1). Low LD will produce sub-inhibitory levels, so that patients are not protected for 1-4 d pre-enrollment and 4-5 d post-enrollment (treatment start 1 d after enrollment and might take 4 d to reach the level required for protection-threshold); (6) although measuring drug levels by using finger-prick to self-collect 10 μm blood samples (VAMS) is well-known, i*n-vivo* Quine IC50 (= 50% Inhibitory Concentration) is never assured; pharmacokinetics from one study proposed VeroE6 cell IC50 of 4.5 μmol/L in 48 h of post-infection (mcM/hpi)[4,5], and another 6.3-5.9 in 24-48 mcM/hpi[6] requiring higher LD (15 and 20 tablets x 200 mg each, respectively); plus 2-3-wk maintenance doses (MD) or until patients develop their own immuno-protection; (7) Finding of safety-thresholds (10% Toxic Concentration = TC10) for liver enzymes elevation (= TCLiver10), for heart QT-prolongation (= TCHeart10), clinical hepatitis and dysrhythmia issues; (8) Since Quine is virostatic, its prophylactic-level must be maintained for at least 2-3 wk to build immunity that can clear virion particles (not possible in VeroE6 cell-kinetic cultures). So, dosing for 5 of 14 d is inadequate; (9) the folate-placebo helps one-carbon atom transfer to thymine to produce uracil, the rate-limiting substrate for RNA synthesis –undesired confounder; and (10) Although using sophisticated statistics to end the study early at a priori statistical power outcome is good, extending Quine prophylaxis (following correct LD) to achieve and define human IC50, is a missed historical landmark in the human/corona-2 contest. Sadly, statistical passion forced ending at only 2.4% incidence reduction rather than a 7% reduction –glorifying statistical-significance sacrificed nearby finding/measuring the more clinically important IC50 –*cf. McNamara fallacy*.

**Conclusion**

Quine's role in corona-2 pandemic prophylaxis can be assured via designing correct LD/MD, therapy duration, and VAMS concentrations, assuring human IC50 and Liver and Heart safety thresholds of TCLiver10 and TCHeart10. Surly, good care will translate VeroE6 Viro-kinetics into human Viro-kinetics and help human-tailored dosing; not misguided by improper models, malaria, or rheumatology doses.

mass interactive quine dose auto designer, viral count and VAMS test help initial Quine LD/MD designing and human-tailored LD/MD dosing.

**ACKNOWLEDGEMENTS**

Dr. Osman Akhtar, Pharmacist in Thuwal Clinic for reviewing and testing the dosing software mass interactive quine dose auto designer.

**REFERENCES**

1 **Boulware DR**, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hullsiek KH. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med* 2020; **383**: 517-525 [PMID: 32492293 DOI: 10.1056/NEJMoa2016638]

2 **McHugh ML**. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 2012; **22**: 276-282 [PMID: 23092060]

3 Drug Name: SYMPROIC. FDA-Approved Drugs. [Approved 23 March 2017]. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208854>

4 **Qu Y**, Brady K, Apilado R, O'Malley T, Reddy S, Chitkara P, Ibarra C, Alexander RV, Dervieux T. Capillary blood collected on volumetric absorptive microsampling (VAMS) device for monitoring hydroxychloroquine in rheumatoid arthritis patients. *J Pharm Biomed Anal* 2017; **140**: 334-341 [PMID: 28391006 DOI: 10.1016/j.jpba.2017.03.047]

5 **Liu J**, Cao R, Xu M, Wang X, Zhang H, Hu H, Li Y, Hu Z, Zhong W, Wang M. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020; **6**: 16 [PMID: 32194981 DOI: 10.1038/s41421-020-0156-0]

6 **Yao X**, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020; **71**: 732-739 [PMID: 32150618 DOI: 10.1093/cid/ciaa237]

**Footnotes**

**Conflict-of-interest statement:** The authors have no any conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Corresponding Author's Membership in Professional Societies:** GMC, 4644640.

**Peer-review started:** June 11, 2020

**First decision:** July 4, 2020

**Article in press:**

**Specialty type:** Virology

**Country/Territory of origin:** United Kingdom

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Song G, Xiao C **S-Editor:** Ma YJ **L-Editor: P-Editor:**

**Table 1 The mass interactive quine dose auto designer**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Body weight (kg)** | **60** |  | **Loading dose** | **Loading days if** | **Maintenance** |  **Post-protect** | **Durations** | **Load/Maint** | **Protective nadir (mcM)** | **5** |
| C rise/tab (mcM) | 0.386 | Target levels | computed | 6 | 7 | 5.0 |  Give to stay on peak doses for  | 6 |  |  |
| Half-life: T 1/2 | 22.4 | level in mcM | tablets to load | tablets used/d | Tablets/wk | Post-last-dose | Doses Ratio | Maintenance interval (d) | 1 |
| Well indications |  1 Tab = 200 mg = 155 × 0.74 | 2 tablets /6 h |  |  |  |  |  |  |
|  Protection |  | 5.0 | 14 | 2.3 | 2.5 | 0 | Until becomes immuno-protected or the pandemic ends | 5.5 |  Protective peak (mcM) | 5.2 |
|  Community helper  | 6.0 | 17 | 2.8 | 3.0 | 6 | 5.5 |  |  |
|  Exposed but well | 7.0 | 20 | 3.3 | 3.5 | 11 | 2 wk | 5.6 |  First dose (200 mg tablets) | 13.4 |
| Unwell indications |  |  |  |  |  |  |  |  |  |
|  Low Infection  |  | 8.0 | 23 | 4 | 4 | 15 | 2 wk | 5.7 |  Maintain dose (tablets) | 0.4 |
|  Medium Infection  | 10.4 | 30 | 5 | 5 | 24 | 2 wk | 5.8 |  |  |
|  High infection  |  | 13.3 | 40 | 7 | 7 | 32 | 2 wk | 6.0 |  PostCourse protected days | 1.0 |

Assuming these doses for weights 40-60 kg: Each 600 mg or 3 tablets is replaced by: Child < 40 kg dose = 12 mg/kg or Adult > 60 kg idealised 3 tablets equivalent = kg/20 Tablets; Micro finger-prick testing (Volumetric Absorptive Micro-Sampling, VAMS) can be used to confirm or guide dosing; All red numbers are editable, so that user's can tailor to the needs and evolving data on effective inhibitory concentrations; Durations: For symptomatic infections, Quine (virostatic) should cover until immune system is able to inactivate the virus; C rise/tab (mcM): Drug concentration rise per tablet in micro-moles/L (mcM).