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Research Article

Chloroquine dosage regimen simulation for pediatric patients with coronavirus disease 2019

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ABSTRACT

Chloroquine (CQ) efficacy was shown in some coronavirus disease 2019 (COVID-19) adult clinical studies. However, its data in children is still limited. Therefore, this study aims to assess the suitability of the dosage regimens from the literature and regimens proposed by the authors for pediatric COVID-19 patients aged 2-12 years old. The efficacy pharmacodynamic (PD) target was calculated for CQ blood concentration based on the literature's successfully treated COVID-19 adult regimen. The safety PD targets were derived from the literature regarding any adverse effects (AEs) and QTc prolongation. The adult pharmacokinetic (PK) parameters were transformed into pediatrics by allometric scaling (AS) method. A 10,000-time Monte Carlo simulation (MCS) was performed to calculate the percentage of probability to target attainment (%PTA). The literature's regimens were not capable of achieving 90%PTA efficacy PD target. The proposed regimens without loading dose (LD) achieved the efficacy target at day 8-10 which was later than the proposed regimens with LD (day 4-7). The 90%PTA below any AEs target was achieved in the first few days of the literature and proposed regimens but was unavoidable thereafter. Nevertheless, the 90%PTA below QTc prolongation target was favorably achieved by all regimens. This study revealed that the proposed regimen with LD seems to be the optimal dosage regimen. Additional studies are needed to validate our proposed regimens, especially among early-stage COVID-19 patients and recent major variants.

Keywords:
Chloroquine, COVID-19, Monte Carlo Simulation, Pediatrics, Pharmacokinetics

1. INTRODUCTION

As of June 2021, around 180 million people worldwide were infected by COVID-19, the newly emerged pandemic disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), with an overall mortality rate as high as 2 percent[1]. Its major symptoms are fever, cough, sore throat, myalgia, and respiratory tract symptoms[2]. Pediatric COVID-19 cases are less severe than adults, with hospitalization in only 8 versus 165 per 100,000 cases. Despite its low severity among children, drug treatments for severe cases in this population are still needed. Moreover, the rapid viral clearance provided by early antiviral administration is one of the treatment strategies that might prevent multisystem inflammatory syndrome in children (MIS-C). This syndrome is a post-infection consequence that explicitly affects children. It affects about 0.4 percent of all pediatric COVID-19 cases, mainly found in school-aged children, and is relatively severe with a mortality rate of 2 to 4 percent[3].

CQ has been used for nearly a century as an antimalarial agent. It was recommended as part of compassionate use for COVID-19 treatment by early clinical practice guidelines (CPGs)[4-6]. Its potency was demonstrated by several *in vitro* tests[7-8] but efficacy was controversial in clinical trials[9-10] with a higher dose than the usual malaria dose. Consequently, in March 2020, the United States Food Drug Administration (USFDA) approved CQ and hydroxychloroquine (HCQ), its derivative, for Emergency Use Authorization (EUA)[11]. However, the EUA was then revoked in June 2020[12]. Furthermore, the current CPGs[13-14] have discouraged use of CQ/HCQ in adult and pediatric COVID-19 patients because of a lack of efficacy and safety concerns, as shown in some meta-analysis studies

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driven largely by HCQ studies[15-16]. Nevertheless, it is still unclear whether CQ/HCQ inefficacy is definite or influenced by starting in late-stage patients who have exceeded the golden period for antivirals, as seen in some viral infections, or even from inappropriate dosage regimen resulting in suboptimal blood concentration[17-19].

CQ has a complex PK profile. It has a wide 2-compartmental model distribution pattern and half of administered CQ is metabolized in the liver by cytochrome P450 enzyme. CQ is excreted into the urine via glomerular filtration and active tubular secretion with a pretty long elimination half-life[20]. Thus, the difference of body composition and metabolic process between adults and children results in fairly contrasting PK parameters. Additionally, some adult COVID-19 regimens have been proposed in literature with relatively high dose of CQ[21]. Therefore, the recommended CQ in pediatrics converted from the "per kilogram" adult dose without adjustment for a PK parameter difference as seen in some CPGs[4] may lead to ineffective treatment or even toxicity resulting from lower or higher blood level than needed. In particular, the QT interval prolongation, a serious adverse drug reaction, is associated with the rapid surge of blood CQ concentration from the first compartment distribution within a few hours after administration[22]. The MCS with appropriated PK model and PK equations is helpful to obtain the possible blood concentration range resulting from the patient variability [23]. This study aimed to define the suitable dosage regimens of CQ for COVID-19 treatment among pediatric patients aged 2-12 years old.

2. MATERIALS AND METHODS

2.1. Pharmacokinetic parameter inputs

There was no available pediatric population PK study specific to the preferred range of age. The CQ whole blood concentration was then computed from adult population PK parameters by adopting the AS method, as shown in Figure 1. The adult population PK parameters of CQ obtained from a study by Hoglund et al.[24] which was chosen based on the type of administration (single- or multiple-dose) and population race. The pediatric volume of distribution (Vd) value is equal to the multiplication of adult Vd value with the sum of the ratio between pediatric weight and standard adult weight (60 kilograms) raised to the exponential power of 0.75. The exponential power number is 1 for clearance (CL)[25]. The adult and pediatric PK parameters was shown in Table 1.

$$\text{Pediatric pharmacokinetic parameter} = \text{Adult pharmacokinetic parameter} \times \left(\frac{\text{Pediatric weight}}{\text{Standard Adult weight}}\right)^{\text{exponential power number}}$$

Figure 1. Allometric Scaling Method.

Table 1. Pharmacokinetic Parameters.

Pharmacokinetic Parameters	k_a (h^{-1})	V_1	V_2	Q	Cl
Adult Value	1.1267	468 L	1600 L	37.7 L/h	6.13 L/h
Pediatric Value	1.1267	7.8 L/kg	26.667 L/kg	1.749 L/kg/h	0.284 L/kg/h
Interindividual variability			20		

Abbreviations: Cl, clearance of elimination; h, hour; k_a, absorption rate constant; kg, kilogram; L, Liter; Q, inter-compartmental clearance, V_1, volume of distribution of central compartment; V_2, volume of distribution of peripheral compartment

2.2. Pharmacodynamic model

Two types of PD targets, namely efficacy and safety, were used in this study. The minimum whole blood concentration of CQ among successfully treated adult COVID-19 patients was chosen for the efficacy PD target. The adult patients in the selected clinical trial by Huang et al.[10] were administered a 500 mg (300 mg base) tablet of chloroquine phosphate (CQP) orally every 12 hours for 10 days. On day 14 after treatment, all patients from the CQP arm had negative nasopharyngeal (NP) swabs, had better computed tomography (CT) chest scans, and were discharged from the hospital. Therefore, the CQ whole blood concentration on the last day of the regimen was selected as the efficacy PD target. The equations for calculation were shown in Figure 2. The efficacy PD target was achieving a minimum blood concentration above 1.9580 mg/L (Table 2).

For the safety PD target, the CQ serum blood concentration related to any AEs was retrieved from the CQ serum-blood concentration study among adult rheumatoid patients treated with a high dose of CQ by Frisk-Holmberg et al.[26] Moreover, because QT prolongation is a serious AE that occurs in a dose-dependent manner, maximum blood concentration was included as one of the PD targets derived from the adult COVID-19 treatment study by Borba et al.[9], from which QT interval data was available by using the equations in Figure 2. After MCS, the maximum blood concentration was ranging between 3.3998 to 6.1644 mg/L. Because 18.9% of the

patients had QT prolongation, assuming these patients had higher CQ concentration, the lowest concentration (5.0278 mg/L) of this subgroup was selected as safety PD target. The safety PD target was set as any blood CQ concentration below 0.9750 mg/L for any AEs and maximum blood CQ concentration of 5.0278 mg/L for rate-corrected QT (QTc) prolongation by Bazett's formula ($QTc=QT/[RR^{0.5}]$) (Table 2). Other serious AEs such as retinopathy, hearing loss, and hematological AEs were not included in this study because they commonly occur with long-term use[22]. The ratio conversion of CQ whole blood to plasma concentration ratio was 5[27] and serum to plasma ratio was 2[28].

Table 2. Pharmacodynamic target of chloroquine.

PD target	Adult regimen	Time-point of CQ blood concentration	Converted CQ whole blood concentration from PK modeling and Monte Carlo simulation (mg/L)
Efficacy target	CQP 500 mg (equivalent to 300 mg CQ base) twice daily for 10 days [10]	Minimum whole blood concentration at day 10 of therapy (at hour 240 of the regimen)	1.9580
Safety target			
Any AEs [23]	Not applicable	Any serum concentration during therapy	0.9750
Rate-corrected QT (QTc) interval longer than 500 msec	CQP 1000 mg twice daily for 10 days [9]	Maximum whole blood concentration during regimen (at hour 230 of the regimen)	5.0278

Abbreviations: AEs; Adverse Effects; CQ, Chloroquine; CQP, Chloroquine Phosphate; L, Liter; mg, milligram; PD, Pharmacodynamic; PK, Pharmacokinetic

$$\text{Whole Blood Concentration at Time t} = \text{Dose} \times [A \times e^{-\alpha \times t} + B \times e^{-\beta \times t} - ((A+B) \times e^{-k_a \times t})]$$

When

- $\alpha = \frac{\frac{Q}{V_2} \times \frac{Cl}{V_1}}{\beta}$
- $\beta = \frac{1}{2} \times [\frac{Q}{V_1} + \frac{Q}{V_2} + \frac{Cl}{V_1} - \sqrt{(\frac{Q}{V_1} + \frac{Q}{V_2} + \frac{Cl}{V_1})^2 - (4 \times \frac{Q}{V_2} \times \frac{Cl}{V_1})}]$
- $A = \frac{k_a}{V_1} \times \frac{\frac{Q}{V_2} - \alpha}{(k_a - \alpha) \times (\beta - \alpha)}$
- $B = \frac{k_a}{V_1} \times \frac{\frac{Q}{V_2} - \beta}{(k_a - \beta) \times (\alpha - \beta)}$
- k_a was calculated from equation $t_{max} = \frac{\ln k_a - \ln k_e}{k_a - k_e}$

Figure 2. Pharmacokinetic Equations.
Parameters Abbreviations: ka, absorption rate constant; k12, distribution rate constant from central to peripheral compartment; k21, distribution rate constant from peripheral to central compartment; V1, volume of distribution of central compartment; V2, volume of distribution of peripheral compartment; Q, inter-compartmental clearance; Cl, clearance of elimination; ke, elimination rate constant; α, first rate constant; β, second rate constant; A, first macro-constant; B, second macro-constant

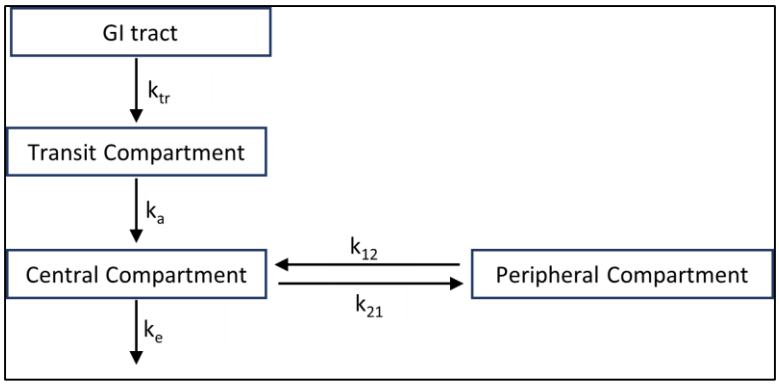

Figure 3. Pharmacokinetic Equations.
Abbreviations: GI, Gastrointestinal; ka, absorption constant, ke, elimination rate constant; ktr, transition constant; k12, distribution constant from central to peripheral compartment; k21, distribution constant from peripheral to central compartment

2.3. Pharmacokinetic model

The CQ whole blood concentration data was back-calculated from the regimen in the aforementioned clinical trials[9-10] by the equations in Figure 2. To obtain the target PD parameter, CQ blood concentration at 10 days or 240-hour since the first dose administration was calculated using the PK model[29] demonstrated in Figure 3. The model was run at a 15-minute interval for each regimen to capture the maximum concentration during the absorption phase. The 2-compartment model with one transit compartment for absorption was implied because it was a better fit for illustrating CQ PK[24]. CQ blood concentrations from our AS method and PK model were compared with pediatric malarial studies using same CQ regimens. The *p*-values from independent t-test are not significant (data not shown), indicating our method is acceptable to be used for simulation.

2.4. Monte Carlo simulation

MCS was performed 10,000 times by Oracle Crystal Ball Program version 2017 (Oracle Corp., Redwood City, CA USA) for each pediatric regimen recommended by some COVID-19 CPG and the regimen proposed by the author as shown in Table 3. Proposed regimens without LD and with LD continued by a maintenance dose (MD) were designed to achieve the efficacy target at its earliest along with the balanced safety target. The between-individual variability was set as log-normal. The 90 percent probability of attainment (90%PTA) of achieving the efficacy PD target was the primary consideration for selecting the most suitable regimen.

Table 3. Chloroquine regimen.

Chloroquine Regimen (as Chloroquine base) (total dose per course)	Reference
5 mg/kg twice daily for 5 days for patients with mild symptoms (50 mg/kg)	Department of Medical Services, Ministry of Health, Thailand[4]
5 mg/kg twice daily for 10 days for patients with severe symptoms (100 mg/kg)	
Children 6 months-12 years of age: Day 1: 10 mg/kg then 5 mg/kg in next 12 hour then Day 2-5: 5 mg/kg twice daily (55 mg/kg)	Verscheijden et al.[29]
Without Loading dose (LD):	
A; 5 mg/kg every 6 hours for 10 days (200 mg/kg)	Proposed Regimen
B: 7 mg/kg every 8 hours for 10 days (210 mg/kg)	Proposed Regimen
C: 10 mg/kg every 12 hours for 10 days (200 mg/kg)	Proposed Regimen
With Loading dose (LD):	
D: LD: 10 mg/kg every 6 hours for 1 day then MD with 5 mg/kg every 6 hours for 9 days (220 mg/kg)	Proposed Regimen
E: LD: 10 mg/kg every 6 hours for 2 days then MD with 5 mg/kg every 6 hours for 8 days (240 mg/kg)	Proposed Regimen
F: LD: 10 mg/kg every 6 hours for 3 days then MD with 5 mg/kg every 6 hours for 7 days (260 mg/kg)	Proposed Regimen
G: LD: 10 mg/kg every 6 hours for 3 days then MD with 5 mg/kg every 8 hours for 7 days (225 mg/kg)	Proposed Regimen

Abbreviations: LD, loading dose; kg, kilogram; MD, maintenance dose; mg, milligram.

3. RESULTS

Various CQ regimens for COVID-19 treatment in pediatric patients were analyzed for %PTA achieving the efficacy and safety PD target. In Table 4, the 90%PTA of achieving the efficacy PD target (1.9580 mg/L) was not shown in both short and long regimen recommended by Thai CPG[4], nor for the regimen suggested by Verscheijden et al.[30] for which the loading dose was included (Figure 4h, 4i, and 4j).

From Table 4, the proposed regimens by the authors without LD (regimen A, B, and C), could achieve 90% PTA of efficacy target at day 8 to day 10. Remarkably, although the regimen A and C consisted of the same total dose per course (200 mg/kg), the regimen A with more frequent (6-hour) administration interval achieved 90% PTA of efficacy target at day 9, one day faster than the regimen C with less frequent (12-hour) administration interval. The graphical data is shown in Figure 4a, 4b, and 4c.

The proposed regimens with LD (regimen D, E, F and G) achieved 90%PTA of efficacy target at some point from day 4 to day 7 (Table 4 and Figure 4d, 4e, 4f and 4g). The greater number of LD days resulted in a shorter time of achieving. Even though the total dose of the regimen F and the regimen G is quite different (260 mg/kg versus 225 mg/kg, respectively), they tend to be equal in time to reach 90%PTA of efficacy target (day 4).

In Table 5 and Figure 4, %PTA of any time point concentration below any AEs target (0.9750 mg/L) is shown (the lower a concentration is below the threshold indicating a lower risk of getting any AEs). The regimens from the literature show minimal risk of any AEs as indicated by nearly 100%PTA in the first 3 days of

Table 4. Percent of Target Attainment of Minimum Concentration above the Efficacy PD Target.

Regimens (total dose per course)	24 hour	48 hour	72 hour	96 hour	120 hour	144 hour	168 hour	192 hour	216 hour	240 hour
Regimens recommended by the existing literature										
5 mg/kg twice daily for 5 days for patients with mild symptoms (50 mg/kg) (Ministry of health, Thailand)[4]	0.0	0.0	0.0	0.0	0.0	Not applicable				
5 mg/kg twice daily for 10 days for patients with severe symptoms (100 mg/kg) (Ministry of health, Thailand)[4]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Children 6 months-12 years of age: Day 1: 10 mg/kg then 5 mg/kg in next 12 hour Day 2-5: 5 mg/kg twice daily (55 mg/kg) (Verscheijden et al.)[29]	0.0	0.0	0.0	0.0	0.0	Not applicable				
Proposed regimen without loading dose										
A: 5 mg/kg every 6 hours for 10 days (200 mg/kg)	0.0	0.0	0.0	0.0	3.3	27.5	65.2	88.5	97.3	99.5
B: 7 mg/kg every 8 hours for 10 days (210 mg/kg)	0.0	0.0	0.0	0.1	6.0	36.1	73.1	92.2	98.4	99.7
C: 10 mg/kg every 12 hours for 10 days (200 mg/kg)	0.0	0.0	0.0	0.0	0.2	5.6	29.2	61.2	84.5	95.3
Proposed regimen with loading dose										
D: LD: 10 mg/kg every 6 hours for 1 day then MD with 5 mg/kg every 6 hours for 9 days (220 mg/kg)	0.0	0.0	0.0	7.4	35.7	71.1	90.9	97.7	99.6	99.9
E: LD: 10 mg/kg every 6 hours for 2 days then MD with 5 mg/kg every 6 hours for 8 days (240 mg/kg)	0.0	29.7	54.7	66.7	87.1	96.1	99.1	99.8	100.0	100.0
F: LD: 10 mg/kg every 6 hours for 3 days then MD with 5 mg/kg every 6 hours for 7 days (260 mg/kg)	0.0	29.0	82.2	97.3	99.2	99.8	99.9	100.0	100.0	100.0
G: LD: 10 mg/kg every 6 hours for 3 days then MD with 5 mg/kg every 8 hours for 7 days (225 mg/kg)	0.0	29.7	82.7	89.1	89.8	90.5	91.2	92.1	92.9	93.7

Abbreviations: LD, loading dose; kg, kilogram; MD, maintenance dose; mg, milligram.

Table 5. Percent of Target Attainment of Concentration of Any Time Point Below the Safety PD Target for Each Day During Regimen.

Regimens (total dose per course)	Type of AE	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Regimens recommended by the existing literature											
5 mg/kg twice daily for 5 days for patients with mild symptoms (50 mg/kg) (Ministry of health, Thailand) [4]	any AEs	100.0	100.0	99.6	89.2	69.0	Not applicable				
	QTc prolongation	100.0	100.0	100.0	100.0	100.0					
5 mg/kg twice daily for 10 days for patients with severe symptoms (100 mg/kg) (Ministry of health, Thailand) [4]	any AEs	100.0	100.0	99.6	89.2	69.0	48.4	27.5	11.9	4.0	1.1
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Children 6 months-12 years of age: Day 1: 10 mg/kg then 5 mg/kg in next 12 hour Day 2-5: 5 mg/kg twice daily (55 mg/kg) (Verscheijden et al.) [29]	any AEs	100.0	100.0	95.9	78.0	57.6	Not applicable				
	QTc prolongation	100.0	100.0	100.0	100.0	100.0					
Proposed regimen without loading dose											
A: 5 mg/kg every 6 hours for 10 days (200 mg/kg)	any AEs	100.0	58.6	3.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
B: 7 mg/kg every 8 hours for 10 days (210 mg/kg)	any AEs	99.0	44.4	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
C: 10 mg/kg every 12 hours for 10 days (200 mg/kg)	any AEs	91.6	52.4	8.3	0.2	0.0	0.0	0.0	0.0	0.0	0.0
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
D: LD: 10 mg/kg every 6 hours for 1 day then MD with 5 mg/kg every 6 hours for 9 days (220 mg/kg)	any AEs	41.5	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
E: LD: 10 mg/kg every 6 hours for 2 days then MD with 5 mg/kg every 6 hours for 8 days (240 mg/kg)	any AEs	41.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Abbreviations: AE, Adverse Effect; LD, loading dose; kg, kilogram; MD, maintenance dose; mg, milligram.

Table 5. Percent of Target Attainment of Concentration of Any Time Point Below the Safety PD Target for Each Day During Regimen. (cont.)

Regimens (total dose per course)	Type of AE	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Proposed regimen without loading dose											
F: LD: 10 mg/kg every 6 hours for 3 days then MD with 5 mg/kg every 6 hours for 7 days (260 mg/kg)	any AEs	41.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
G: LD: 10 mg/kg every 6 hours for 3 days then MD with 5 mg/kg every 8 hours for 7 days (225 mg/kg)	any AEs	41.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	QTc prolongation	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Abbreviations: AE, Adverse Effect; LD, loading dose; kg, kilogram; MD, maintenance dose; mg, milligram.

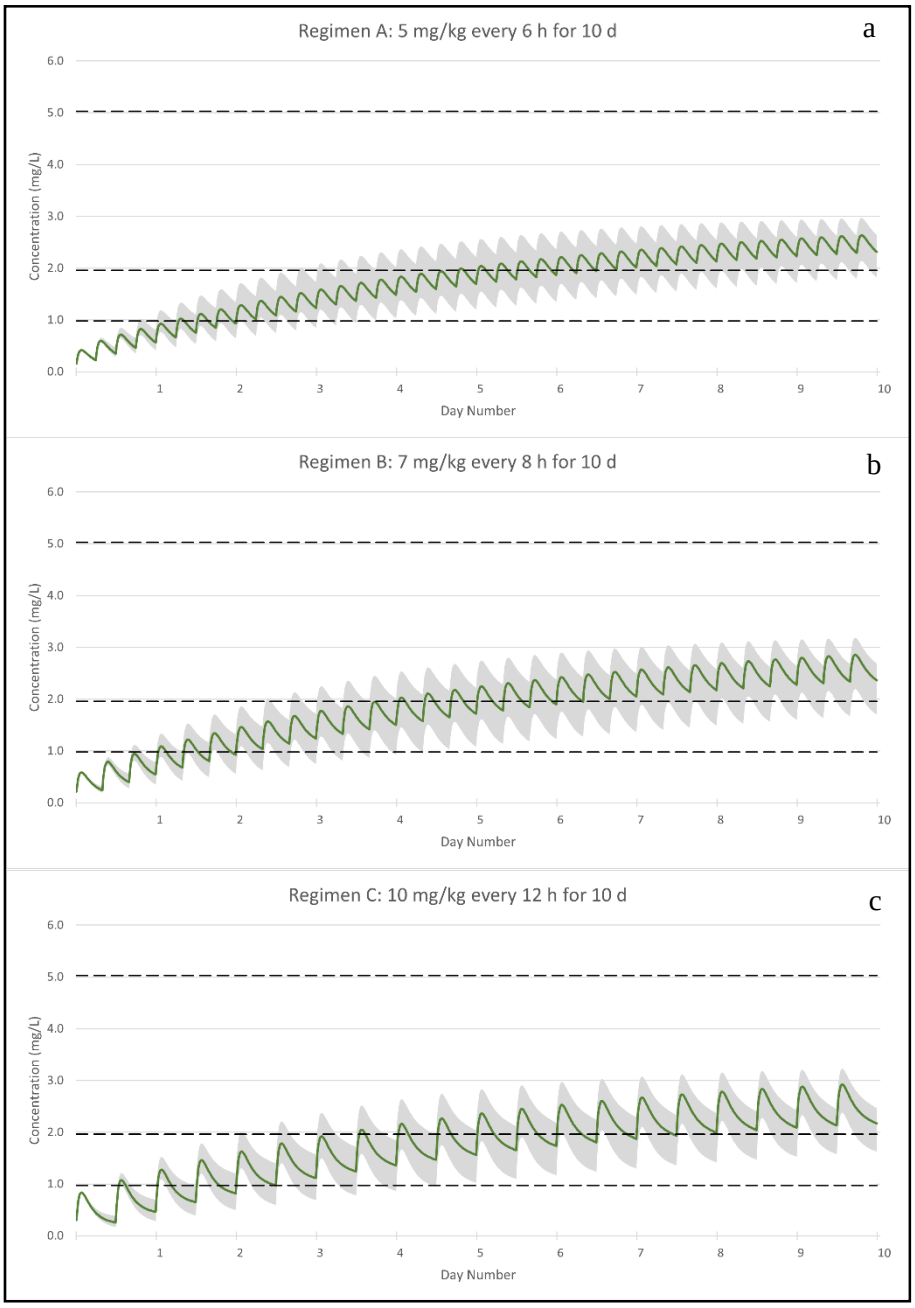

Figure 4. Concentration-time relationship graph of various regimens.
The solid line indicates the mean value from the Monte Carlo simulation. The dash lines indicate various PD targets (upper line for the QTc prolongation safety PD target, middle line for the efficacy PD target, and lower line for the any-AEs safety PD target). The grey area illustrates the maximum and minimum range from the Monte Carlo simulation.
Figure 4a, 4b, and 4c are the proposed regimens without loading dose (regimen A, B and C, respectively).
Abbreviations: d, day; h, hour; kg, kilogram; mg, milligram

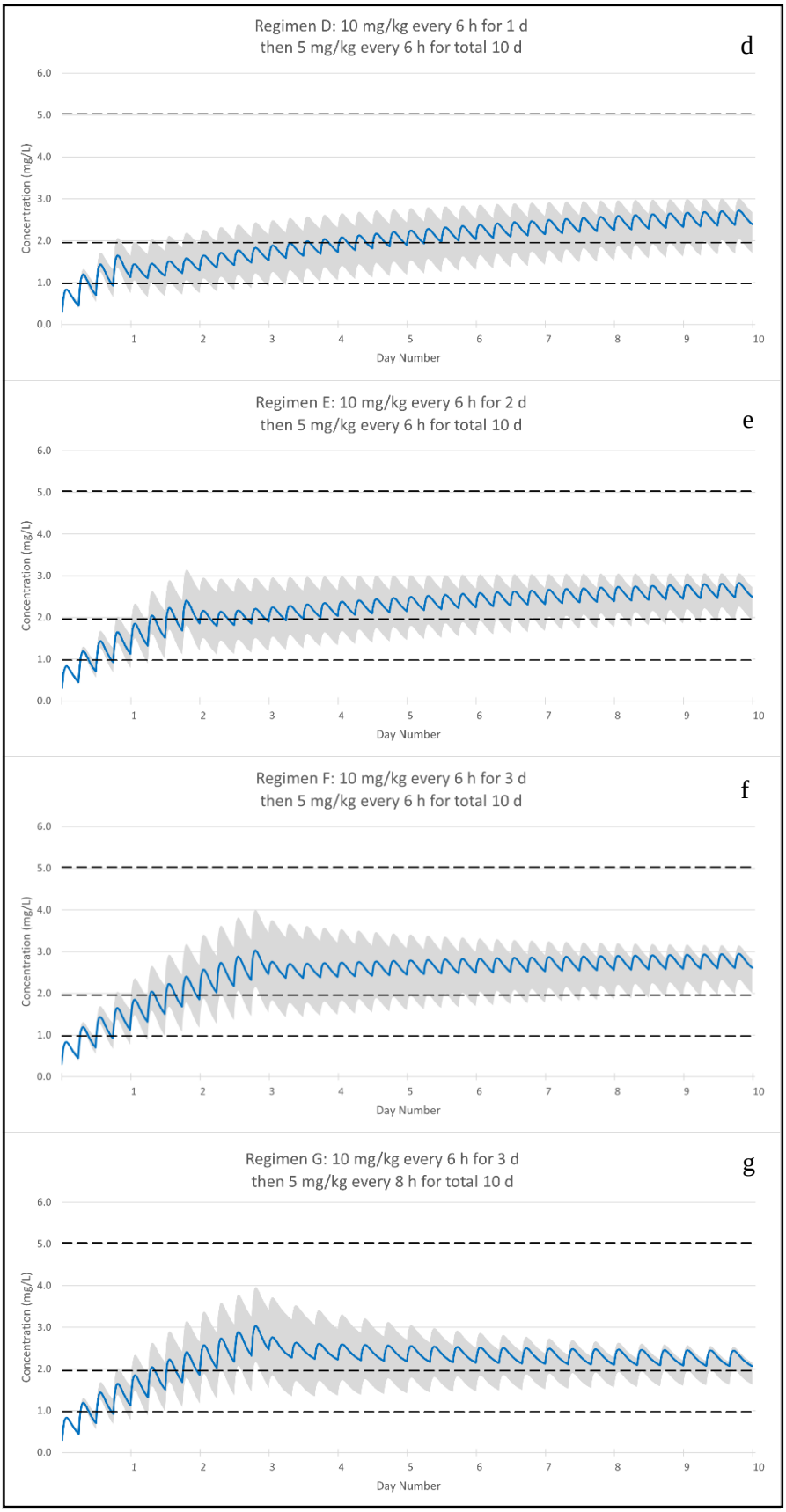

Figure 4. Concentration-time relationship graph of various regimens.
The solid line indicates the mean value from the Monte Carlo simulation. The dash lines indicate various PD targets (upper line for the QTc prolongation safety PD target, middle line for the efficacy PD target, and lower line for the any-AEs safety PD target). The grey area illustrates the maximum and minimum range from the Monte Carlo simulation.
Figure 4d, 4e, 4f, and 4g are the proposed regimens with loading dose (regimen D, E, F, and G, respectively).
Abbreviations: d, day; h, hour; kg, kilogram; mg, milligram

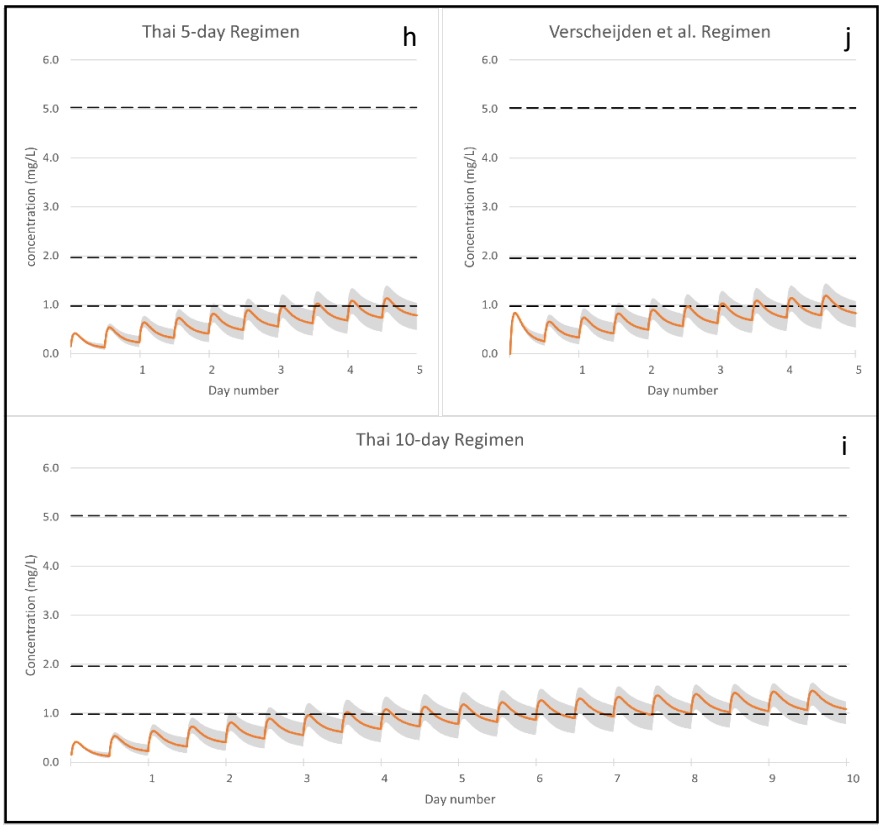

Figure 4. Concentration-time relationship graph of various regimens.
The solid line indicates the mean value from the Monte Carlo simulation. The dash lines indicate various PD targets (upper line for the QTc prolongation safety PD target, middle line for the efficacy PD target, and lower line for the any-AEs safety PD target). The grey area illustrates the maximum and minimum range from the Monte Carlo simulation.
Figure 4h, 4i, and 4j are the existing literature regimens (5-day Thai regimen, 10-day Thai regimen, and Verscheijden et al. regimen, respectively).
Abbreviations: d, day; h, hour; kg, kilogram; mg, milligram

Thai 5-day regimen[4] and Verscheijden et al. regimens[30]. Moreover, the risk of getting any AEs in the Thai 10-day regimen[4] is gradually increases in its last 7 days.

The risk of getting any AEs from the proposed regimens without LD was considerably high since day 2 (44.4 to 58.6 %PTA), and increased overtime. It is noticeable that the risk of AEs from the proposed regimen with LD was relatively high since day 1, as shown to be about 40 %PTA, and decreases to nearly 0 %PTA at day 2. The higher each dose of CQ administered resulted in a higher maximum concentration, leading to a risk of developing AEs. Remarkably, at the comparable total dose per course between regimen D and G (220 and 225 mg/kg, respectively), the regimen with higher LD has a comparable %PTA below any AEs threshold with higher %PTA of achieving efficacy threshold.

The risk of QTc prolongation was not seen in any regimens from the literature or regimens proposed by the authors, as shown by 100 %PTA of concentration below QTc prolongation PD target (5.0278 mg/L) for the entire regimen time. The concentration-time chart for mean, minimum and maximum results from MCS for all regimens is demonstrated in Figure 4.

4. DISCUSSION

To define the concept of our efficacy PD target, the available *in vitro* data was used at first because the data related to CQ against SARS-CoV-2 is lacking. The concentration-dependent antiviral characteristics of CQ to SARS-CoV-2 was suggested by the *in vitro* studies[7-8]. Besides, the trend of lower half-maximal effective concentration (EC_{50}) with longer incubation time (7.65 mg/L and 1.75 mg/L at 24- and 48-hours incubation time, respectively) has been revealed[7]. This correlated to the antiprotozoal characteristics of CQ against malarial protozoa where maintained blood concentration above MIC was associated with the lowest rate of treatment failure and resistance rate[31]. Therefore, keeping blood concentration above EC_{50} concentration may exert antiviral activity and be the optimal efficacy PD target. However, considering that clinical outcomes may be influenced by complex human body processes despite blood concentration successfully achieving the target, the clinical outcome data was chosen instead, along with an application of the concept from *in vitro* studies.

Our efficacy PD target (1.9580 mg/L) was vastly higher than the concentration generally required for malaria treatment (0.075-0.15 mg/L for non-resistant strain)[32], signifying the requirement of higher dose than usual. The recommended regimens existing in the

literature[4,30] did not meet our efficacy PD target, but our proposed regimens did. This can be explained by the much lower and inadequate pediatric dose in the literature compared to ours. Furthermore, the Verscheijden et al. study[30] did not mention the rationale behind its recommendations. Consequently, our proposed regimens are more rigorous in terms of being supported by clinical data.

Specifically, our proposed regimens without LD (regimen A, B, and C) were able to achieve 90%PTA at day 8 to day 10. Faster achievement was seen in the proposed regimens with LD (regimen D, E, F, and G) from day 4 to day 7 (Table 4). The regimen F is considered to be the optimal regimen because it can achieve the efficacy PD target fastest (day 4). However, regimen G tended to achieve at same day with a balanced safety profile and less frequent interval. It is expected that the patients treated with this regimen may experience clinical outcomes faster than our reference study by Huang et al.[10] which the median time to negative NP swab, better CT scan, and discharge from hospital are 6.5, 9, and 11 days, respectively. Additionally, the faster viral clearance may be helpful in severe MIS-C prevention[33].

Another adult study in severe patients by Borba et al.[9] which demonstrated 2 regimens, higher (CQP 1000 mg twice daily for 10 days) and lower (750 mg twice daily on the first day then 750 mg once daily for 4 more days), has associated with 39% and 15% of mortality rate, respectively. On day 4, 22.2% of patients had negative NP swab which is likely lower than our reference outcome. Moreover, the MCS study by Tidwong et al.[21] has investigated for the optimal dosage regimen in adult COVID-19. It was shown that high CQ dose was needed (such as the higher dosage regimen by Borba et al.[9] or its own designed regimens of 2,000-3,000 mg LD in 1-2 days with 500 mg MD twice daily for total 10 days) which is quite different from our reference study regimen (CQP 500 mg twice daily for 10 days)[10]. Considering the discrepancy in these data, the effectiveness of CQ is questionable. Nevertheless, this difference might be affected by higher-risk patients for COVID-19 severity in Borba et al. study[9] (indicated by higher baseline severity, higher respiratory rate, more hypertension, and more diabetes). The timing of antiviral administration may be another possible explanation too. There were suggestions that antiviral benefit is maximized when administered shortly after infection, which can be clearly seen in influenza[17], herpes simplex[18], and varicella-zoster infection[19]. For COVID-19, few reviews have proposed a disease-course conceptual model of 3 stages of clinical presentation[34]. The viral replication is at its peak at phase I, which the symptoms are usually mild, and becoming more severe through stage II and III. As marked by more severe patient proportions in Borba et al.[9] study, this suggested that the golden period for antiviral administration is likely missed. Therefore, antivirals should be used in recently infected patients before entering stage III, at which point the mainstay therapy should be the anti-inflammatory drugs instead[13]. Consequently, our proposed regimens with LD may be able to provide the quick rise of blood CQ concentration to the level needed for the desired outcomes.

Our proposed regimens contributed blood concentrations higher than any AE thresholds (0.9750 mg/L) for most of the time course. This threshold was derived from the Frisk-Holmberg et al. study where visual disturbances was frequently found[26]. The other minor AEs include gastrointestinal symptoms (nausea, vomiting, abdominal pain, anorexia), dizziness, headache, and fatigue[22]. It was more intensive when the concentration was at around its peak or in the less frequent regimens. Despite causing mild and reversible common AEs, the high probability of AE occurrence among patients may lead to lower adherence, principally in pediatrics which potentially has a reduced unacceptable taste tolerance, and intensified dizziness, nausea, and vomiting AEs. Thus, as only an oral form of CQ is available, close observation should be conducted for a few hours after administration to ensure adherence which could be AEs-induced, or the poor acceptance from bad formulation palatability.

Cardiac arrhythmia was the most serious AE selected in this study analyses because the proposed regimens have contained high dose CQ given in a short duration. The development of Torsades de Pointes, the fatal form of arrhythmia, is associated with QTc prolongation. However, even with the same amount of QTc prolongation, the risk of its development varies depending on risk factors such as older age, female sex, electrolyte disturbances, endocrine dysfunction, and predisposing heart conditions[35].

Our proposed regimen resulted in a relatively low risk of getting the QTc prolongation because the 100% PTA of concentration below the QTc prolongation target (5.0278 mg/L) is maintained for the whole regimen time. This correlates with the pediatric malarial study by Scragg et al.[36], which did not find any serious AEs, including arrhythmia in cohort using total 100 mg/kg of CQ over 5 days. Another malarial study by Ursing et al. used 70 mg/kg of CQ divided over 5 days, resulting in a median whole blood CQ concentration of 1.08-1.14 mg/L and a QTc interval for 13-14 milliseconds (msec) longer than baseline[37]. Remarkably, there was still one patient who had 64 msec QTc interval longer than baseline even though no one had QTc interval exceeding 500 msec nor arrhythmia in that study[37].

Nevertheless, the adult COVID-19 study by Borba et al.[9], which used a higher dose CQP regimen than our reference study regimen[10], is associated with 18.9% and 11.1% of patients with QTc interval prolongation. However, all patients in Borba et al. study[9] concomitantly took azithromycin, a well-known QTc prolongation

precipitator. These emphasized that the risk factors apparently play an essential role in QTc prolongation development. Therefore, although being young is a protective factor of QTc prolongation in pediatrics, the overall risk factors must be crucially criticized before making an individualized treatment plan. This may highlight the importance of close electrocardiogram (EKG) monitoring, particularly while the high dose CQ regimen was dispensing in the COVID-19 setting where the QTc prolongation may be aggravated by the displayed hyperinflammation[38].

There are some limitations in this study. First, implementation of the population PK value for MCS from the malarial patient may differ from COVID-19 patients in some aspects. Some evidences suggested that during a period of acute COVID-19 infection, a prolonged fever results in increased insensible water loss compared to the shorter fever in malaria infection (one high fever period per 2-3 days). It then might be compensated by a higher reduction of renal clearance that finally affects drug clearance. Secondly, the fever seems to shorten QTc interval which returns to normal (longer) when the fever reduces[39]. Thus, the data about QTc prolongation threshold derived from fever patients as used in our study may be limited its use in the defervescence stage and caution must be exercised when applying. Finally, generalizability respecting viral mutation is concerned. As of June 2021, there are 5 predominantly circulating variants of SARS-CoV-2, whereas the clinical result of CQ used in this study was from the period during which only wild-type variant existed. The mutation of those main variants occurred with the spike protein which might affect its infectivity and severity[40]. Therefore, the alteration on CQ efficacy is possible because one of its proposed mechanisms was related to the glycosylation during the entry process of the virus. Concerning possibly emerge variants that can escape vaccine-derived immunity or unsusceptible to COVID-19 specifically made drugs, the higher CQ dosage regimen might be a fallback for pediatric COVID-19 treatment. The further clinical study needed to confirm this study result by applying the higher dose and sooner administration concept which is seems to be optimal for efficacy and safety. Validation in cases infected with other main variants should also be done.

5. CONCLUSION

The findings of this study suggest that the COVID-19 pediatric treatment CQ regimens recommended by current CPGs could not achieve the efficacy PD target. The proposed regimen with LD was shown to achieve the desired efficacy PD target with the expected faster time to achieve the target and a balanced safety profile. Although the higher administered dose correlates with a higher risk of getting common AEs, all proposed regimens were lower than the concentration at risk for QTc prolongation. Therefore, the risk factors for severe COVID-19 and QTc prolongation for each patient should be intensively appraised before making a personalized medication plan. CQ might be the last resort option for vaccine-evading and drug-resistant emerging variants. Further study is needed regarding the novel perspective of the antiviral efficacy during the early stage of infection and generalizability to other main variants.

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