International Journal of Antimicrobial Agents 50 (2017) 542–551

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Optimal antimalarial dose regimens for chloroquine in pregnancy based on population pharmacokinetic modelling

Sam Salman [a], Francesca Baiwog [b], Madhu Page-Sharp [c], Kay Kose [b], Harin A. Karunajeewa [d], Ivo Mueller [d,e], Stephen J. Rogerson [f], Peter M. Siba [b], Kenneth F. Ilett [a], Timothy M.E. Davis [a,*]

[a] School of Medicine and Pharmacology, University of Western Australia, 35 Stirling Hwy, Crawley, WA 6009, Australia
[b] Papua New Guinea Institute of Medical Research, P.O. Box 378, Madang, Madang Province, Papua New Guinea
[c] School of Pharmacy, Curtin University of Technology, Kent Street, Bentley, WA 6102, Australia
[d] Population Health and Immunity, Walter and Eliza Hall Institute, 1G Royal Parade, Parkville, VIC 3052, Australia
[e] Barcelona Institute for Global Health (ISGlobal), Carrer del Rosselló 132, 08036 Barcelona, Spain
[f] Department of Medicine (RMH), The University of Melbourne, 300 Grattan Street, Parkville, VIC 3050, Australia

ARTICLE INFO

Article history:
Received 27 February 2017
Accepted 25 May 2017

Keywords:
Malaria
Pregnancy
Chloroquine
Pharmacokinetics

ABSTRACT

Despite extensive use and accumulated evidence of safety, there have been few pharmacokinetic studies from which appropriate chloroquine (CQ) dosing regimens could be developed specifically for pregnant women. Such optimised CQ-based regimens, used as treatment for acute malaria or as intermittent preventive treatment in pregnancy (IPTp), may have a valuable role if parasite CQ sensitivity returns following reduced drug pressure. In this study, population pharmacokinetic/pharmacodynamic modelling was used to simultaneously analyse plasma concentration–time data for CQ and its active metabolite desethylchloroquine (DCQ) in 44 non-pregnant and 45 pregnant Papua New Guinean women treated with CQ and sulfadoxine/pyrimethamine or azithromycin (AZM). Pregnancy was associated with 16% and 49% increases in CQ and DCQ clearance, respectively, as well as a 24% reduction in CQ relative bioavailability. Clearance of DCQ was 22% lower in those who received AZM in both groups. Simulations based on the final multicompartmental model demonstrated that a 33% CQ dose increase may be suitable for acute treatment for malaria in pregnancy as it resulted in equivalent exposure to that in non-pregnant women receiving recommended doses, whilst a double dose would likely be required for an effective duration of post-treatment prophylaxis when used as IPTp especially in areas of CQ resistance. The impact of co-administered AZM was clinically insignificant in simulations. The results of past/ongoing trials employing recommended adult doses of CQ-based regimens in pregnant women should be interpreted in light of these findings, and consideration should be given to using increased doses in future trials.

1. Introduction

Although chloroquine (CQ) use has declined due to increasing *Plasmodium* resistance, it remains one of the few antimalarial drugs regarded as safe throughout gestation [1]. In addition, removal of drug pressure has resulted in the return of CQ-sensitive *Plasmodium falciparum* and thus clinical efficacy in Malawi [2], and other African countries are following suit [3–5]. The re-introduction of CQ-based combination therapy could become a reality given the emergence of parasites resistant to currently recommended regimens that include artemisinin derivatives and partner drugs such as lumefantrine and piperaquine [6,7]. In addition, the efficacy of sulfadoxine/pyrimethamine (SP), the only drug or combination currently recommended for intermittent preventive treatment in pregnancy (IPTp) [8], is also threatened by increasing parasite resistance [4,9].

The re-introduction of CQ-based therapy for prevention and/or treatment of malaria requires optimised dosing that maximises efficacy while minimising the risk of re-emergent parasite resistance. This is particularly important in pregnancy as most [10–12] if not all [13] studies have suggested that exposure to CQ and its active metabolite desethylchloroquine (DCQ) is reduced following recommended doses. The choice of a CQ partner drug in pregnancy would need to take pharmacokinetic and pharmacodynamic interactions into consideration. The antibiotic azithromycin (AZM), which is also safe in pregnancy [1], is one candidate [14]. There have been

* Corresponding author. School of Medicine and Pharmacology, Fremantle Hospital, University of Western Australia, P.O. Box 480, Fremantle, WA 6959, Australia.
E-mail address: tim.davis@uwa.edu.au (T.M.E. Davis).

https://doi.org/10.1016/j.ijantimicag.2017.05.011
0924-8579/

no reports of AZM-resistant parasites, whilst in vitro [15,16] and in vivo [15,17] data suggest that CQ and AZM have a synergistic effect against *P. falciparum*. The antimalarial activity of AZM is weak and of slow onset [18,19] and it has a shorter terminal elimination half-life than CQ and most other antimalarial drugs used for prevention, but the effects of AZM on the parasite persist after plasma concentrations have declined [20].

Clinical studies have shown that CQ/AZM has good efficacy in *P. falciparum* infections in non-pregnant patients [21]. A 3-day fixed-dose regimen has been developed and preliminary results suggest that it is effective for asymptomatic parasitaemia in pregnancy and that it has similar preventive efficacy to SP, if not as well tolerated [22,23]. In addition, AZM is effective against non-malarial infections, including sexually transmitted diseases, which can complicate pregnancy [14,24]. A previous report using non-compartmental methods in healthy non-pregnant adults has suggested that there is no pharmacokinetic interaction between CQ and AZM [25], but there are no pregnancy-specific data.

We have previously performed two separate studies of CQ in pregnant and non-pregnant women. In one study the pharmacokinetics of CQ, DCQ and SP following CQ/SP administration were characterised [11,26], and in the other the disposition of AZM following CQ/AZM administration was assessed without consideration of a possible interaction with CQ [27]. In both studies, women were recruited from the same area of coastal Papua New Guinea (PNG) and pregnant women were matched with non-pregnant women from their communities. We have therefore pooled plasma CQ and DCQ concentration data, published from the first study [11] and new data from the second study [27], to develop evidence-based pregnancy-specific CQ dosing recommendations both for acute treatment and IPTp based on population pharmacokinetic modelling. To address pharmacodynamic considerations, the relative antimalarial potencies of CQ and DCQ [28,29] and accepted in vitro threshold concentrations for parasite resistance [30] were incorporated. A secondary aim was to determine whether AZM influences the pharmacokinetics of CQ and/or DCQ in pregnant and non-pregnant women.

2. Materials and methods

2.1. Study site, sample and approvals

The two clinical studies were conducted at the Alexishafen Health Centre, Madang Province (Papua New Guinea) between February 2006 and March 2008. In the present analyses, all women given CQ with either SP or AZM were included. Safety, tolerability and efficacy data have been published previously [26,27]. Both studies were approved by the Medical Research Advisory Committee of PNG Department of Health, and the Human Ethics Research Committee of the University of Western Australia (Crawley, WA, Australia) approved the study involving CQ/AZM.

2.2. Clinical procedures

Clinical procedures were similar in both studies [26,27]. Women in the CQ/SP group received three CQ tablets (Chloroquin®; Astra, Sydney, NSW, Australia; 150 mg CQ base/tablet) daily for 3 days plus single-dose SP (Fansidar®; Roche, Basel, Switzerland; 1500 mg sulfadoxine, 75 mg pyrimethamine) with the first CQ dose. Those in the CQ/AZM group received CQ 450 mg base daily for 3 days but with 2 g of AZM (Zithromax®; Pfizer, New York, NY) at enrolment and at 24 h. All dosing was directly observed. In addition to a baseline sample, venous blood for drug assay was drawn at 1, 2, 4, 6, 12, 18, 24, 30, 48 and 72 h and then at 7, 10, 14, 28 and 42 days in the CQ/SP group, and at 1, 2, 3, 6, 12, 24, 32, 40, 48 and 72 h and then at 4, 5, 7, 10, 14, 28 and 42 days in the CQ/AZM group.

2.3. Assay methods

Extraction and validated assay of CQ and DCQ were performed as described previously [31].

2.4. Pharmacokinetic modelling

Log_e plasma concentration–time data sets for CQ and DCQ were analysed by non-linear mixed-effects modelling using NONMEM v.7.2.0 (ICON Development Solutions, Ellicott City, MD) and the first-order conditional estimation (FOCE) with interaction estimation method. The minimum value of the objective function (OFV), conditional weighted residuals (CWRES) plots, visual diagnostic plots and condition number <1000 were used to choose suitable models. A significance level of $P < 0.01$ was set for comparison of nested models. Allometric scaling was employed a priori, with volume terms multiplied by $(\text{body weight}/70)^{1.0}$ and clearance terms by $(\text{body weight}/70)^{0.75}$. Residual variability was estimated as additive error for the log-transformed data. Base models were parameterised using k_a (first-order absorption rate constant), LAG (lag time), V_c/F (central volume of distribution), CL/F (clearance), and V_p/F and Q/F (peripheral volume of distribution and the respective intercompartmental clearance), where F represents bioavailability. As complete conversion of CQ to DCQ was assumed to allow for identifiability, all DCQ parameters were relative to bioavailability and metabolic conversion denoted as F^*.

Plasma CQ concentration profiles were modelled alone, initially using one-, two- and three-compartment models (ADVAN 2, 4 and 12) with zero-, first- and mixed-order absorption with and without a lag time. After an adequate base structure was obtained, additional compartments for DCQ were added. Once the model structure was established, interindividual variability (IIV), interoccasion variability (IOV) and correlations between IIV terms were estimated where possible. Relationships between model parameters and covariates including maternal age, pregnancy status, gestational age, AZM co-administration (assuming that SP does not affect the disposition of CQ or DCQ [32]), malaria status and haemoglobin concentration were identified through inspection of scatterplots and boxplots of individual parameter values versus covariate, and subsequently evaluated within NONMEM. The effect sizes (%) of categorical data (pregnancy, AZM treatment and malaria positivity) were assessed, whilst both linear and power relationships were evaluated for continuous covariates (gestational age, maternal age and haemoglobin). For effect size:

$$\text{Individual parameter value} = \text{population average} \times (1 + \text{effect parameter} \times \text{covariate value}).$$

For linear relationships:

$$\text{Individual parameter value} = \text{population average} \times \left(1 + \text{effect} \times \frac{\text{individual covariate value}}{\text{median covariate value}}\right).$$

For power relationships:

$$\text{Individual parameter value} = \text{population average} \times \left(\frac{\text{individual covariate value}}{\text{median covariate value}}\right)^{\text{effect parameter}}.$$

The potential effect of AZM administration on F was also assessed. A stepwise forward inclusion and backward elimination