Single-Dose Pharmacokinetics of Chloroquine and its Main Metabolite in Healthy Volunteers

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Summary

The pharmacokinetic properties of chloroquine are still under debate. To establish the pharmacokinetics of a single dose of chloroquine and its metabolites, 19 healthy volunteers, including one Black and one albino subject, received a single dose of chloroquine 600mg. In addition, one participant also received an oral dose of de-ethylchloroquine 150mg. Blood and saliva samples were obtained up to 77 days after drug administration. High-performance liquid chromatography was used to measure the concentrations of chloroquine, de-ethylchloroquine and bis-de-ethylchloroquine. The mean volume of distribution (Vd), elimination half-life (t½) and clearance (CL) of chloroquine were 411 L/kg, 432 hours and 0.77 L/h/kg, respectively. For de-ethylchloroquine these values were 161 L/kg, 649 hours and 0.18 L/h/kg. The results of the Black and albino subject were similar. When 150mg of this compound was administered, the Vd of de-ethylchloroquine was 122 L/kg, t½ was 529 hours and CL was 0.16 L/h/kg. Bis-de-ethylchloroquine was detectable in 6 volunteers. No evidence for a bimodal distribution of chloroquine elimination was found in this study. Concentrations of chloroquine in saliva in the terminal elimination phase were 3-fold higher than in plasma.

Chloroquine is still widely used as a prophylactic and therapeutic antimalarial drug, despite widespread prevalence of resistant Plasmodium falciparum strains and, as was recently reported, of P. vivax strains. Chloroquine is inexpensive, widely available and relatively well tolerated. For these reasons chloroquine is still regularly used in antimalarial treatment.

It is also in use as an anti-inflammatory drug in the treatment of rheumatoid arthritis. The pharmacokinetic properties of chloroquine have important consequences for its clinical application.

The antimalarial activity of this agent appears to be related to its plasma concentration, although high concentrations also occur in intracellular vesicles of the Plasmodium spp. as well as in blood cells.¹,² Resistance is also related to the blood or plasma concentrations that can be achieved during treatment. In the first reported pattern of resistant parasites during prophylactic use, resistance could be overcome by raising plasma concentrations. In established resistance, however, this is no longer possible.

Adverse effects are sometimes related to the
plasma concentration. Retinopathy is an adverse reaction related to accumulation of the drug in the eye. Itching is another adverse reaction, almost exclusively affecting Black patients; binding of chloroquine to melanin pigments was suggested as the cause, which would imply a larger volume of distribution in pigmented subjects. Acute toxic effects are particularly related to the height of the peak plasma concentrations.

Potential pitfalls of pharmacokinetic studies of chloroquine are the large volume of distribution (Vd) and long elimination half-life (t1/2) of the drug. These require long sampling periods and sensitive and selective bioanalytical techniques. The first estimations of the pharmacokinetic properties of chloroquine were based on fluorometric techniques, which were not sensitive enough to detect chloroquine levels during the actual elimination phase. More recent methods, based on high-performance liquid chromatography (HPLC), opened the possibility for accurate pharmacokinetic studies. Despite this, the pharmacokinetics of chloroquine have still not yet unequivocally been resolved, and standard textbooks on pharmacology and pharmacotherapy still reflect this. This issue has recently been addressed again.

In the present study, the pharmacokinetics of chloroquine and its metabolites were assessed in a single-dose experiment. Plasma and saliva concentrations were measured. The aim of these experiments was to characterise in detail the single-dose pharmacokinetics of chloroquine and of de-ethylchloroquine, based on the assumption of linear pharmacokinetics. Uncertainties of previous studies were addressed by: the sensitivity of our assay, long sampling times, the large number of samples (blood and saliva) per individual, and the large number of study participants.

Methods

Study Participants and Sampling

A total of 19 healthy volunteers (10 males and 9 females), with a mean (± SD) age of 26 (± 4) years and a mean (± SD) weight of 65kg (± 8kg) were recruited. The group included 17 white Caucasians, one Black volunteer and one albino Caucasian subject. The study protocol was approved by the Institutional Review Board of the Academic Medical Centre.

After informed consent was obtained, participants received a single oral dose of chloroquine 600mg (Nivaquine®, Specia, Alkmaar, The Netherlands) with 150ml of tapwater. Blood samples were drawn before and at 0.5, 1, 2, 3, 4, 6, 10, 24, 32, 48, 72 and 96 hours and at days 6, 9, 14 and from then on once-weekly up to 63 days after administration. Saliva samples were obtained weekly from day 21 to 77.

In a separate pilot experiment, one of the volunteers (no. 5) received de-ethylchloroquine 150mg formulated by the hospital pharmacy as a powder with lactose for oral administration. This part of the study was conducted more than 1 year after the first experiment.

Bioanalysis of Chloroquine and Metabolites

Blood was centrifuged and plasma was collected within 30 minutes after sampling. Plasma and saliva samples were stored at −20°C until analysis. Plasma samples were analysed for chloroquine, de-ethylchloroquine and bis-de-ethylchloroquine using a previously published HPLC method.

The fluorescence detector was operated with λ = 330nm for excitation and λ = 410nm for emission. With this assay, blank plasma from several pools did not show any interfering peaks. Calibration plots using 4 concentrations of 25, 50, 100 and 200 μg/L chloroquine and its metabolites were linear, with correlation coefficients larger than 0.998. Duplicate measurements revealed coefficients of variation of 6.5% for the range of 0 to 100 μg/L and 7.1% for 100 to 400 μg/L chloroquine. The detection limit appeared to be 1 μg/L.

For the analysis of saliva samples, the same chromatographic system was used. However, a small column (4.6 × 30mm) packed with 30μm C18 pellets (C0-Pell ods) was mounted in the in-