Bulletin of the World Health Organization, 65 (1): 47-50 (1987)

Influence of route of administration on the pharmacokinetics of chloroquine and desethylchloroquine

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The pharmacokinetics of chloroquine following a single oral dose of 600 mg or an intramuscular injection of 200 mg of the drug was studied in seven healthy adult Africans. Each subject received chloroquine by both routes, with an interval of at least 4 months between them. Intramuscular injection led to rapid absorption of chloroquine, which attained a maximum concentration in plasma after 15 minutes and occasionally reached toxic levels; plasma levels fell below therapeutically useful concentrations 2–4 hours after administration. In contrast, oral administration of chloroquine produced therapeutic levels of the drug within 30 minutes and were maintained for up to 3 days. Peak levels in plasma were not high enough to produce adverse reactions. The terminal half-life and renal clearance time of chloroquine were not influenced by route of administration.

Chloroquine is usually administered orally in cases of uncomplicated malaria, and considerable data are available on the absorption, distribution, metabolism, and excretion of the drug (*1–4*). However, in cases of severe or complicated malaria, oral administration may not be feasible and parenteral injection has to be employed. Although both intravenous and intramuscular injection of chloroquine have been used, the choice of route as well as the dose and its frequency have been based on clinical inference from data on oral administration, rather than on rational pharmacokinetic considerations.

Because of the continued effectiveness of chloroquine in the treatment of falciparum malaria in West Africa and the controversy surrounding parenteral administration of the drug, we investigated the pharmacokinetics of chloroquine and its major metabolite (desethylchloroquine) in a group of normal healthy adults and report our findings here.

MATERIALS AND METHODS

Seven normal, male African adults, who were medical students at the College of Medicine, University College Hospital, Ibadan, Nigeria, volunteered for the study. They were aged 19–23 years and were judged healthy on the basis of clinical examination, normal blood and urinary biochemical findings as well as electrocardiogram. All were non-smokers and took alcohol only occasionally. None of the volunteers had taken chloroquine in the 3 months preceding the investigation and during the study period took no doses of the drug other than those administered as part of the investigation. Also, none of the volunteers was taking any regular drug treatment. The objective of the study and its procedure were carefully explained to the volunteers and the protocol was approved by the Ethical Committee of the College of Medicine.

Study design

Each of the seven volunteers was given a single oral dose of 600 mg chloroquine[a] followed not less than 4 months later by a single intramuscular injection of 200 mg chloroquine phosphate[b] (doses are based on the amount of chloroquine base).

Chloroquine was taken orally along with 200 ml of water after an overnight fast, while the intramuscular injection was administered in the morning also after fasting. A sample of blood (10 ml) was withdrawn from an antecubital vein of each subject at the following times: before administration, and at 5

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[a] Bayer AG, Leverkusen, Federal Republic of Germany.

[b] Helm Pharmaceuticals, Hamburg, Federal Republic of Germany.

minutes, 15 minutes, 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h after administration as well as on days 3, 5, 7, 14, 21, 28, and 35 of the study. However, for oral doses the 5- and 15-minute samples were omitted. Blood was collected in a heparinized container and centrifuged at 1200 *g* within 10 minutes; the plasma was stored frozen at −70 °C until analysed. Twenty-four-hour urine samples were collected from each subject on days 1, 7, 14, 21, 28, and 35, the volumes carefully noted, and 10-ml aliquots stored at −70 °C until analysed.

Analytical techniques

Chloroquine and desethylchloroquine were extracted from plasma and urine and analysed in duplicate by high-performance liquid chromatography (HPLC) (*5*). The mobile phase consisted of a mixture of acetonitrile and methanol (1.5:1.0 (v/v)). 7-Chloro-4-(4-dimethylamino-1-methylbutylamino)quinoline was used as internal standard, while the column was packed with silica (5 μm diameter).[c] A fluorescence detector was used (excitation wavelength λ = 335 nm; emission, λ = 380 nm).

Pharmacokinetic analysis of data

The chloroquine concentration–time data, the total dose of drug administered, and the weight of each volunteer were determined and analysed using the GPHARM nonlinear program. The analysis assumed a two-compartment open model. The "terminal" half-life of chloroquine ($t_{1/2}$) in plasma was calculated by linear regression from the log concentration–time plots using the final four or five experimentally measured values, while the area under the plasma concentration–time curve (AUC) was estimated by the trapezoidal rule. The area under the curve extrapolated to t_∞ was calculated using the relation C_{tn}/β, where C_{tn} is the final concentration of chloroquine and β is the slope of the least-squares linear regression of the log concentration–time curve. The plasma clearance (Cl_p) was calculated using equation 1:

$$Cl_p = F \cdot D/AUC \quad (1)$$

where D = dose of chloroquine and F = the fraction of the dose absorbed.

Renal clearance (Cl_R) was calculated from the urinary and plasma concentration data on days 7, 14, 21, 28, and 35 using equation 2:

$$Cl_R = (\textit{Amount of drug excreted per unit time})/C_p \quad (2)$$

where C_p is the plasma concentration of chloroquine at the midpoint of the urine collection interval.

[c] Ultrasphere-Si, available from Beckman Instruments Inc., Berkley, CA, USA.

The apparent volume of distribution at equilibrium (V_D) was calculated from equation 3:

$$V_D = Dose/B \quad (3)$$

where B is the intercept of β on the concentration axis.

RESULTS

Oral dose

Fig. 1 shows log concentration–time plots of the mean levels of chloroquine and desethylchloroquine in plasma for all seven subjects after the single oral dose of 600 mg chloroquine base. Chloroquine was rapidly absorbed from the gastrointestinal tract and was detectable in plasma 30 minutes after administration. The concentration in plasma increased rapidly, reaching a maximum in 2–8 hours (mean 5.1 ± 2.8 hours). From the maximum level of 363.8 μg/l (range 308.8–430 μg/l) the concentration fell gradually and chloroquine was still detectable 35 days after administration. The terminal half-life varied from 157 to 248 hours (mean 190 ± 27.7 hours) and renal clearance from 142 to 443 ml/min (mean 239 ± 138.0 ml/min).

The onset of metabolism of chloroquine was rapid, desethylchloroquine being detectable in the blood 30 minutes after administration. The peak concentration of desethylchloroquine in plasma ranged from 71.2 to 162.5 μg/l (mean 114.8 ± 32.3 μg/l) and was attained within 2–8 hours (mean 7.4 ± 1.5 hours). Like that of the parent compound, the concentration of desethylchloroquine decreased slowly and was still detectable in plasma 35 days after commencement of the study.

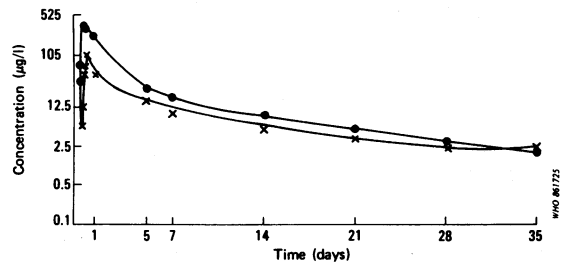

Fig. 1. Variation of mean plasma concentration (μg/l) of chloroquine (●) and desethylchloroquine (X) with time in subjects after an oral dose of 600 mg chloroquine.

Intramuscular dose

Chloroquine was rapidly absorbed when administered intramuscularly and reached a maximum concentration within 5 minutes for two subjects and within 15 minutes for the remaining five. Initially, the concentration decreased markedly and after 2 hours was about only 6% of the maximum value. Thereafter, the reduction in concentration was slow, and 28 days after administration was still about 40% that of the 2-hour level (Fig. 2). The central volume of distribution (V_c), the apparent volume of distribution (V_D), and the plasma clearance (Cl_p) were calculated from the intramuscular concentration–time data, since this mode of administration is characterized by very rapid absorption. Total absorption of the drug was assumed following intramuscular injection, since previous studies have indicated that almost complete absorption occurs after oral administration (*2*). The "terminal" half-life ranged from 60 to 360 hours (mean, 217 ± 94 hours), while renal clearance was 145 ± 93.7 ml/min, approximately 22% that of plasma clearance (657 ± 425 ml/min). The central volume of distribution was 10.2 ± 3.3 l/kg, while the equilibrium or apparent volume of distribution was 181 ± 48.6 l/kg.

Desethylchloroquine was present in blood 15 minutes after administration, rose to a maximum value after 1 hour, and was still detectable in plasma 28 days after administration.

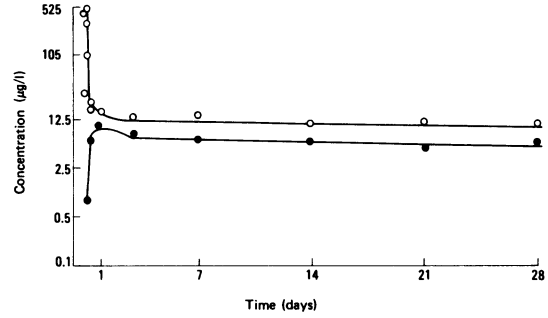

Fig. 2. Variation of mean plasma concentration (µg/l) of chloroquine (○) and desethylchloroquine (●) with time in subjects after an intramuscular injection of 200 mg chloroquine phosphate.

DISCUSSION

The standard initial oral dose of chloroquine for cases of acute falciparum malaria in adults is 600 mg. This is followed 6 hours later, especially for those who are not immune, by a second dose of 300 mg and subsequently by 300 mg daily for 2 days (resulting in a total dose of 1500 mg chloroquine). For semi-immune adults in endemic areas, the initial 600-mg dose is generally held to be adequate. When given intramuscularly, the initial dose is usually 200 mg, but there appears to be no standardization of subsequent doses, largely because of the lack of basic pharmacokinetic data. The results we have reported here indicate that intramuscular injection of an amount of chloroquine corresponding to one-third that of the usual oral dose results in a maximum mean level of the drug in plasma that is significantly higher than that produced by oral administration; however, in some individuals the intramuscular route produces plasma levels of chloroquine that are sufficiently high to cause toxic effects. The sudden collapse and death that have followed intramuscular injection of chloroquine in some instances, especially of children (*6*, *7*), might therefore be due to this effect. Also, therapeutic levels of chloroquine in plasma (>20 µg/l) are not as persistent as those associated with the oral route of administration. Our results therefore suggest that, for all cases of malaria where the patient is able to tolerate it, oral administration of chloroquine is the therapeutic route of choice. Whenever oral therapy is not possible, chloroquine can be injected intramuscularly, taking care to ensure that individual doses, the interval between them, and the total amount administered produce a level of the drug in blood that is adequate, without being excessive, and is above 20 µg/l during most of the treatment. However, in cases of severe or complicated falciparum malaria, where it is essential to have sustained therapeutic levels of chloroquine during the first 24–48 hours of treatment, the preferred parenteral mode of administration is slow intravenous infusion, since this permits the control of the concentration of the drug in blood by suitable adjustment of the infusion rate.

The other pharmacokinetic parameters for oral administration of chloroquine found in this study are similar to those reported previously (*1–3*). Thus, the drug is characterized by a long terminal half-life, a large volume of distribution, and a high plasma clearance, while the renal clearance is greater than the glomerular filtration rate. Pharmacokinetic parameters obtained from the intramuscular data are not significantly different ($P>0.05$) from those associated with oral administration, apart from the initial rate of appearance of chloroquine in blood. The route of administration, therefore, does not appear to affect its subsequent pharmacokinetics.

ACKNOWLEDGEMENTS

This investigation was supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

RÉSUMÉ

INFLUENCE DE LA VOIE D'ADMINISTRATION SUR LA PHARMACOCINÉTIQUE DE LA CHLOROQUINE ET DE LA DÉSÉTHYLCHLOROQUINE

La pharmacocinétique de la chloroquine, après une dose unique de 600 mg par voie buccale ou une injection intramusculaire de 200 mg du médicament, a été étudiée chez sept Africains adultes sains. Chaque sujet a reçu la chloroquine par les deux voies, avec un intervalle d'au moins quatre mois entre les deux doses. L'injection intramusculaire a provoqué une absorption rapide de la chloroquine qui a atteint une concentration plasmatique maximale dans les 15 minutes suivantes et a parfois atteint des niveaux toxiques. Les taux plasmatiques sont descendus en dessous des concentrations d'utilité thérapeutique 2 à 4 heures après l'administration. A l'opposé, avec la chloroquine, par voie buccale les taux plasmatiques ayant un effet thérapeutique étaient obtenus dans les 30 minutes et persisté jusqu'à 3 jours. Les pics plasmatiques n'étaient pas assez élevés pour produire des réactions indésirables. En définitive, l'hémikrèse (la demi-vie) et la clairance rénale de la chloroquine n'étaient pas modifiées par la voie d'administration.

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