Clinical Pharmacokinetics and Metabolism of Chloroquine
Focus on Recent Advancements

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Summary

This paper presents the current state of knowledge on chloroquine disposition, with special emphasis on stereoselectivity and microsomal metabolism. In addition, the impact of the patient’s physiopathological status and ethnic origin on chloroquine pharmacokinetics is discussed.
In humans, chloroquine concentrations decline multiexponentially. The drug is extensively distributed, with a volume of distribution of 200 to 800 L/kg when calculated from plasma concentrations and 200 L/kg when estimated from whole blood data (concentrations being 5 to 10 times higher).

Chloroquine is 60% bound to plasma proteins and equally cleared by the kidney and liver. Following administration chloroquine is rapidly dealkylated via cytochrome P450 enzymes (CYP) into the pharmacologically active desethylchloroquine and bisdesethylchloroquine. Desethylchloroquine and bisdesethylchloroquine concentrations reach 40 and 10% of chloroquine concentrations, respectively; both chloroquine and desethylchloroquine concentrations decline slowly, with elimination half-lives of 20 to 60 days. Both parent drug and metabolite can be detected in urine months after a single dose.

In vitro and in vivo, chloroquine and desethylchloroquine competitively inhibit CYP2D1/6-mediated reactions. Limited in vitro studies and preliminary data from clinical experiments and observations point to CYP3A and CYP2D6 as the 2 major isoforms affected by or involved in chloroquine metabolism.

In vitro efficacy studies did not detect any difference in potency between chloroquine enantiomers but, in vivo in rats, S(+)-chloroquine had a lower dose that elicited 50% of the maximal effect (ED950) than that of R(-)-chloroquine. Stereoselectivity in chloroquine body disposition could be responsible for this discrepancy. Chloroquine binding to plasma proteins is stereoselective, favouring S(+)-chloroquine (67% vs 35% for the R-enantiomer). Hence, unbound plasma concentrations are higher for R(-)-chloroquine. Following separate administration of the individual enantiomers, R(-)-chloroquine reached higher and more sustained blood concentrations. The shorter half-life of S(+)-chloroquine appears secondary to its faster clearance. Blood concentrations of the S(+)-forms of desethylchloroquine always exceeded those of the R(-)-forms, pointing to a preferential metabolism of S(+)-chloroquine.

In spite of the increasing prevalence of resistant strains of malaria, 4 decades after its introduction chloroquine is still one of the most widely used antimalarial drugs, alone or in combination with other agents. Chloroquine is inexpensive, easily available, relatively well-tolerated, and curative after only a few doses. These are essential features for its clinical use in developing countries with limited resources.

Although the appearance of chloroquine-resistant *Plasmodium falciparum* is a serious clinical problem, any documentation of resistance in previously-sensitive strains requires the careful exclusion of confounding factors, such as noncompliance, inadequate drug administration, and dosage, and more importantly, the influence of drug-drug or drug-disease interactions. Hence, the development of sensitive and specific analytical methods and the careful planning of pharmacokinetic studies are key to the adequate recognition of these important factors, and to the safe and effective use of existing antimalarial agents.

In view of the expanding indications of antimalarial agents to the long term treatment of rheumatoid arthritis and systemic lupus erythematosus, the clinical pharmacokinetics of chloroquine need to be reassessed. This paper presents the current state of knowledge on chloroquine disposition, with special emphasis on the more recent investigations of stereoselectivity and microsomal metabolism. In addition, the impact of the patient’s physiopathological status and medication profile on the drug pharmacokinetics are discussed.