PHARMACOKINETICS OF ANTIMALARIAL DRUGS: THEIR THERAPEUTIC AND TOXICOLOGICAL IMPLICATIONS

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Summary. - Recent studies on the pharmacokinetics of currently used antimalarial drugs have led to the accumulation of extensive data on their absorption, distribution, metabolism and excretion. The data have provided a rational basis for safer and more effective use of these drugs especially in relation to total dosage, frequency of dosing and route of administration.

Riassunto (Farmacocinetica dei farmaci antimalarici: implicazioni terapeutiche e tossicologiche). - Recenti studi sulla farmacocinetica di farmaci antimalarici in uso corrente hanno portato ad accumulare dati cospicui sul loro assorbimento, sulla loro distribuzione, sul loro metabolismo e sulla loro escrezione. Questi dati forniscono una base razionale per un uso più efficace e più sicuro di questi farmaci, soprattutto per quanto riguarda dose totale, frequenza di dosaggio e via di somministrazione.

The antimalarial drugs in common use at the present time can be classified as follows:
1. 4-aminoquinolines e.g. chloroquine, hydroxychloroquine and amodiaquine.
2. 8-aminoquinolines e.g. primaquine.
3. Cinchona alkaloids e.g. quinine.
4. Dihydrofolate reductase inhibitors e.g. proguanil and pyrimethamine.
5. Dihydrofolate reductase inhibitor plus a sulphonamide or sulphone e.g. pyrimethamine plus sulphadoxine (Fansidar®) and pyrimethamine plus dapsone (Maloprim®).
6. Antibiotics e.g. tetracycline and erythromycin.
7. Quinoline methanol e.g. mefloquine.

Although many of the antimalarials in current use have been in use for decades, surprisingly little was known about their pharmacokinetics until recently. The renewed interest in the drugs owed much to the activities of the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases that has stimulated research on the pharmacodynamics, pharmacokinetics and metabolism of the drugs in order to improve their use in its ultimate goal of improved malaria control world wide.

In spite of widespread resistance of Plasmodium falciparum to it, especially in South-East Asia, South America and parts of East and Southern Africa, the 4-aminoquinoline, chloroquine, appears to be still the most widely used antimalarial drug and certainly the one whose pharmacokinetics have been most extensively studied. The pharmacokinetics, toxicity and side effects of this drug will therefore be described first and in some detail. This will be followed by a summary of what is now known of the pharmacokinetics, toxicity and side effects of the other antimalarial drugs.
CHLOROQUINE

The basic pharmacokinetics of chloroquine (CQ) were described in the 1940s by Berliner et al. (1), Most et al. (2), Alving et al. (3) amongst others. Further pharmacokinetic studies on CQ were reported in the 1960s by McChesney and his colleagues after various oral doses of the drug (4-9). Pharmacokinetics as a scientific discipline has expanded considerably since the studies of McChesney and his colleagues and in the last 5 years the pharmacokinetics of chloroquine have been reinvestigated in a number of laboratories all over the world, using more sensitive and more specific techniques for the determination of CQ and its metabolites in body fluids and tissues (10-11). Our present knowledge of the pharmacokinetics of CQ comes from these recent studies as well as the much earlier ones.

Absorption

Recent studies in healthy adult volunteers and malarial children have shown that CQ is rapidly and almost completely absorbed from the intestinal tract. Adelusi, Dawodu and Salako (12) administered 10 mg/kg CQ in the form of tablets to malarial children. The peak plasma concentration was found to be about 250 ng/ml. This was reached in 2 hours with an absorption half-life of 0.56 h. The concentration reached in plasma in the first half hour after administering a 10 mg/kg dose of CQ orally is usually more than the therapeutic level for sensitive P. falciparum (i.e. 30 g/litre) (12-13). Gustafsson et al. (14) gave 300 mg CQ base orally in the form of tablet or solution to healthy male adults weighing between 65 and 91 kg. They obtained peak plasma concentrations of 56-102 ng/ml (mean 75 ng/ml), which were reached in 1-6 h (mean 3), and bioavailability of 75%. In this study, the same dose of chloroquine (300 mg) was given as a slow intravenous infusion over a period of about 25 minutes. The Cmax was reached 5-15 min (mean 12 min) after starting the infusion and had a magnitude 10 times the Cmax after the oral dose. Whereas the subjects who received the oral dose had no adverse reactions, every subject who received the i.v. dose experienced one or more adverse reactions.

These included difficulty in swallowing, diplopia, dizziness, difficulty in accommodation, squinting, tiredness and "heaviness" of the legs. The adverse reactions were concentration-dependent and corresponded to plasma CQ concentrations of over 150 ng/ml. There is no recent data on the rate of absorption of CQ after i.m. administration in man, but in rabbits, Salako and Adelusi (15) have shown that the Cmax after i.m. administration of 10 mg/kg CQ was reached in ½ h. This Cmax was approximately twice the Cmax after administration of the same dose orally.

There is therefore a real danger of toxicity if CQ is given parenterally. This danger is all the more likely in developing countries where CQ is readily available without prescription and is widely taken as the first line home remedy in the treatment of any febrile illness. Thus, Walker et al. (16) found that approximately 50% of children diagnosed as having malaria in a teaching hospital in Nigeria had high plasma CQ concentrations before receiving CQ in the hospital suggesting that the drug had been used in self medication at home before reporting at hospital. If intravenous CQ is given to such patients the plasma CQ level attained may be so high as to produce severe or even fatal toxic effect. In view of the rapid and almost complete absorption of CQ (even in the presence of pyrexia) after oral administration, the need to administer the drug parenterally should arise very infrequently. When the need arises (e.g. persistent vomiting, comatose patient) the intramuscular route may be preferable to the intravenous, the intramuscular dose being not more than half of the oral dose.

After absorption, CQ is widely distributed throughout the body. Early studies showed that the drug was strongly bound to tissues such that concentrations in the spleen, kidney, lungs, heart and liver were 300 to 500 times higher than those in the plasma (1,6,8). The drug has a particularly high affinity for melanin-containing tissues of the skin and eye. These studies have
been confirmed by the more recent studies of Adelusi and Salako (17-18). Because of the extensive tissue distribution and binding, CQ has an exceptionally large apparent volume of distribution which is about 200 times the total body fluid volume. Binding of CQ to brain tissue has attracted attention because abnormal involuntary movements similar to those that occur in parkinsonism have been reported in some patients treated with chloroquine and amodiaquine (19-22). Majumdar (23) suggested a mechanism for chloroquine-induced involuntary movements. Chloroquine and the phenothiazines are known to bind avidly to melanin-containing tissues. Melanin is derived from DOPA, the biosynthetic pathway being phenylalanine - tyrosine - DOPA quinone - melanin. In view of the structural relationship between DOPA and melanin it was inferred that chloroquine would also bind avidly to tissues rich in dopaminergic receptors. When this occurs in dopaminergic receptors in the nigrostriatal system, dopaminergic transmission in this system may be blocked leading to Parkinsonism. Osifo (24) tested this hypothesis by studying the concentration and distribution of chloroquine in different tissues of the brain but found no difference between catecholamine-rich and catecholamine-poor tissues of the brain.

Chloroquine-induced retinopathy is also widely presumed to be associated with the high affinity of chloroquine for melanin which is abundant in retinal tissue. Kuhn et al. (25) found that flunitrazepam which is similar to chloroquine and has a high affinity for melanin in retinal cells did not induce chloroquine-like retinal changes after long-term administration to cats and mice. Chloroquine under similar conditions induced the well-known changes. These investigators therefore concluded that the retinotoxic effect of chloroquine is not the result of its affinity for melanin-containing tissues and that the affinity of a drug for melanin cells is not enough to regard it as potentially harmful to the eye.

Since the malaria parasite is intraerythrocytic during the acute malaria phase of its life cycle, the concentration of CQ in red blood cells has always been of interest to investigators. The early studies of Macomber et al. (26-27) and Warhurst and Hockley (28) showed that the erythrocyte/plasma CQ concentration ratio was approximately 100 in mice infected with P. berghei and only 10 in uninfected mice. The ratio was also less in mice infected with chloroquine-resistant parasites than in those with sensitive strains. The erythrocyte/plasma CQ concentration ratio was investigated by Adelusi et al. (12) in children with acute malaria. The erythrocyte CQ concentration was higher than the plasma concentration throughout the sampling period of 7 days. In the height of the parasitaemia the ratio was 21 and this fell to steady value of about 5.3 after 4 days when parasitaemia had completely disappeared. This study thus confirmed in man the preferential concentration of CQ in red blood cells and the further enhancement of that concentration by the presence of malaria parasites in the red cells. The other cellular elements of the blood - leucocytes and thrombocytes have also been shown to concentrate CQ even more than do erythrocytes (29), and because of the elution of CQ into the serum during clotting, serum CQ concentrations are usually higher than those of plasma.

In all studies which have addressed the problem of the kinetics of the distribution of chloroquine in different tissues, peak concentrations of CQ have been found to occur in erythrocytes and plasma at the same time (12,14,30). By contrast, peak concentration was reached in different organs (e.g. liver, kidney, lungs, heart) at different times which also differed from the time to peak concentration in the plasma and red blood cells (17-18). The pharmacokinetics of CQ can therefore be described by a multicompartment model in which plasma and red blood cells constitute the central pool and the various organs the peripheral pools with which the central pool is ultimately in equilibrium.

The binding of chloroquine to plasma proteins is much less than would have been expected from its extensive tissue binding, being only a little over 50% (31).

The percentage binding to human serum albumin is less than the binding to plasma suggesting that it is bound to plasma proteins other than albumin (31).
The non-albumin protein to which CQ is bound has been shown by Walker et al. (16) to be alpha-acid glycoprotein. The percentage binding of CQ to protein is not affected by aspirin which is usually given along with CQ in the treatment of acute malaria.

Metabolism

Chloroquine is 7-chloro-4-(4'-diethylamino-1-methylbutyl-amino) quinoline. It is metabolised by side chain deethylation leading successively to, first, desethyl- and then bisdesethyl-chloroquine which is a primary amine. This compound can undergo deamination to form an alcohol (i.e. the 4'-hydroxy compound) which then undergoes oxidation to the 4'-carboxylic acid derivative. Successive dealkylation of the side chain ultimately leads to the compound 4-amino-7-chloroquinoline (6,32). The quinoline nucleus is resistant to degradation. Metabolism of chloroquine occurs slowly and the main metabolite varies in different species. In man it is desethylchloroquine (7,14,30,33).

Gustafsson et al. (14) found the peak plasma concentration of desethylchloroquine (DCQ) to be 2-5 ng/ml after i.v. administration of 300 mg CQ, the peak concentration being reached in about 6 hours. The C_{max} of the metabolite after oral administration of the same dose was 10-20 ng/ml and the time to peak concentration (T_{max}) was approximately the same as that of the parent compound. Walker et al. (13) also monitored the plasma concentrations of CQ and DCQ in children after a dose of 10 mg/kg CQ orally. DCQ was detected in plasma at 30 min and reached peak level at between 2 and 12 hours - the same as for the unchanged drug. In both these studies the concentration of DCQ remained at a value of 25-40% of that of CQ after peak levels have been reached. The desethyl metabolite of CQ has the same profile of distribution and tissue binding as the parent drug (33).

Individual variations in the pattern of distribution of CQ and DCQ may have important bearing on the pattern of adverse reactions to the drug. Thus, Olatunde (34) studied the concentrations of CQ and DCQ in the plasma and skin of two groups of African subjects - those who itched after CQ and those who did not. Plasma CQ and DCQ were similar in the two groups. However, skin from subjects prone to CQ-induced pruritus contained higher concentrations of CQ and lower concentrations of DCQ than skin from other subjects. Recent studies have also shown that DCQ has about the same activity as the parent drug against CQ-sensitive plasmodium species (35).

Elimination

Chloroquine is eliminated from the body very slowly such that after a single dose of 300 mg, the drug and its metabolite could be detected in plasma for up to 56 days depending on the sensitivity of the assay method for CQ. The decline of erythrocyte CQ concentration after peak level has been reached parallels that of plasma concentration showing that equilibrium is reached quickly and is subsequently steadily maintained between these two media. They can therefore be regarded as behaving pharmacokinetically as a single compartment with regard to CQ (12,14). By contrast, the decline phase of the log concentration-time curves for the various tissues diverge away from the plasma curve with time. The tissues therefore behave as separate compartments with slower elimination rate constants than plasma (17-18). Estimates of the plasma half-life of CQ have varied between 2½ days obtained by Alving et al. (3) and 9 days by Gustafsson et al. (14), the range possibly reflecting the multicompartment distribution of the drug.

Frisk-Holmberg et al. (36) suggested that the kinetics of CQ was capacity-limited or dose-dependent on the basis of a study in which they gave three different doses (250, 500 and 1000 mg) of CQ and obtained three significantly different half-lives (3.1, 42.9 and 312 h respectively). However, later studies have failed to confirm this (31,37).

The total plasma clearance of CQ varies between 750 and 1050 ml/min of which renal clearance is between 400 and 450 ml/min (14,31). Since the value for
renal clearance is more than the glomerular filtration rate the drug is probably excreted by both glomerular filtration and tubular secretion. The kidney is the main route of elimination of CQ from the body and the drug is detectable in the urine over a period of 120 days after a dose of 300 mg. Maximum excretion occurs in the first 24 hours, about 10% of the administered dose being excreted in that interval. Subsequently, urinary excretion decreases exponentially, with a computed total quinoline urinary recovery of between 50 and 60% of the administered dose. Chloroquine is excreted predominantly in the unchanged form, the excreted DCQ being only about 25% of the excreted CQ.

Summary of pharmacokinetics of chloroquine in man
The pharmacokinetics of CQ can now be summarised as follows:

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<tr>
<td>Half-life (t½ days)</td>
<td>3 - 9</td>
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<tr>
<td>Vol. of Distribution (Vd, l/kg)</td>
<td>170 - 200</td>
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<tr>
<td>Plasma Clearance (Clp, ml/min)</td>
<td>750 - 1050</td>
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<tr>
<td>Renal Clearance (Clr, ml/min)</td>
<td>400 - 450</td>
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<tr>
<td>Urinary recovery %</td>
<td>50 - 60</td>
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<tr>
<td>Bioavailability %</td>
<td>75 - 90</td>
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Effect of race
McChesney et al. (7) compared the pharmacokinetics of CQ in whites with those in blacks and found them to be basically the same. The pharmacokinetic data obtained in the recent studies of Salako and his colleagues in Africans (12,13,16) have not differed substantially from values in the literature for whites. Evans et al. (38) compared the rate of excretion of CQ in the first 7 hours after administration of the drug in 4 racial groups - British, Gambian Africans, Sudanese and Thais. The values obtained for the British, Gambians and Sudanese were similar but the Thais excreted significantly more CQ than the other three racial groups. The proportion of excreted DCQ to CQ was however similar in all 4 groups.

Effect of disease
Wharton and McChesney (39) studied the effect of malnutrition on the metabolism of CQ. The subjects studied were African children suffering from kwashiorkor, a condition in which there is fatty liver. The malnourished children excreted in the urine less DCQ (as a percentage of excreted CQ) before treatment than after, suggesting that CQ was being metabolised to a less extent in kwashiorkor. There is as yet no definitive study to compare CQ kinetics in normal subjects and those with hepatic insufficiency. Salako et al. (40) investigated the kinetics of elimination of CQ in patients with renal insufficiency after a single oral dose (600 mg) of the drug. They found that the rate of decline of plasma CQ concentration with time in the renal failure patients was less than in normal subjects. They thus estimated that the elimination half-life of CQ would be longer in renal failure patients than in patients with normal renal function. The studies of Adelusi et al. (12) and Walker et al. (13) have not revealed any effect of malaria infection on the pharmacokinetics of chloroquine except for the increased concentration of the drug in parasitised red blood cells.

AMODIAQUINE

The only other 4-aminquinoline in common use at the present time is amodiaquine. There has been increased interest in this drug recently because of the observation that malaria parasites with R1 or RII level of resistance to chloroquine might still show full sensitivity to amodiaquine. Until recently, it was generally believed that the 4-aminquinolines did not differ from one
another in their pharmacokinetics. Some recent studies have shown that this is not so. Using a highly specific and sensitive HPLC method, it has not been possible to detect amodiaquine in the blood 1 h and above after an oral dose of 600 mg amodiaquine in adults (41-42). However, in the same subjects, it was possible to detect the desethyl metabolite of amodiaquine and monitor its concentration for up to 14 days after the single dose of the parent compound. Amodiaquine (AM) thus appears to be a pro-drug which produces its in vivo effect after its metabolic conversion to desethyl-amodiaquine (DAM). Desethylamodiaquine has been shown to be active against malaria parasites in vitro (42). It is also noteworthy that the preferential partitioning into red blood cells which is so characteristic of CQ and DCQ is not seen with DAM. It is therefore obvious that there is significant difference in the pharmacokinetics of CQ and AM the extent of which will only be known when the pharmacokinetics of AM have been studied in greater detail.

PRIMAQUINE

Studies of the pharmacokinetics of primaquine have been boosted in recent years by the development of sensitive HPLC techniques for the determination of primaquine and its metabolites in body fluids.

In a recent study by Breckenridge and his colleagues (unpublished) peak plasma levels of 153 ng/ml were observed 2-3 hours after a single oral dose of 45 mg primaquine. The drug is well absorbed with a bioavailability of about 75%. The drug is distributed throughout the body water with an apparent volume of distribution of about 3.5 l/kg. Only a very small amount is fixed in the tissues. The elimination phase of the plasma concentration-time curve is monoexponential with a half-life of about 6 h. The plasma clearance is about 21 l/h and is probably due predominantly to metabolism since only 1% of an administered dose is recovered in the urine as unchanged primaquine in 24 h (43). The major metabolite of primaquine in man appears to be the carboxy derivative. In the study by Breckenridge and his colleagues, peak levels of the carboxy metabolite were ten times higher than the parent compound. Its concentration declined slowly and was still over 60% of the peak level 24 hours after the dose. None of the carboxymetabolite is detected in the urine suggesting that it is further metabolised before excretion. Studies with ¹⁴C-labelled primaquine have shown that only about 2% of the plasma radioactivity is due to primaquine, 55% to carboxyprimaquine and remainder to unidentified metabolites. About 60% of and administered dose is excreted in the urine in 1 week, but only about 3.6% is unchanged primaquine.

The studies of Greaves et al. (43) did not show any significant difference between the primaquine kinetics of British and Thai subjects neither were the kinetics altered in subjects deficient in the enzyme glucose-6-phosphate dehydrogenase. The primaquine-induced haemolytic anaemia which is prone to occur in subjects deficient in this enzyme is therefore not due to anomalous primaquine kinetics in such subjects.

QUININE

Quinine is rapidly and almost completely absorbed from the intestine. Peak plasma concentrations are reached 1-3 hours after a single oral dose. After absorption, it is distributed throughout most of the body fluid. The concentration in red blood cells is approximately one-fifth of that of plasma and in cerebral malaria, the concentration in the cerebro-spinal fluid is approximately 0.07 of that of plasma. The apparent volume of distribution is about 2.5 litres/kg. Quinine is metabolised in the liver and is excreted partly unchanged but mainly as the hydroxylated metabolite. Elimination from the body