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Antimalarial pharmacokinetics and treatment regimens

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The sheer numbers of people infected with malaria (approximately 200 million), and the annual death toll (one to two million) make this the most important parasitic disease of man. As a consequence antimalarial drugs are consumed on a vast scale in tropical areas of the world (WHO, 1990a). Indeed it has been suggested that the majority of the population in sub-saharan Africa has detectable blood chloroquine concentrations at any time. Armed conflict in tropical areas has provided the main stimulus to antimalarial drug research in the past, but with peace, and the lack of commercial incentives, the development of new drugs has not kept pace with the development of resistance in the potentially lethal malaria parasite *P. falciparum*. Most of the drugs now in use were introduced before the modern era of dosage design based on pharmacokinetic and pharmacodynamic principles. Antimalarial dose regimens have tended to be empirical. Legacies of the colonial era, they have often sounded more like recipes from a cook book than advice from a manual of therapeutics. Dose recommendations for relatively toxic drugs have varied enormously (up to six fold for chloroquine, and eight fold for quinine!). Observations of minor drug toxicity in uncomplicated malaria have led to limitation of antimalarial doses in severe disease—where minor adverse effects are irrelevant, and the object of treatment is to save life. Total doses in the critical first hours of treatment have been too small, but serious toxicity has been produced by giving the quinoline antimalarials (which have potent cardiovascular effects) too rapidly (e.g. by intravenous injection).

The quinoline antimalarials (quinine, chloroquine, amodiaquine, primaquine and mefloquine) comprise the majority of world antimalarial drug usage. These compounds have narrow therapeutic ratios. None of them is younger than twenty years old. The object of this article is to illustrate how the treatment of malaria has changed in recent years with better definition of the pharmacokinetic and pharmacodynamic properties of the antimalarial drugs. These recent studies have led to revisions in the originally empirical and seldom questioned dose recommendations, and optimisation of the treatment regimens—particularly in severe malaria. There has also been a welcome trend in recent years to larger well controlled therapeutic trials in which antimalarial drug concentrations have been measured, and thus to more confident conclusions—although most therapeutic studies reported are still too small and imprecise.

Quinine

After 350 years of use, quinine is now finding increasing application in the treatment of severe chloroquine-resistant malaria. The pharmacokinetic properties of quinine are altered in proportion to the severity of the infection (White *et al.* 1982; White 1985); the total apparent volume of distribution is contracted (from approximately 2.5 l kg^{-1} to 1 l kg^{-1} in cerebral malaria) and systemic clearance is reduced (from approximately 3 ml min^{-1} kg^{-1} to 0.9 ml min^{-1} kg^{-1} in cerebral malaria). As a consequence the elimination half-time is prolonged from approximately 11 h in healthy adults (White *et al.*, 1983a), to 18 h in cerebral malaria (Figure 1). The coefficient of variation for these parameters is approximately 40%. Plasma or serum quinine concentrations are higher in malaria than in health, but because of increased binding to the acute phase protein α_1-acid glycoprotein, the free quinine fraction is reduced from 15% to between 5 and 10% (Silamut *et al.*, 1985, 1991). Red cell quinine concentrations are one third to one half those in plasma (White *et al.*, 1983b). Total plasma quinine concentrations over 10 mg l^{-1} are usual in the treatment of malaria, and in the majority of patients with severe malaria will peak between 15 and 20 mg l^{-1}, but contrary to widespread opinion (WHO, 1990a), serious cardiovascular or nervous system toxicity (dysrhythmias, hypotension, blindness, or deafness) is very uncommon. This contrasts with self-poisoning, where α_1-acid glycoprotein concentrations are normal, and total plasma concentrations over 10 mg l^{-1} are often associated with serious toxicity (Boland *et al.*, 1985; Dyson *et al.*, 1985). Children and pregnant women have total apparent volumes of distribution approximately 30% smaller than in adults, but systemic clearance estimates are similar (Phillips *et al.*, 1986; Sabcharoen *et al.*, 1982). Weight adjusted doses are therefore the same. Because of different assessments of the risks associated with quinine, dose recommendations have varied widely. Fears concerning the toxicity of quinine have been assuaged considerably over the past 10 years. The low doses recommended in earlier decades for the treatment of severe malaria have now been supplanted by parenteral regimens which begin with a loading dose, usually of twice the maintenance dose (i.e. 20 mg salt/kg), followed by maintenance doses of 10 mg kg^{-1} two or three times daily (Davis *et al.*, 1988; White *et al.*, 1983c; WHO, 1990a,b). This allows therapeutic concentrations to be reached within hours of starting

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treatment for a potentially life-threatening infection, whereas with the conventional regimen, concentrations over 10 mg l^{-1} are often not reached for 24 h or more. There are still widespread misconceptions concerning use of the loading dose (WHO, 1990a,b). There is no evidence that it conveys any toxicity above that of the conventional regimen; peak plasma drug concentrations on the second and third day of treatment are usually higher than those immediately following the loading dose. Furthermore previous quinine treatment is only a contraindication if plasma concentrations are likely to exceed 3 mg l^{-1}, i.e. one or two quinine doses in the days before admission (i.e. > 24 h previously) should not prevent administration of the full loading dose. Serious toxicity is very unusual if quinine is given by rate controlled infusion or intramuscular injection. The rate of drug administration is important for all the quinoline antimalarials. Rapid injection causes predictable hypotension while the drug is distributing out from the vascular compartment. Quinine disposition is adequately described by a two compartmental model in which V_1 is approximately one third of V_{ss} and the distribution half-time ($t_{1/2,\alpha}$) is 1–2 min. Quinine should not be given by intravenous injection or infused at a rate faster than 5 mg kg^{-1} h^{-1} to allow sufficient leeway for distribution (Davis *et al.*, 1988).

Unfortunately facilities for close monitoring of intravenous infusions are usually unavailable in the rural tropics. After many years of contentious debate, there is now a general consensus that intramuscular quinine is safe, and well absorbed, even in severe malaria (Waller *et al.*, 1990). Injections of concentrated solutions (300 mg ml^{-1}) of the acidic dihydrochloride salt are painful and may cause sterile abscesses. More dilute solutions are preferable. Peak plasma quinine concentrations usually occur within four hours of intramuscular injection in severe malaria (Figure 1). Dose regimens for intramuscular and intravenous routes are similar. Oral quinine is also well absorbed in acute uncomplicated malaria (Supanaranond *et al.*, 1991) and gives blood concentrations similar to those observed after parenteral treatment.

Quinine is usually given for seven days. As the patient recovers, clearance increases, and the distribution volume expands. As a result blood drug concentrations fall (White *et al.*, 1982). In children, reduction in blood drug concentrations below 10 mg l^{-1} in the latter half of the treatment course has been associated with treatment failure (Chongsuphajaisiddhi *et al.*, 1981). This has led to the suggestion that the paediatric dose of quinine should be increased by 50% after the fourth day of treatment in drug-resistant areas. In severe malaria, plasma drug concentrations tend to be maximal on the second or third day of treatment and then fall. But, if the patient remains seriously ill, clearance does not increase and concentrations continue to rise. In such cases, to avoid cumulative toxicity, the dose should be reduced by one third to one half after the second day of treatment (White, 1988; WHO, 1990c). The principle adverse effect of quinine in malaria stems from its powerful stimulatory action on the pancreatic beta cell. Hyperinsulinaemic hypoglycaemia is a particular problem in patients with falciparum malaria who remain severely ill for several days, and also in pregnancy (White *et al.*, 1983d). Provided the drug is not administered rapidly, cardiovascular toxicity is most unusual. Cardiac monitoring is unnecessary.

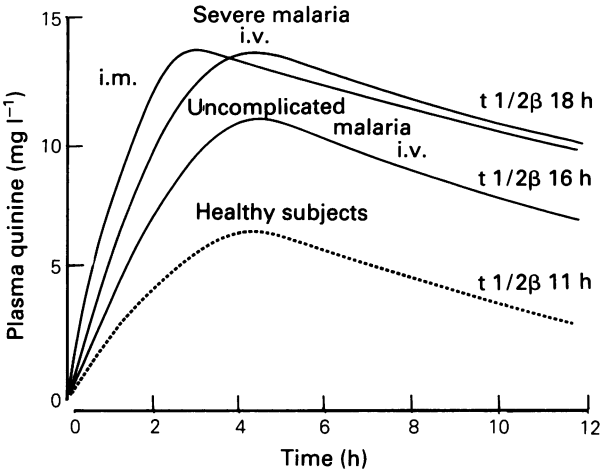


Figure 1 Average plasma quinine concentrations following administration of a loading dose of 20 mg (salt) kg^{-1} to patients with severe, and uncomplicated malaria, compared with those predicted to occur in normal subjects (based on pharmacokinetic data from White *et al.*, (1982, 1983) and Waller *et al.* (1990).

Quinidine

The dextrorotatory stereoisomer of quinine is both intrinsically more active as an antimalarial and more cardiotoxic than its antipode. The pharmacokinetic properties of quinidine are also different; the apparent volume of distribution is larger, clearance is greater with a larger proportion (35% compared with 20%) eliminated by the kidney, and the terminal elimination phase is shorter (Philips *et al.*, 1985; White, 1985). Much of this difference is explained by lower plasma protein binding. Pharmacokinetic-dynamic modelling suggests that in terms of free drug action at the receptor site, quinine and quinidine have equal effects on myocardial repolarisation, whereas quinine has a much greater inhibitory effect on high tone hearing (Karbwang, Davis & White: unpublished observations). Despite these various differences, dose regimens for the two drugs in the treatment of malaria are similar. In

Table 1 Pharmacokinetic properties of the antimalarial drugs used in severe malaria

	i.m. time to peak (h)	V *(l kg^{-1})*	*CL (ml kg^{-1} min^{-1})*	$t_{1/2,z}$ *(h)*
Parenteral administration				
Quinine	3	1.2	0.9	18
Quinidine	–	1.7	1.8	13
Chloroquine	0.3	25[1]	18[1]	20[1]

[1]Derived from two compartment model which ignores long terminal elimination phase.

countries outside the tropics quinidine is often available (for the treatment of ventricular arrhythmias) where quinine is not. Quinidine is now the only drug available in the United States for the treatment of imported severe chloroquine resistant malaria.

4-aminoquinolines

Chloroquine is still the most important antimalarial drug in the world, but the sun is now setting on three decades of use in the treatment of falciparum malaria. Resistance has spread to most tropical countries. The demise of chloroquine has enormous economic as well as medical implications. All the alternative antimalarials are considerably more expensive than chloroquine (WHO, 1990a,b,c), and the other quinolines are less well tolerated. Fortunately, chloroquine still retains its efficacy against *P. vivax*, *P. malaria* and *P. ovale*, although resistance in *P. vivax* has now been reported in Oceania (Rieckmann *et al.*, 1990). The pharmacokinetic properties of chloroquine are complex; it has an enormous apparent volume of distribution (100–1000 l kg^{-1}) and a very long terminal elimination phase ($t_{1/2,z}$ *circa* 1–2 months) (Frisk–Holmberg *et al.*, 1984; Gustafsson *et al.*, 1983). Chloroquine is metabolised to a biologically active metabolite, desethylchloroquine, which contributes to the drug's efficacy when it is used as a prophylactic, but is probably unimportant in determining the response to therapy in acute malaria. The pharmacokinetic properties of chloroquine are similar in children and adults (White *et al.*, 1987, 1988a). For many years opinion was divided as to whether parenteral chloroquine was safe in severe malaria, and if so, what dose should be given. No pharmacokinetic data were available. Dose recommendations varied by a factor of six. At one stage parenteral chloroquine was even considered too dangerous to be used at all (WHO, 1984). It is now clear from a series of pharmacokinetic and toxicity studies that chloroquine can be given safely by intravenous, intramuscular and subcutaneous routes—provided that it does not enter the blood too rapidly (White *et al.*, 1987). During treatment blood drug concentration-time profiles are determined principally by distribution rather than elimination processes (White *et al.*, 1988a). Chloroquine is absorbed very rapidly after i.m. or s.c. injection and, because the initial distribution volume is approximately one thousand times smaller than the total apparent volume of distribution, transiently high blood drug concentrations may follow doses of 5 mg base kg^{-1} or greater. These may cause potentially fatal hypotension. Oral chloroquine is safer. It is well absorbed, even in comatose children given the drug by nasogastric tube (Walker *et al.*, 1983; White, 1988). After oral treatment with single doses of up to 15 mg base kg^{-1}, absorption does not outpace efflux from the central distribution volume, and transiently toxic concentrations do not result. The traditional, empirically-derived, oral dose regimen of 25 mg base kg^{-1} is given usually as 10 mg kg^{-1} stat followed 6 h later by 5 mg kg^{-1}, and then further doses of 5 mg kg^{-1} are given on the next 2 days (WHO, 1990a). Various permutations on this theme have been suggested. A recent simple and practical alternative, supported by efficacy, toxicity and blood drug concentration data, is to give 10 mg kg^{-1} immediately followed by 5 mg kg^{-1} at 6, 12, 24 and 36 h, i.e. a total dose of 30 mg kg^{-1} within 2 days (Pussard *et al.*, 1991). Parenteral chloroquine should be given either by constant rate intravenous infusion (no faster than 0.83 mg base kg^{-1} h^{-1}), or by small frequent intramuscular (i.m.) or subcutaneous (s.c.) injections (these two routes give very similar concentration profiles) in doses not exceeding 3.5 mg base kg^{-1} to a total dose of 25 mg kg^{-1} (White *et al.*, 1988).

Amodiaquine is more effective than chloroquine against resistant strains of *P. falciparum*. It may be considered largely as a pro-drug for the biologically active metabolite desethylamodiaquine (Winstanley *et al.*, 1987). There is extensive first-pass metabolism and after oral administration blood concentrations of the parent compound are low or absent,. The metabolite is also extensively distributed and slowly eliminated. Amodiaquine is associated with a high rate of serious adverse effects (*circa* 1:2000), particularly agranulo-

Table 2 Pharmacokinetic properties of the antimalarial drugs after oral administration

	Time to peak (h)	*Plasma protein binding (%)*	V *(l kg^{-1})*	*CL (ml kg^{-1} min^{-1})*	$t_{1/2,z}$ *(h)*
Uncomplicated malaria					
Quinine	6	91	0.8	1.5	16
Quinidine	1	85	1.3	1.7	10
Chloroquine	5	55	100–1000	2	30–60 days
Mefloquine	17	>98[2]	19	0.4	20 days
Halofantrine[1]	16	>98[2]	—	1.5	113
Healthy subjects					
Primaquine	2		3	6	6
Proguanil[1]	3		24	19	16
Pyrimethamine	4		2.9	0.4	85

[1]Metabolite contributes significantly to antimalarial activity.
[2]Measurement difficult because of drug adsorption to the apparatus.

cytosis and hepatitis when used prophylactically, and is not widely used in treatment (WHO, 1990a).

Mefloquine

Mefloquine is effective against multidrug resistant strains of *P. falciparum*. The bioavailability of the current oral formulations (Lariam® Roche, Mefloquine Mepha) are better than that of the original formulation developed by the Walter Reed Army Institute of Research in the USA (Desjardins *et al.*, 1979), but the absolute bioavailability in man is unknown because there are no parenteral preparations. After oral administration mefloquine reaches peak blood concentrations at approximately 17 h (Karbwang & White, 1990). However, the absorption is biphasic and, in practice, if the patient vomits after 1 h, blood drug concentrations are not usually reduced and the therapeutic response is unimpaired. Mefloquine is distributed extensively and eliminated slowly (Desjardins *et al.*, 1979). It can therefore be given in a single antimalarial treatment dose. With a terminal elimination half-life of approximately 20 days, prophylactic administration once every 2 weeks would seem appropriate—but breakthrough infections have been reported in the second week of the dosing interval. Once weekly administration is therefore preferable. When mefloquine was introduced for the treatment of malaria in Thailand in 1984, it was released in combination with sulphadoxine and pyrimthamine (MSP). The objective of this was to 'protect' mefloquine from the development of resistance. This was rather optimistic as the elimination of both pyrimethamine and sulphadoxine is considerably faster than that of mefloquine (White, 1987). Low concentrations of mefloquine therefore persist for months 'unprotected' by the other two drugs, and it is difficult to see how resistance could be prevented in these circumstances. Furthermore in Thailand, the only country where mefloquine (as MSP) has been widely available, *P. falciparum* was already highly resistant to sulphadoxine and pyrimethamine when the drug was introduced. The slow clearance of mefloquine, once considered a considerable advantage, has proved to be its Achilles heel. Large numbers of treated patients live in endemic areas exposed to reinfection with low concentrations of the drug in their blood. This is the perfect milieu for the development of drug-resistance. The combination with sulphadoxine and pyrimethamine has not worked. In Thailand resistance has developed rapidly in *P. falciparum* (Nosten *et al.*, 1991). As a result the use of MSP is being discontinued and the recommended dose of mefloquine (alone) has been increased from 15 to 25 mg kg^{-1}. The therapeutic response has improved, but the incidence of minor adverse effects has also increased (particularly nausea, late vomiting and dizziness in the days following treatment). Splitting the dose (15 mg kg^{-1} stat followed by 10 mg kg^{-1} 8–12 h later) does not reduce these adverse effects (ter Kuile; personal communication). Mefloquine commonly induces nausea, dysphoria and giddiness (particularly in healthy subjects and more commonly in women than in men) and may rarely cause a self limiting psychosis or convulsions, but these serious adverse effects are not related to high blood concentrations of the drug. Neuropsychiatric reactions are approximately ten times more common following treatment (approximately 1: 1,700) than with prophylaxis (approximately 1:15,000) (Bjorkmann *et al.*, 1991; Luxemburger *et al.*, 1991; Weinke *et al.*, 1991).

Early vomiting is a particular problem with single dose antimalarial treatment. It is more common in children than adults, and is more likely if the child is febrile and agitated. In Malawi early vomiting was associated with subsequent low blood concentrations of mefloquine and a poor therapeutic response (Slutsker *et al.*, 1990). It is now recommended that all patients should be observed for 1 h, and give a second full treatment dose if there is vomiting within this period.

Halofantrine

This is the most recent introduction to the small antimalarial pharmacopoea. Halofantrine is more active *in vitro* than mefloquine against multi-drug resistant falciparum malaria. When given by mouth halofantrine has proved effective in treatment (Watkins *et al.*, 1988a; Wirima *et al.*, 1988). There is no parenteral formulation available for clinical use yet. Whereas mefloquine commonly induces nausea and dysphoria, and quinine predictably cause the symptom complex of cinchonism (tinnitus, high tone deafness, nausea, giddiness), halofantrine causes very little adverse central nervous system effects. Overall, it is well tolerated although high doses cause diarrhoea. Thus halofantrine is highly active, and causes few side effects. The main drawback is variable bioavailability with considerable variability in blood concentration-time profiles—a most important consideration in the treatment of a potentially life-threatening infection. Absorption is dose-limited (Milton *et al.*, 1989). Doses of more than 500 mg produce no increments in blood drug concentration. Absorption is increased by fats (we currently give it to children together with condensed milk). *In vivo* halofantrine is converted to the biologically active metabolite desbutyl-halofantrine (Milton *et al.*, 1989). This is eliminated more slowly than the parent compound ($t_{1/2}$ 4–7 days) and undoubtedly contributes to the overall antimalarial effect. Halofantrine is currently administered in three to nine doses of 8 mg kg^{-1} given 6–8 h apart. In one recommendation, it has been suggested that the treatment course should be repeated 1 week later. This does not seem to be sensible. If the initial doses are ineffective then a week is a long time to wait with a potentially life-threatening disease, and if the initial dose is effective, then it is unlikely the patient would remember to take the second dose, even if inclined to.

The antimalarial biguanides

Proguanil and chloroproguanil can both be considered pro-drugs for the antimalarial triazine metabolites cycloguanil and chlorcycloguanil respectively. (There

is conflicting evidence as to whether the parent compounds possess any antimalarial activity). Proguanil is used only for prophylaxis, but chlorproguanil combined with dapsone is used in treatment (Watkins *et al.*, 1988b). In contrast to the quinoline antimalarials where the exact mode of action is unknown, the mechanism of antimalarial action of the arylbiguanides and pyrimethamine is known. These drugs, or their active metabolites, inhibit the plasmodial dihydrofolate reductase enzyme (DHFR) and they are often called antifols. Single base pair mutations in the DHFR gene confer reduced affinity to the drugs and thus resistance (Peterson *et al.*, 1990). There may be resistance to pyrimethamine and not the biguanides, and *vice versa*, depending on the site of the point mutation. The antifols act at three stages in the parasite life cycle; the pre-erythrocytic (hepatic) phase, the asexual (blood) stage, and they also inhibit sporozoite development in the mosquito. They are well absorbed. Elimination of cycloguanil is faster than that of proguanil, so blood concentrations of the active metabolite are determined by clearance of the parent compound (Wattanagoon *et al.*, 1987). Proguanil is given once daily. Chlorproguanil was given once weekly for approximately 30 years, until blood concentration data were obtained. These studies have shown that chloproguanil has pharmacokinetic properties similar to proguanil (Watkins *et al.*, 1987). It is now given once daily as well. When proguanil is used in antimalarial prophylaxis some subjects develop breakthrough infections. Drug resistance both in *P. falciparum* and *P. vivax* accounts for some of these infections, but others may be related to a failure of cyclisation to the active metabolite. This biotransformation is mediated by the 2C subfamily of the cytochrome P450 mixed function oxidases. Poor metabolic conversion of the biguanides cosegregates with the mephenytoin hydroxylase genetic polymorphism (Ward *et al.*, 1991). Approximately 3–5% of the Caucasian population do not cyclise, but approximately 20% of Orientals are 'poor metabolisers'. The metabolic conversion of proguanil to cycloguanil is also reduced in pregnancy (unpublished observations). Thus many cases of apparent parasite resistance may in fact result from a failure of the host to convert the prodrug to its active metabolite.

Pyrimethamine

Pyrimethamine alone is now used rarely in prophylaxis or treatment because resistance is widespread. However, combinations of pyrimethamine with long acting sulphonamides with similar pharmacokinetic properties, (sulphadoxine/sulphalene) are still widely used for the treatment of malaria (Bjorkman & Wilcox 1986). Prophylactic use of the combination is no longer recommended because of the potential for serious sulphonamide toxicity (Miller *et al.*, 1986). Pyrimethamine is well absorbed and slowly eliminated, which allows single dose therapy (White, 1985). The pharmacokinetic properties of pyrimethamine in malaria have been characterised recently (Winstanley *et al.*, 1992). Blood concentrations are lower in malaria than in healthy subjects reflecting either incomplete absorption or an expanded volume of distribution. There is debate regarding the use of intramuscular sulphadoxine-pyrimethamine in severe malaria. A preparation is available (Salako *et al.*, 1990), but absorption is slow, and peak blood concentrations are lower than following oral administration (Winstanley *et al.*, 1992), which raises the question of bioavailability in severe disease. More importantly, pyrimethamine acts relatively late in the 48 h parasite life cycle, allowing development to the mature trophozoite stage of the parasite. This may be too late to prevent pathological effects (White & Krishna, 1989) despite cosmetic effects on peripheral blood parasitaemia. Studies are in progress to determine whether these theoretical concerns are justified.

Qinghaosu

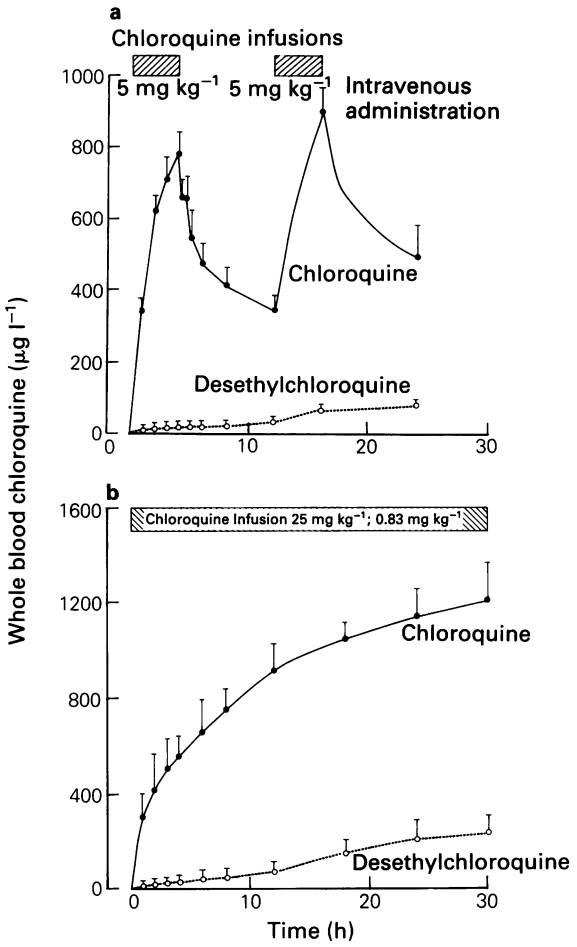
Progress with the exciting series of compounds related to qinghaosu (artemisinin) has been disappointingly slow. The antimalarial properties of extracts of qinghao (*Artemisia annua*) were characterised and the active constituent identified by Chinese scientists in 1972. By 1979 large clinical series were reported documenting the rapid therapeutic response to crude extracts of the plant, and synthetic derivatives, particularly in severe malaria (Li *et al.*, 1982; Qinghaosu Antimalaria Coordinating Research Group 1979). Three different compounds were produced; a crude plant extract containing principally artemisinin (qinghaosu), an oil soluble methyl ether (artemether), and a water soluble hemisuccinate derivative (artesunate). Since then studies in Burma, Vietnam, Thailand and The Gambia have confirmed the excellent efficacy and lack of serious toxicity of these compounds. In addition to the Chinese drugs, preparations of artemisinin itself have been produced in oral, and suppository formulations in Vietnam. The rest of the tropical world has been waiting with increasing impatience to have access to these remarkable compounds.

Satisfactory and readily applicable assay methods have so far eluded development and there are no reliable pharmacokinetic studies with any of these compounds in human malaria (Ding, 1988). From studies in animals and volunteers reported using a variety of assay methods (radioimmunoassay, colorimetry, t.l.c., h.p.l.c., h.p.l.c.-e.c. and GC MS) it appears that all the compounds are hydrolysed rapidly to the biologically active metabolite dihydroqinghaosu (dihydroartemisinin) and this is rapidly cleared (estimated $t_{1/2,z}$ = 45 min). A series of other metabolites have been characterised, but dihydroqinghaosu appears to be the most important (Lee & Hufford, 1990). The interpretation of conventional pharmacokinetic measures derived from plasma drug concentration-time data is complicated by the tight binding of these compounds to red cell membranes. This binding involves the peroxide bridge of the sesquiterpene—the biologically active moiety (Edwards *et al.*, 1992).

In most clinical studies the drugs have been given once daily with good effect despite having short

apparent elimination half-lives. The two parenteral compounds most widely used at present are the Chinese drugs artemether, which is given by intramuscular injection with peak blood drug concentrations reached between 4 and 6 h, and artesunate, which is dispensed as a powder of artesunic acid and is dissolved in 5% w/v sodium bicarbonate solution immediately before intravenous or intramuscular injection. Unlike the quinoline antimalarials, these compounds do not appear to have any acute adverse cardiovascular effects; artesunate is therefore given by intravenous injection and not infusion and is equally effective when given by intramuscular injection (Hien *et al.*, 1992). Oral formulations of both artesunate and artemether are also available and have been effective in several studies.

The World Health Organization and the US Army drug development programme continue to develop a drug structurally very similar to artemether. This compound, arteether, has an ethyl group substituted for the methyl group of the Chinese compound. Arteether is also oil soluble, and were it available, would be given by intramuscular injection. However, unlike artermether, which has been given to many thousands of patients with severe malaria over the past fifteen years with excellent results, arteether will be given to man for the first time in 1992 (following 8 years of development). There has been considerable recent publicity concerning arteether (Brown, 1991; Seneviratne 1991, WHO, 1991), but it seems unlikely that the drug will become widely available in the near future. Clearly much more work is needed to define the pharmacokinetic properties of the drugs already in use, their toxicity and best dosage regimens.



Figures 2a and b The effects of rate of administration on whole blood chloroquine concentrations in children with severe malaria. (From White *et al.* (1988a), with permission).

Drug dosage

Disease effects

In severe malaria, the dose of quinine or quinidine should be reduced after the second day of treatment if there has been no clinical improvement. This prevents excessive accumulation (White, 1988). Iatrogenic hypoglycaemia becomes increasingly likely if patients do not recover rapidly. Chloroquine and the artemisinin drugs should be given in full doses irrespective of disease severity. The effect of renal failure and severe liver disease on antimalarial drug disposition are not characterised adequately, but in practice the doses of the drugs are not reduced in patients with these conditions. This is particularly important for long term prophylactic use of the antimalarials. More work is needed on this subject. There is also relatively little information on antimalarial drug disposition in malnutrition, but where it has been studied, the pharmacokinetic parameters have been unchanged (White, 1985).

Age and pregnancy

Although the disposition of quinine is altered in children and pregnant women, the magnitude of these changes does not warrant dose adjustment (White 1985). The pharmacokinetic properties of chloroquine and mefloquine are similar in children and adults (Karbwang & White 1990; Nosten *et al.*, 1991; White *et al.*, 1987). Pregnant women eliminate mefloquine more rapidly than non pregnant women but again the differences are not large (Nosten *et al.*, 1990). However, the conversion of proguanil to the active metabolite cycloguanil is reduced in pregnancy by approximately 50%, which would suggest that the dose should be doubled (unpublished observations). This is currently under investigation. More information is needed on the disposition of antimalarial drugs in the very young, the very old, and the very fat.

Relevance of pharmacokinetic properties to antimalarial pharmacodynamics

Plasmodium falciparum can be cultured *in vitro*, but the other human malaria parasites cannot. *In vitro* antimalarial sensitivity testing is therefore possible, analagous to antibiotic sensitivity testing. The MIC or IC_{50} values derived from *in vitro* cultures do give some guide to parasite drug sensitivity, and they are of use in plotting the epidemiology of drug resistance. However, because the conditions in a small puddle of diluted

Table 3 Factors determining the therapeutic response to an antimalarial drug

Dose factors	– use of loading dose
	– dosing interval
	– duration of therapy/total dose
	– use of combination preparations
Pharmacokinetic factors	– bioavailability
	– absorption (vomiting of oral drugs)
	– plasma protein binding
	– disposition
Pharmacodynamic factors	– killing rate per parasite cycle
	– number of 48 h cycles exposed to therapeutic blood drug concentrations
	– stage specificity
	– effects on cytoadherence and other pathological processes
Host factors	– non-specific host defence
	– immunity
	– pregnancy
Parasite factors	– intrinsic drug sensitivity
	– synchronicity
	– parasite burden
	– presence of resistant subpopulations
	– mutation rate

blood, lying in a plastic tray in a candle jar, are very different to those confronting the parasite *in vivo*, it has not been possible to extrapolate directly from inhibitory concentrations *in vitro* to therapeutic blood drug concentrations *in vivo*. Minimum inhibitory concentrations cannot be quoted with the same confidence, or the same implications, as for the use of antibiotics in bacterial infections. In malaria many factors contribute towards the therapeutic response *in vivo*, and these are likely to be different in every patient (Table 3).

Antimalarial plasma drug concentrations are undoubtedly important, but as malaria is an intraerythrocytic parasite, it has been suggested that concentrations within the red cells may be more relevant. This is probably too simplistic. Most red cells are not parasitised, and measurements of red cell concentrations therefore reflect the majority uninfected population of cells. Furthermore, the membrane transport properties of a parasitised cell are very different from those of a normal cell. The concentration 'seen' by the parasite is probably the free plasma drug concentration. Indeed it has been suggested recently that a visible communication, a 'parasitophorous tube' may connect the parasite to the plasma. There are other important differences in comparison with antibacterial susceptibility testing. Whereas pyogenic bacteria can multiply every 20 min, the asexual blood stage falciparum malaria parasite multiplies every 48 h. Infections tend to be synchronous from the outset, and there is a considerable variation in drug susceptibility during the life cycle. The middle third of the life cycle is most sensitive to the antimalarials, and the very young and very mature parasites are least affected (Yayon *et al.*, 1983; Zhang *et al.*, 1986; ter Kuile *et al.*, personal communication). Thus in circumstances where blood concentrations of the antimalarials fluctuate widely (e.g. chloroquine, artemisinin), the stage and synchronicity of the infecting parasite population become important determinants of immediate therapeutic response. Peak drug concentrations should theoretically coincide with the most sensitive stage of parasite development (although this is, of course, difficult to organise in practice!).

There may be up to 10^{12} parasites circulating or sequestered in the vasculature. It is asking a lot of any drug to kill all these parasites within one life cycle. Even if there was 99.99% kill/cycle, therapeutic concentrations would still be needed for four cycles (8 days) to eradicate all of the parasites in the body (White & Krishna, 1989). Host defence mechanisms, both non-specific splenic clearance function and specific immune responses, are important allies in the therapeutic attack on the malaria infection. These processes can remove the residual burden of parasites after a brief period of antimalarial drug exposure. The therapeutic response is always better in semi-immune or immune subjects, and drug trials need to be interpreted with this in mind. In malaria endemic areas, adults therefore tend to respond better than children because they have acquired a more effective immune response (Nosten *et al.*, 1991). Short course treatments are often effective in semi-immune patients. However, in non-immunes therapeutic antimalarial drug concentrations are probably needed for at least 3 to 4 parasite life cycles (6–8 days), unless the parasites are very drug sensitive.

The relationship between antimalarial drug concentrations and treatment failure has been studied on relatively few occasions. For quinine, recrudescent infections in Thai children were more likely if serum drug concentrations fell below 10 mg l^{-1} in the latter half of the treatment course (Chongsuphajaisiddhi *et al.*, 1981). For chloroquine treatment, parasitaemia rose when the median whole blood drug concentrations were 790 nmol l^{-1} in Tanzanian children with high-grade resistant (R2) infections (Hellgren *et al.*, 1989). The corresponding estimated median *in vivo* M.I.C. for low-grade resistant infections was 147 nmol l^{-1}. For mefloquine in Thailand, where resistance is also increasing rapidly, parasitaemias in resistant infections rose through median serum mefloquine concentrations of 638 ng ml^{-1} (Nosten *et al.*, 1991). In contrast in Malawi where the parasites are more sensitive, whole blood mefloquine concentrations of over 500 ng ml^{-1} in children were associated with cures (Slutsker *et al.*, 1990). These examples obviously refer to particular populations whose infecting parasites were at a particular stage in the development of antimalarial resistance. The 'MIC' values derived cannot be extrapolated to other geographic locations or populations.

In severe malaria the objective of treatment is to save life. Eradication of all the infecting parasites (i.e. prevention of recrudescence) is of less importance. Treatment aims to halt the pathological processes induced by the parasite as quickly as possible. This would be best achieved by switching off all the para-

site's vital functions as soon as possible (White & Krishna, 1989). There is no evidence that rapid parasite killing is harmful; i.e. there is no evidence for a Jarisch-Herxheimer reaction in malaria. Thus therapeutic blood drug concentrations should be achieved as soon as possible without risking toxicity. Where possible loading doses should be given by rate controlled intravenous infusion, although intramuscular administration of quinine or artemether is equally effective. The quinoline antimalarials are potent hypotensive agents and should never be given by bolus intravenous injection. Stage specificity of drug action should also be considered. Antimalarial drugs with a broad stage specificity and rapid action such as the artemisinin derivatives, would be theoretically preferable to narrow spectrum drugs acting late in the parasite life-cycle such as pyrimethamine (White & Krishna, 1989). These theoretical predictions need now to be confirmed in clinical studies.

Additional therapeutic approaches to attenuation or reversal of the pathophysiological processes that lead to death from malaria should be considered. At present the only 'adjuvant' therapy known to be beneficial is the administration of a single prophylactic dose of phenobarbitone in cerebral malaria to prevent convulsions (White *et al.*, 1988b). Steroids are known to be deleterious (Warrell *et al.*, 1982). Heparin and dextran are probably harmful. Studies are in progress to evaluate therapeutic administration of antibodies to TNF. The role of mannitol in childhood cerebral malaria, and dichloroacetate in the treatment of malarial lactic acidosis need to be defined. As with new antimalarial drug regimens, careful prospective studies will be needed, ultimately in large numbers of patients.

Finally the practical realities of managing severe malaria in the rural tropics need to be faced. Complex intravenous drug regimens may give ideal blood drug concentration-time profiles, but most patients with severe malaria never reach a sophisticated hospital. The current strategies for primary health care assessment and administration of oral antimalarials, with referral of complicated malaria cases may lead to long delays in starting life-saving treatment. Simple methods of administering antimalarial treatment to unconscious patients in remote rural areas need to be developed. The pharmacokinetics, safety and efficacy of intramuscular injections, nasogastric instillation and suppository administration need to be evaluated prospectively. Treatment recommendations should be made only when this information is available.

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