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# Pharmacokinetic and Pharmacodynamic Considerations in Antimalarial Dose Optimization

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**Antimalarial drugs have usually been first deployed in areas of malaria endemicity at doses which were too low, particularly for high-risk groups such as young children and pregnant women. This may accelerate the emergence and spread of resistance, thereby shortening the useful life of the drug, but it is an inevitable consequence of the current imprecise method of dose finding. An alternative approach to dose finding is suggested in which phase 2 studies concentrate initially on pharmacokinetic-pharmacodynamic (PK-PD) characterization and *in vivo* calibration of *in vitro* susceptibility information. PD assessment is facilitated in malaria because serial parasite densities are readily assessed by microscopy, and at low densities by quantitative PCR, so that initial therapeutic responses can be quantitated accurately. If the *in vivo* MIC could be characterized early in phase 2 studies, it would provide a sound basis for the choice of dose in all target populations in subsequent combination treatments. Population PK assessments in phase 2b and phase 3 studies which characterize PK differences between different age groups, clinical disease states, and human populations can then be combined with the PK-PD observations to provide a sound evidence base for dose recommendations in different target groups.**

The primary objective of treating severe malaria is to save life. Other considerations such as preventing recrudescence or minor toxicity are secondary. In uncomplicated malaria, the main objective of antimalarial drug treatment is cure of the infection. Speed of response is also important, as this reflects the rate at which the disease is controlled and the corresponding reduction in the risk of progression to severe malaria. Less-serious adverse effects therefore become a more important factor in determining dose. The therapeutic response in malaria is determined by the concentration profile (pharmacokinetics [PK]) of active antimalarial drug or drugs in the blood (as the asexual parasites which cause malaria pathology are confined to the blood), their intrinsic pharmacodynamic (PD) properties, the susceptibility of the infecting parasites to the drug(s), the number of asexual malaria parasites in the blood, and the activity of host-defense mechanisms. Ideally, antimalarial treatment should be 100% effective in everyone, but this may not be possible without producing toxicity or recommending a long course of treatment with consequent poor adherence. It is now recommended that all antimalarial treatments for uncomplicated malaria should aim at a >95% cure rate for the blood-stage infection (1). In recent years, a general agreement has been reached on methods of clinical and parasitological assessment to measure the cure rates in cases of uncomplicated falciparum malaria (1–3). In *Plasmodium vivax* and *P. ovale* infections, persistent liver-stage parasites (hypnozoites) cause later relapses, despite cure of the blood-stage infection, which complicates therapeutic assessment. These infections require additional treatment with 8-aminoquinolines (radical cure). Relapses are often genetically heterologous and cannot be distinguished reliably from recrudescences or new infections. This necessitates a different approach for assessment of treatment efficacy in the relapsing malarias—which is yet to be agreed upon.

Many of the antimalarial drugs in current use were introduced at suboptimal doses. For various reasons, quinine, sulfadoxine-pyrimethamine, primaquine (for radical cure of tropical frequent relapsing *P. vivax* infections), mefloquine, halofantrine, artemisinin derivatives, artemether-lumefantrine, and dihydroartemisinin-piperaquine (i.e., 7 of the 12 current antimalarials) were all deployed initially at doses which were too low in some or all age groups. Pyrimethamine and sulfadoxine doses for children were extrapolated from experience in Caucasian and Asian adults. Their pharmacokinetic properties were not studied in younger age groups before widespread deployment in Africa, where children are the main target group (4). The dose was too low in young children. The primaquine dose regimen (15 mg base/day adult dose) was developed largely on the basis of studies of the long-latency Korean vivax malaria, but this dose was then recommended widely in areas with the more resistant tropical relapse *P. vivax* phenotypes (5). In Southeast Asia and Oceania, this dose is too low. Five-day primaquine regimens were deployed very widely for radical cure of vivax malaria for over 30 years—yet these regimens were largely ineffective. Fourteen-day courses are now recommended. Mefloquine was first introduced at a single dose of 15 mg base/kg of body weight (6, 7), which may have hastened the emergence of resistance (8). The total dose now recommended is 25 mg/kg divided over 2 or 3 days. The doses of artemisinin derivatives used initially as monotherapy, and then subsequently in combination treatments (artemether at 1.6 mg/kg/dose in artemether-lumefantrine and dihydroartemisinin at 2.5 mg/kg/dose together with piperaquine), may not provide maximal effects in all patients. The initial treatment regimen of artemether-lumefantrine deployed was a four-dose regimen which provided insufficient lumefantrine and gave high failure rates (six doses are now recommended) (9). The dose of dihydroartemisinin in the first

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formulations of the dihydroartemisinin-piperaquine combination was <2 mg/kg (it is now 2.5 mg/kg, which may still be too low) (10). The pharmacokinetic properties of piperaquine are different in children from in adults, and there is evidence that current dosing schedules in children may be suboptimal (11). After 3 centuries of reasonable dosing based originally upon the Schedula Romana, treatment recommendations for quinine in severe malaria were suddenly reduced in the 1970s to a dose as low as 5 mg/kg/24 h, which is eight times lower than that now recommended. In contrast, the quinine loading dose in severe malaria was not introduced until the early 1980s, and it is still not recommended universally (12). The initial recommendation for artesunate treatment in severe cases of malaria was a daily maintenance dose of half the initial dose (1.2 mg/kg). As oral bioavailability is approximately 60%, this corresponds to an oral dose of 2 mg/kg (13, 14). The currently recommended parenteral dose is twice this and is the same as the recommended initial dose, 2.4 mg/kg/day (1, 15, 16). Recent evidence suggests that this dose should be increased in young children (17).

Optimizing drug dosing requires characterization of the pharmacokinetic and pharmacodynamic properties of the drug in the target populations. There are four main determinants of the therapeutic response: antimalarial pharmacokinetics (affected by variables such as coadministration with food, age, pregnancy, disease severity, vital organ dysfunction, partner drug, and coinfections/other drugs), parasite susceptibility (incorporating effects on different stages of asexual parasite development, dormancy, propensity for resistance to develop, and level of resistance first selected), host defense (influenced by age, pregnancy, and transmission intensity/exposure history), and parasite burden. In addition, mixed infections can be a factor. For antimalarials, *ex vivo* systems are useful for predicting resistance (18) and they provide valuable pharmacodynamic information (19), but they are simply not good enough yet to replace *in vivo* evaluations for dose finding. In uncomplicated falciparum malaria, it is generally agreed that combinations, preferably, fixed-dose combinations (FDC), should be used. The same should apply to vivax malaria, although chloroquine and primaquine can be considered a combination. When drugs are first developed, there is a limited window of opportunity to define the dose-response (or concentration-effect) relationship for the single new compound, but this opportunity must be taken (20). Once the drug is available only as an FDC, the dose ratio is, by definition, fixed and it is too late for optimization of the individual component doses. Characterizing the individual drug dose-response relationships is essential for rational dose optimization, and so a good drug development approach involves documenting the blood concentrations that are associated with submaximal antimalarial effects. Studies in animal models, particularly with *P. falciparum*, may be informative, but studies in humans will also be needed. It is important to accept that this may result in temporary therapeutic failures in some volunteers. There is a natural reluctance to accept this, but sensitive detection methods to measure low parasite densities now provide us with safe methods that should avoid any risk or discomfort to the patient (21). Suggestions are provided here for an alternative PK-PD approach for dose finding which, if validated, may improve and accelerate dose finding and so avoid systematic underprescribing and thus underdosing. It might also prove more rapid and less expensive. The primary objective is determination of the *in vivo* MIC as the basis for rational dosing (the MIC is the concentration at which the parasite multiplication factor per asexual cycle is 1). It is necessary first to consider the factors which affect the pharmacokinetic properties of antimalarials in malaria and then to consider antimalarial pharmacodynamics and how PK-PD relationships should be assessed.

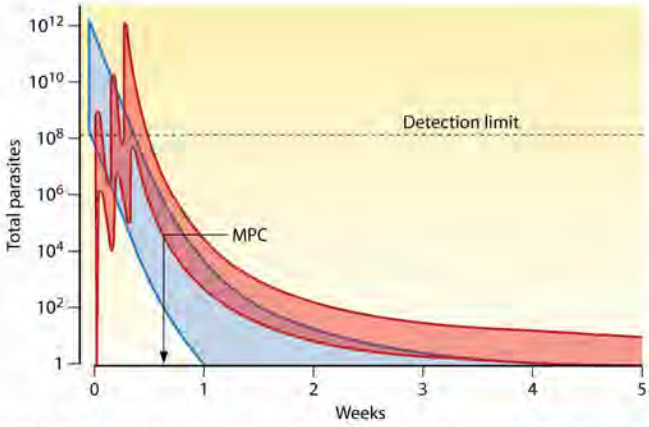


FIG 1 Population PK-PD responses following a 3-day treatment with a hypothetical slowly eliminated antimalarial drug. The total numbers of malaria parasites in the body over time are depicted in blue in a range of patients presenting with parasite densities between approximately 50 and 200,000/μl. The ranges of drug concentration profiles are shown in red, with the corresponding ranges of parasitological responses in blue. Parasitemia levels cannot be counted reliably by microscopy below 50/μl (corresponding to ~100,000,000 parasites in the body of an adult). The MPC is the lowest blood, plasma, or free plasma concentration which produces the maximum parasiticidal effect (i.e., the maximum parasite reduction ratio). This corresponds to the concentration associated with first slowing of the first-order (log-linear) decline in parasitemia.

## PHARMACOKINETICS

The pharmacokinetic (PK) properties of antimalarial drugs are often altered in patients with malaria compared with healthy subjects. The PK properties therefore change as the patient recovers. PK properties are also often significantly different in important patient subgroups such as young children and pregnant women (22). Several of the antimalarial drugs, notably those which are hydrophobic and lipophilic, are poorly absorbed after oral or intramuscular administration and show wide interindividual differences in concentration profiles. In general, this variation in blood concentrations is inversely proportional to bioavailability, which emphasizes the importance of improving bioavailability in drug development. Increasing bioavailability provides the twin benefits of reducing the required dose and thus the cost of the drugs and reducing the individual probabilities of underdosing or overdosing. In considering antimalarial dosing in the past, we tended to concentrate on mean or median values of PK variables, but it is the patients with the lowest blood concentrations who are most likely to fail treatment and facilitate the emergence of resistance and those with the highest concentrations who are most likely to experience drug toxicity (23). These extremes need to be defined, which means that characterizing the distributions of PK variables in important target groups is as important as assessing their measures of central tendency (Fig. 1). Characterizing these distributions well eventually requires sampling of relatively large numbers of patients, which in turn usually necessitates sparse sampling and population PK modeling. Optimal design approaches can be used to ensure that the information is gathered most efficiently (24). It

is essential that key patient groups such as young children and pregnant women are studied specifically, and there should be a postregistration commitment to this if such investigations have not been conducted during preregistration studies. There may also be clinically relevant pharmacogenetic differences in drug metabolism between different ethnic groups. Thus, characterizing the distributions of pharmacokinetic variables is a gradual process accrued during phase 2 and phase 3 of drug development, but it must continue into phase 4 to cover all relevant populations.

Malaria is often worst in remote rural areas. The recent development of simple methodologies such as drug measurement from capillary blood filter paper samples (25, 26) will facilitate community-based assessments in remote settings and make sampling of infants and children feasible. Thus, population PK information will eventually be needed in all important target groups (i.e., infants, children, pregnant women, lactating women, malnourished patients, patients receiving antituberculosis [anti-TB] and antiretroviral drugs, etc.) (22) to provide optimal dose recommendations. There is currently limited bioanalytical capacity to support such studies, but there are international schemes to assist antimalarial drug measurement and ensure the accuracy of the results, which should facilitate future laboratory bioanalytical capacity development in tropical countries (27, 28).

In drug development, where a new compound has not been used previously, there is little information on distributions of PK variables and so the important but difficult issue is to determine how much PK-PD information is enough to decide upon a dosage recommendation. For safety reasons, the PK information is usually gathered in the following standard sequence: experimental animals, healthy normal volunteers, adult patients with uncomplicated malaria, children, and, much later, infants and pregnant women.

## PHARMACODYNAMICS

**(i) Action of the drugs.** The antimalarial drugs differ in their stage specificities of action against malaria parasites. The 8-aminoquinolines are unusual in killing pre-erythrocytic-stage parasites, hypnozoites, and mature gametocytes of *P. falciparum* but having weak activity against its asexual stages (29). They are more active against asexual stages of *P. vivax* and *P. knowlesi*. All other antimalarial drugs in current use kill the asexual and sexual stages of sensitive *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* and the asexual stages and early gametocytes (stages I to III) of sensitive *P. falciparum*, but they do not kill the mature *P. falciparum* gametocytes (stage V). The artemisinins have a broader range of effect on developing *P. falciparum* sexual stages, as they also kill stage IV and younger stage V gametocytes. Atovaquone and the antifols kill preerythrocytic stages and have sporontocidal activity in the mosquito (interfering with oocyst formation and therefore blocking transmission). Apart from the 8-aminoquinolines, none of these drugs have significant effects on *P. vivax* or *P. ovale* hypnozoites. Even within the asexual cycle there are differences in antimalarial activity in relation to parasite development. None of the currently used drugs have significant effects on very young ring stages or mature schizonts, and all have their greatest effects on mature trophozoites in the middle of the asexual cycle (30). In addition, the artemisinins (and other antimalarial peroxides) have substantial ring-stage activity which underlies their life-saving benefit in treatment of severe falciparum malaria (15, 16, 31). Several antimalarials, notably, some antibiotics with antimalarial activity, have greater effects in the second than in the first drug-exposed asexual cycle (23). The pharmacokinetic-pharmacodynamic relationships (PK-PD) have not been very well characterized for any of these activities.

**(ii) *In vivo* pharmacodynamic measures.** In severe malaria, the primary therapeutic concern is the speed of parasite killing and, in particular, the killing of circulating ring-stage parasites before they mature and sequester (30, 31). Rapid killing of young *P. falciparum* parasites by artemisinin and its derivatives explains much of the superiority of artesunate over quinine in the treatment of severe falciparum malaria (15, 16). In uncomplicated malaria, rapid ring-form killing is also important, as it contributes to the speed of patient recovery, but the main therapeutic objective is to reduce parasite multiplication. Once antimalarial treatment is started, then, after a variable lag phase, parasite killing *in vivo* approximates to a first-order process (32–34) as represented by the following equation:

$$P_t = P_0 e^{-k_p t} \quad (1)$$

where $P_t$ is the parasitemia level at any time $t$ after starting treatment, $P_0$ is the parasitemia level immediately before starting treatment, and $k_p$ is the first-order parasite elimination rate constant. The parasite clearance half-life is therefore $0.693/k_p$. In equation 1, parasite killing equates with parasite removal from the circulation, but in falciparum malaria (but not the other malarias) there is an additional major factor removing parasites from the circulation, and that is cytoadherence. Only parasites in the first third of the asexual cycle circulate, and the more mature parasites are sequestered. This complicates interpretation of the parasite clearance curve following treatment with drugs which do not kill ring-form parasites, as initial declines in parasitemia result mainly from sequestration and not drug effects (33). Parasite killing can be expressed as the parasite reduction ratio (PRR), which is the fractional reduction in parasite numbers per asexual cycle, or the reciprocal of ring-form $k_p$ per cycle (32). This cancels out the effects of cytoadherence, as the parasite populations are assessed at the same stages of development separated by one cycle. The shape of the concentration-effect relationship *in vivo* is assumed always to be sigmoid, as it is *in vitro* (Fig. 2), per the following equation:

$$k = k_{max} \cdot [C^n/EC_{50}{}^n + C^n] \quad (2)$$

where $k$ is the parasite killing rate and $k_{max}$ is the maximum parasite killing rate (i.e., the maximum effect, or $E_{max}$) for that drug in that infection, $C$ is the concentration of drug in blood or plasma, $EC_{50}$ is the blood or plasma concentration resulting in 50% of the maximum effect, and $n$ is a parameter defining the steepness of the dose-response relationship. For most drugs, maximum effects are probably achieved initially. The evidence for this is the lack of a relationship between peak concentrations and parasite clearance (the exception is quinine treatment of severe malaria without a loading dose, which provides submaximal effects in some patients) (12). So while concentrations exceed the minimum parasiticidal concentration (MPC), $k_p$ in equation 1 is equal to $k_{max}$. It should be noted that each end of the sigmoid curve approaches 0% and 100% effects asymptotically—so the MPC is an approximation, whereas the $EC_{50}$ is a more robust and precise estimate. Once antimalarial concentrations in blood decline to a level below the MPC, the parasite killing rate declines (see the "Antimalarial pharmacokinetic-pharmacodynamic relationships" section below). For drugs in current use, maximum PRRs range from approxi-

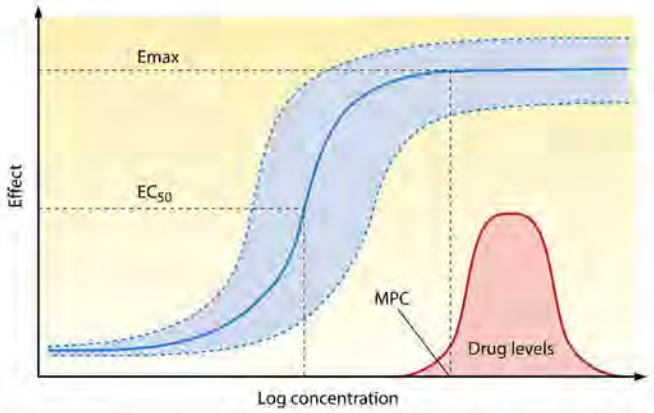


FIG 2 The concentration-effect relationship; for antimalarial drugs, the effect is parasite killing, which can be measured in different ways. The Emax is the maximum parasite killing that a drug can produce, which translates *in vivo* into the maximum parasite reduction ratio. The $EC_{50}$ is the blood or plasma concentration providing 50% of maximum killing. The median and range values for a hypothetical population of malaria parasites are shown in blue, and the distribution of average drug levels in patients is shown as a red bell-shaped curve (i.e., concentrations are log-normally distributed). Clearly, some of the patients have average drug levels below the MPC and would not have maximum responses with this dose regimen.

mately 10-fold to approximately 10,000-fold reductions in parasitemia per asexual cycle. The mean values and their variance *in vivo* have not been established for several important antimalarial drugs in current use (notably lumefantrine and piperaquine), and for others, where monotherapies have been evaluated, the estimates are often imprecise. There is no evidence for saturation of parasite clearance, but, obviously, the higher the initial biomass, the longer it takes to eliminate all the parasites from the body (33). Consequently, patients with high-biomass infections need more antimalarial drug exposure than those with low-biomass infections.

**(ii) *In vitro* susceptibility.** For antimalarial effects, the shape and position of the concentration-effect curve studied *ex vivo* depends on the susceptibility of the infecting parasites and the PD readout (typically, for blood stages, inhibition of growth or maturation, inhibition of hypoxanthine uptake, inhibition of protein or nucleic acid synthesis, etc.). Furthermore, each *in vitro* method assesses a slightly different section of the asexual life cycle, which may result in important differences between methods in the results for drugs with ring-stage activity. It is not clear exactly how the effects of these static drug concentrations in a small volume of dilute blood in the laboratory correspond with *in vivo* effects (18, 19, 35). Neither is the relationship between inhibition of parasite growth and subsequent inhibition of multiplication well established. Inhibition of growth is measured in most *in vitro* tests, whereas in *in vivo* patient studies, inhibition of multiplication (parasite clearance) is recorded. In the absence of *in vivo* information on the concentration-effect relationship, for predictive modeling purposes the slopes of the linear segments of the *in vitro* and *in vivo* sigmoid concentration-effect relationships have been assumed to be similar (8, 35), but whether or not such an assumption is justified remains to be established. Most agree that the antimalarial drug concentration that is biologically relevant in assessing blood-stage effects is the (unbound) fraction in plasma. Total red cell concentrations are less informative as the parasitized red cells behave very differently from their unparasitized counterparts. In the patient, the blood concentrations of the antimalarial drug are changing constantly, and the parasite age distributions may differ considerably between patients. *Ex vivo* systems with changing antimalarial concentrations that are more biologically relevant than the simple static drug susceptibility assays have therefore been developed, and measurement of multiplication inhibition can yield valuable information (19). Rodent models capable of sustaining human malaria infections have also been developed recently (36). Human malaria infections in immunodeficient mice allow PK-PD characterization and thus provide useful information in predicting therapeutic responses in patients. These laboratory studies have the great advantage that parasites from many different locations or with known resistance profiles can be studied and compared. It is argued below that if the relationship between the standard *in vitro* susceptibility measures (50% inhibitory concentrations [$IC_{50}$], $IC_{90}$, etc.) and *in vivo* PK-PD responses in patients with malaria could be characterized, then this would facilitate dose finding.

## ANTIMALARIAL PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS

Some of the best research on antimalarial PK-PD relationships came from the period of intense antimalarial drug investigation in the United States during and shortly after the Second World War (Fig. 3). Studies were conducted to determine the optimum dosing strategies for mepacrine (atebrine, quinacrine), the Cinchona alkaloids, and both the 4- and 8-aminoquinolines (37–39). Pharmacokinetic analysis had yet to be invented, and methods for quantitation of drugs in serum or plasma were in their infancy, but the spectrophotometric assays that were conducted still provided valuable information. Relatively large numbers of nonimmune adult male volunteers artificially infected with single "strains" of *P. falciparum* or *P. vivax* received different dose regimens, serum levels were measured, and therapeutic responses were assessed. This research provided dose-response or concentration-effect relationships and led to the mepacrine loading-dose regimen, characterization of the comparative antimalarial effects of the four main Cinchona alkaloids (quinine, quinidine, cinchonine, and cinchonidine), and development of the standard dosing regimen for chloroquine (one of the few antimalarial dose recommendations which has stood the test of time). This was still the era of malaria therapy, and the war had focused military attention on malaria. Such volunteer studies are no longer possible today. Since that time, PK-PD relationships have been inferred mainly from clinical studies of antimalarial treatment (8, 9, 40–43).

**(i) PK-PD correlates.** Studies of PK-PD relationships for antibacterial effects have shown that for some antibiotics (those with steep concentration-effect relationships and without postantibiotic effects), bacterial killing is dependent on the duration for which the antibiotic exceeds the MIC for the bacterial population ("time above MIC"). For other antibiotics (where concentrations achieved with current regimens remain on the steep part of the concentration-effect relationship), it is the maximum concentration achieved ($C_{max}$) or the related area under the plasma concentration-time curve (AUC) that is the best correlate of bacterial killing (Fig. 4). These PK variables are all interrelated (i.e., the higher the $C_{max}$, the larger the AUC and the longer the time above the MIC). With some adjustments, these PK measures can be applied to antimalarial effects (32), although correlates with parasite

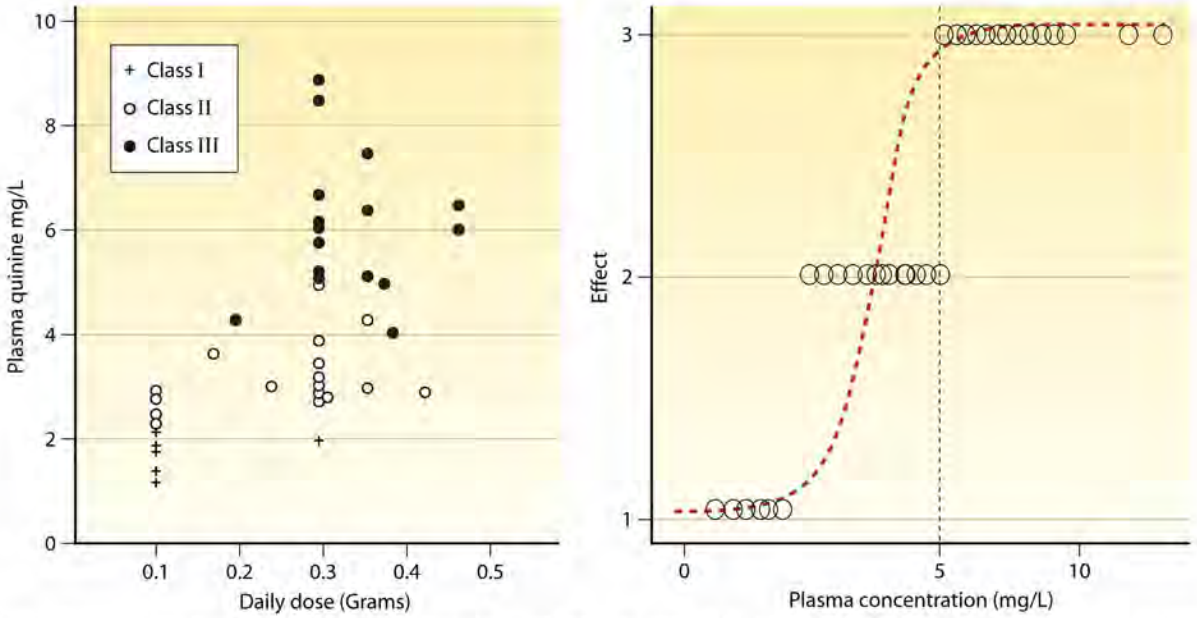


FIG 3 Dose-response relationships obtained between the years 1945 and 1946 for quinine in blood-induced vivax malaria (McCoy strain) in volunteers (38). Plasma concentrations after protein precipitation were measured spectrophotometrically, which overestimates parent compound concentrations. The left box shows the variable relationships between dose and mean plasma concentrations, and the right graph shows the concentration-effect relationship divided into three effect measures: class I, no certain effect; class II, temporary suppression of parasitemia and/or fever; class III, "permanent" effect, i.e., absence of parasitemia for 14 days.

killing have not been established for most antimalarial drugs. Whereas most bacteria replicate every 20 to 40 min, asexual malaria parasites infecting humans replicate every 1 to 3 days. Symptomatic infections usually comprise one predominant brood of malaria parasites, but multiple genotypes are often present—particularly in higher-transmission settings—and so within one host there may be subpopulations with different drug susceptibilities (and also different stages of asexual development). The lowest blood, plasma, or free plasma concentration which produces the maximum PRR is the MPC (Fig. 5). These PK-PD variables reflect the antiparasitic effects of the antimalarial drug and host immunity and so are specific for an individual and that individual's infection. Innate host-defense mechanisms and acquired immune responses contribute significantly to therapeutic responses—effectively shifting dose-response curves to the left. The contribution of the host immune response, which may be significant even in previously nonimmune patients (44), has not been well characterized.

With current dosing for all antimalarial drugs except the artemisinin derivatives, drug elimination is sufficiently slow that the antimalarial effects of a treatment persist for longer than one asex-

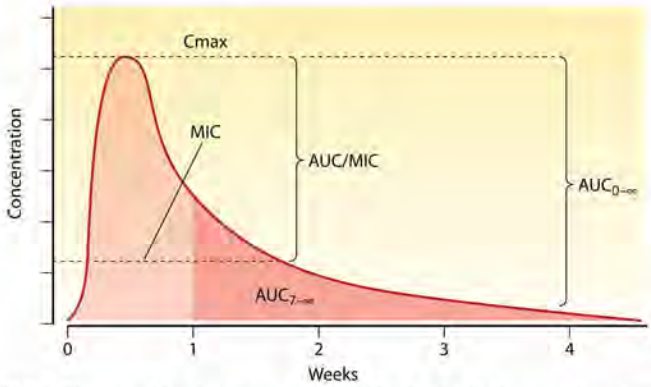


FIG 4 Plasma or blood concentration profile of a slowly eliminated antimalarial drug showing an arbitrary MIC. The AUC is the area under the curve, and Cmax is the maximum concentration in blood or plasma. AUC from 7 days to infinity is shown in darker pink. Blood concentrations are increasingly measured on day 7 in therapeutic assessments of slowly eliminated antimalarials (49).

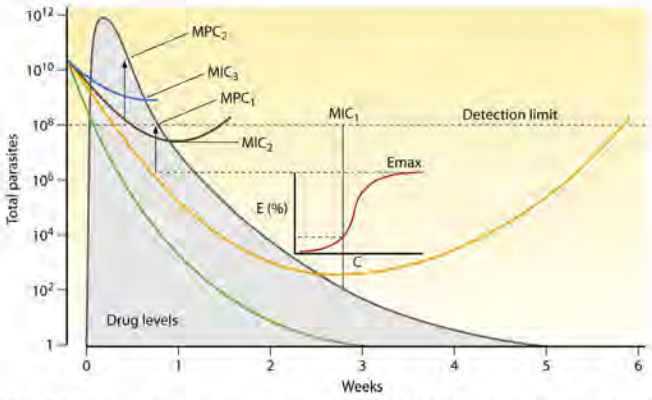


FIG 5 Different therapeutic responses to a slowly eliminated antimalarial drug in a malaria infection of $10^{10}$ parasites (parasite density, ~2,000/μl). The blood concentration profile in gray is shown in the background. Parasitological responses range from fully sensitive (green) to highly resistant (blue). Each response is associated with a different level of susceptibility and thus a different MIC and MPC (arrows pointing to concentration profile). The inset represents the concentration-effect relationship for the lowest level of resistance (resulting in a late failure), showing corresponding points for the MIC and MPC (orange curve).

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