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Abstract

Artemisinin and its derivatives are highly effective antimalarial drugs. These compounds combine potent and rapid antimalarial activity with a wide therapeutic index. An initiation of artemisinin resistance, described by a delayed parasite clearance time, is unlikely to cause high-level resistance. Artemisinins as a class demonstrate poor efficacy as monotherapy. This shortcoming can be overcome using oral artemisinin-based combination therapies (ACT) and intravenous-artesunate (IV-AS) in combination with slow-acting partner drugs. Pharmacokinetic and pharmacodynamic (PK/PD) evaluation demonstrates that the rapid efficacy of artemisinins is largely due to drug peak concentrations. Critical evaluation also demonstrates that AS is superior in PK/PD either following oral or intravenous administration when compared to the other rapid-acting artemisinins. This rapid efficacy and decreased mortality demonstrates that currently available artemisinins have a great advantage when combined with slow-acting antimalarial drugs for uncomplicated malaria or in sequential therapy with AS injection initially for severe and complicated malaria. Compared to other ACTs, dihydroartemisinin-piperaquine (DP) demonstrates a superior in PK/PD profile, most likely due to the long half-life of piperaquine. These findings will help us better understand the PK/PD profiles of rapid-acting (artemisinins) and slow-acting (piperaquine) drugs, and suggest how to best use ACTs in the future.

Keywords: artemisinin, artesunate, piperaquine, pharmacokinetics, pharmacodynamics

1. Introduction

The artemisinin group of antimalarials is considered to be highly and rapidly effective compared with other traditional malaria drugs. Resistance to artemisinins emerged in 2008 in parts of Southeast Asia and continues to spread [1]. Although there is more evidence to confirm drug resistance [2, 3], artemisinin and its derivatives are still widely used in current malaria therapy [2, 4]. Clinical artemisinin resistance is demonstrated as a delayed clearance phenotype; that is, infection finally resolves with treatment with artemisinin-based combination therapies (ACTs), but the time required for parasite clearance substantially increases [5].
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High rates of recrudescence with daily monotherapy of artemisinins for 3–5 days are observed in humans. However, this shortfall is being overcome using oral ACTs and injectable artesunate (IV-AS) in combination with slow-acting antimalarial drugs. The rapid parasite killing of artemisinins in the treatment of early uncomplicated malaria with ACTs may prevent its progression to more severe disease with subsequent reduction in severe cases and associated mortality [6]. ACTs are currently the preferred treatment for malaria due to their enhanced efficacy and the potential to lower the emergence and spread of resistance [7].

The WHO has endorsed ACTs as the “policy standard” for all malaria infections in areas where *P. falciparum* is the predominant infecting species. Four ACTs recommended by a WHO Expert Consultative Group in 2001 are artemether (AM)-lumefantrine (Coartem), AS-mefloquine (Artequin), AS-amodiaquine, and AS-sulfadoxine/pyrimethamine [8]. Monotherapy with the artemisinins was significantly decreased after 2001 to prevent the emergence of resistance. However, IV-AS, as a monotherapy, is still in first line of treatment for both adults and children in Asian countries [9] for complicated and severe malaria, as well as some areas in Africa [10].

Recent trials have used IV-AS with its more favorable pharmacokinetic profile [11, 12]. The SEAQUAMAT trial, a large multicenter randomized trial carried out in Bangladesh, Thailand, Myanmar, Indonesia, India, and Vietnam, showed a 34.7% reduction in mortality from all causes associated with IV-AS as compared to intravenous quinine [13]. This remains the largest trial performed for severe malaria and was the first to conclusively demonstrate a benefit over standard quinine therapy. There is strong evidence that IV-AS will reduce the risk of death by one-third when compared to quinine therapy in cases of severe malaria. Consequently, IV-AS was immediately recommended for patients with severe malaria by The European Network on Imported Infections Disease Surveillance (TropNetEurop) after these trials [14].

The most recent development in antimalarial therapy is the use of artemisinin derivatives, especially IV-AS, which will potentially revolutionize the management of severe and complicated [15]. Therefore, there is a strong case for continued need for AS as a monotherapy, if only for this niche indication [16]. However, there is currently no useable formulation available that is produced under good manufacturing practice (GMP) conditions. The Walter Reed Army Institute of Research (WRAIR) continues to develop a novel cGMP injection of AS since 2004, which is in the process of US FDA approval [17, 18].

2. PK/PD evaluation of the artemisinins in patients

Pharmacokinetics (PK), in general, comprises three distinct phases (absorption, distribution, and elimination) of artemisinin drugs in blood after oral, intravenous, or intramuscular administration. Following single oral administration, AS and dihydroartemisinin (DHA) have short mean residence times (MRT) of 2.0 and 2.7 h, respectively, and artemisinin (QHS) has a longer MRT of 7.4 h. Following intramuscular injections, arteether (AE) and AM both display very long MRTs at 13.9 and 42.9 h respectively. However, IV-AS displays the shortest MRT (0.90 h) after intravenous injection (Table 1). It is obvious that the different artemisinins and the method of their delivery result in significant differences in PK characteristics in humans. After multiple administrations, four drug concentrations of QHS, DHA, AS, and AM have been reported to decline daily due to autoinduction metabolism [19–23] that may result in the high rates of recrudescence with the monotherapy at a multiple dosing.

Pharmacodynamics (PD) has similarities to PK profiles but instead measures parameters of efficacy. For any antimalarial, the mean parasitemia-time curve
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<tr>
<td>Route of administration</td>
<td>Intravenous</td>
<td>Oral</td>
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<td>Intramuscular</td>
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<tr>
<td>First loading dosage</td>
<td>120 mg</td>
<td>100 mg</td>
<td>200 mg</td>
<td>500 mg</td>
<td>3.2 mg/kg</td>
<td>4.8 mg/kg</td>
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<td>Maintaining dosage</td>
<td>Oral 100 mg at 8 h</td>
<td>50 mg b.i.d. x 4</td>
<td>100 mg x 4</td>
<td>250 x 2 x 5</td>
<td>1.6 mg/kg x 4</td>
<td>1.6 mg/kg x 5</td>
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<tr>
<td>Total dose</td>
<td>220 mg and mefloquine**</td>
<td>500 mg</td>
<td>600 mg</td>
<td>3000 mg</td>
<td>9.6 mg/kg</td>
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**| PK parameters (day 1) |
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<tr>
<td><strong>C</strong>&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
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<td><strong>MRT</strong> (h)</td>
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**| PD parameters (day 1)* |
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<tr>
<td><strong>Time of lag phase (h)</strong></td>
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<td><strong>AUCI (%) h/μl</strong></td>
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<td><strong>PC&lt;sub&gt;50&lt;/sub&gt; (h)</strong></td>
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<tr>
<td><strong>E&lt;sub&gt;max&lt;/sub&gt; (%) or MPC</strong></td>
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<tr>
<td><strong>Curative rate (%)</strong></td>
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*The data was fitted with WinNonlin (V5.0) by author.
**Oral 750 mg mefloquine at 24 h after IV injection. PK = pharmacokinetics; PD = pharmacodynamics; MRT = mean residence time; PC<sub>50</sub> = mean time for parasitemia to fall by half; AUCI = area under inhibitory curve; QHS = artemisinin; DHA = dihydroartemisinin; AM = artemether; AE = arteether; AS = artesunic acid; MPC = minimum parasiticidal concentration; IM = intramuscular.

Table 1. Pharmacokinetics/pharmacodynamics (PK/PD) parameters of IV-AS (IV 120 mg and oral 100 mg at 8 h, then oral 750 mg mefloquine at 24 h), AS (oral, 100 mg and then 50 mg b.i.d x 4), DHA (oral, 200 mg and then 100 mg x 4), QHS (oral, 500 mg and 250 b.i.d x 4 and then 500 mg on D6), AM (IM, 3.2 mg/kg and 1.6 mg x 4), and AE (IM, 4.8 mg/kg at 0 h and 1.6 mg/kg at 6 h and then day 2-5 daily) in human treatment with uncomplicated and severe/complicated malaria on day 1."
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following administration presents as a lag phase. This lag phase is then followed by a sharp drop in parasite burden (representing the clearance phase), which is then followed by a slow decrease to very low parasitemia levels. Subsequent phases of this process are usually under the limits of microscopic detection of both the dormant and terminal phases (Figure 1, top). The artemisinins affect this profile in multiple ways. First, they prevent the continuation of merogony at later stages of parasite development as compared to quinine or mefloquine. This stops the occasional alarming sharp rise in parasitemia immediately following treatment described earlier (lag phase).

Figure 1.
Standard parasite clearance curve in different stages (lag phase, clearance phase, dormant and terminal phase) and synchronicity of parasite development under antiparasitic drug received at 0 h (top chart). The mean parasite clearance curves (bottom chart) of AS (solid line) at single intravenous 120 mg and oral 300 mg at 8 h, then oral 75 mg mefloquine at 24 h [26, 27]; oral AS (dashed line) at 100 mg first day and 50 mg b.i.d 2–5 days orally [22, 28, 29]; oral DHA (dot and dashed line) at 200 mg first day and 100 mg 2–5 days orally [30, 31]; oral QHS (solid line) at 500 mg first day, 250 mg b.i.d 2–5 and 500 mg last day orally [29–31, 29]; intramuscular AM (dashed line) at 3.2 mg/kg first day and 1.6 mg/kg 2–5 days intramuscularly [35, 36]; and intramuscular AE (dot line) of 4.8 mg/kg at 0 h and 1.6 mg/kg at 6 and then 2–5 days intramuscularly [38, 39], in malaria patients (bottom chart) (Table 1). The parasitemia at 0 h was set as 100% of parasitemia.
Second, the drop in parasite load is accelerated. This is explained by enhanced clearance of erythrocytes infected with ring forms (clearance phase) [24]. Rapid termination, surviving and stage unaffected parasites display very low levels of dormancy [25], which is the basis of the recrudescence (dormant and terminal phase). Different artemisinins with varied methods of delivery show different parasitemia-time profiles (Figure 1, bottom). Although the PK/PD publication record is very limited, the possible PK and PD evaluations for individual drugs with the same regimens in monotherapy for human-malaria are described below; and the PK data of five artemisinin drugs (AS, DHA, QHS, AM, and AE) corresponding with parasitological consequences in malaria patients are shown in Table 1, Figures 1 and 2.

2.1 Intravenous-artesunate (IV-AS)

PK/PD profiles in humans were studied following AS intravenous administration at doses of 120 mg/person on the first day at 0 h followed by oral 100 mg at 8 h (Figure 2, top left). A mean peak level (C\text{max}) of 11.343 ng/ml was displayed for IV-AS, which rapidly cleared with an elimination half-life of 0.05 h. The C\text{max} of DHA, the primary metabolite of AS, was 2646 ng/ml with an elimination half-life...
of 0.67 h (Table 1). The mean AUC for DHA was 2378 ng h/ml, which is 2 times higher than that of the parent compound, AS, (AUC of 1146 ng h/ml) [26, 27].

In this trial, the lag phase for the parasitemia curve was estimated as 1.92 h (Table 1), which was the shortest as compared to oral AS and 4 other drugs (Figure 1, bottom), indicating that the IV-AS injection very efficiently kills parasites, with a mean time of 3.18 h for clearance of half the parasitemia (PC₅₀), which is the lowest PC₅₀ and has the lowest area under inhibitory curve (AUIC) at 397.3% h/μl in this evaluation (Table 1). After modeling, an Eₘₐₓ of 0.00111% parasitemia was estimated for IV-AS therapy on the first day. The Eₘₐₓ was the principal pharmacodynamic parameter determining maximum antimalarial effects for the artemisinins, as it displayed a sharp concentration-effect relationships. This relationship may be due to the time that blood concentrations exceeded the minimum parasiticidal concentration (MPC), as opposed to being driven by either Cₘₐₓ or AUC [25]. For the data presented in this chapter, the MPC was the lowest after administration of 100 mg per patient of IV-AS, with parasitemia remaining in blood (0.0011%) as compared to the other four artemisinin derivatives addressed (Table 1).

2.2 Oral artesunate (AS)

PK/PD profiles in plasma were studied following oral AS administration of 100 mg/person tablets on first day, followed by 50 mg twice daily for 2–6 days (Figure 2, top right). The mean peak plasma concentration of DHA was measured at 1052 ng/ml, with an elimination half-life of 0.75 h (Table 1). Also, the AS concentration declined day-over-day for the 5-day duration of dosing [22]. Mean AUC of DHA was calculated to be 1334 ng h/ml, 6.4 times higher than that of the parent compound (AUC of 210 ng h/ml), AS [28].

With the same oral dose regimen of AS, the time of lag phase in the parasitemia curve was only 2.81 h, shorter when compared to the four other artemisinins, with a range of 4.03–8.89 h (Figure 1, bottom) but longer than that of IV-AS (1.92 h), indicating that the effect of AS tablets was very efficient with a 0.36 h absorption half-life and a Cₘₐₓ of 1052 ng/ml [29]. Similarly, rapid parasite clearance with a mean time of 8.48 h for clearance of half the parasite load (PC₅₀), the lowest PC₅₀ of the four drugs and the lowest AUIC with 921.2% h/μl (Table 1). After modeling, an Eₘₐₓ of 0.0016% parasitemia was calculated for oral treatment with AS on the first day. For the data presented here, the MPC was the lowest, with parasitemia remaining in blood after dosing with 100 mg of AS per patient as compared to other four artemisinin derivatives (Table 1).

2.3 Oral dihydroartemisinin (DHA)

Profiles of PK/PD in plasma following administration of 200 mg/person in tablets DHA on day 1 followed by 100 mg at day 2–5 are shown in Figure 2 (middle left). After 200 mg of DHA, the mean peak plasma concentration of DHA was 437 ng/ml with an elimination half-life of 0.85 h. The mean AUC of DHA was calculated to be 1329 ng h/ml. With the 200 mg oral dose regimen, the time of lag phase in the parasitemia curve was 4.03 h, longer than that of oral (1.92 h) and IV-AS (2.81 h) but still shorter than either QHS (5.76 h), AM (7.26 h), or AE (8.89 h), indicating that the rapid clearance effect of DHA tablets was inferior to AS, but superior to QHS, AM, and AE regimens. Additionally, this rapid parasite clearance resulted in a mean time of 10.05 h of PC₅₀ and an AUIC of 11679.9% h/μl (Table 1, Figure 1, bottom). After the first day, modeling estimates of the Eₘₐₓ were 0.213% parasitemia for oral DHA treatment. For the data presented here, after 200 mg per patient of DHA, high
MPC remained in the blood as compared to the other three artemisinin derivatives (Table 1). Absorption of DHA tablets, with 0.67 h half-life, was 50% slower than that of AS (0.36 h) in this trial as well, indicating that the relatively slow reduction of parasitemia may have resulted from the slow absorption [30, 31].

As compared to oral AS, the AUCs of treatments with either AS or DHA (in oral form) the same, with only \( C_{\text{max}} \) of oral AS differing, and was two times higher than oral DHA treatment, suggesting that this high peak concentration \( C_{\text{max}} \) may be causally related to the decrease of parasitemia in patients [30, 31]. DHA appeared to have very low bioavailability (<50%). If calculated with an equal dose level, the \( C_{\text{max}} \) and AUC\(_{\text{DHA}}\) estimated from AS treatment were four- and twofolds, respectively, higher than the DHA dosage regimen. Our data demonstrate that the DHA tablet (Cotexin) in beagle dogs had only 24.4% absolute bioavailability [32].

In malaria patients, rebound parasites (3%) on day 3 and one-fourth recrudescence rate (24%) were found in subjects treated with DHA tablets in clinical work [30]. The 3% of rebound parasites were only found in DHA oral treatment in this comparison (Figure 2).

2.4 Oral artesinin (QHS)

PK/PD evaluation in plasma following artesinin (QHS) oral administration of 500 mg/person on the first day followed by 250 mg twice daily for 4 days and then another 500 mg on 6th day is seen in Figure 2 (middle right). After 500 mg of QHS by oral dosing, the mean peak plasma concentration of QHS was reached at 588 ng/ml and then declined with an elimination half-life calculated at 2.4 h. The mean AUC of QHS was estimated at 2601 ng h/ml, which was a comparatively high AUC due to the oral dose taken. With the 500 mg oral dosage regimen, the lag time in the parasitemia curve was 5.76 h, which was longer than oral and IV-AS (1.92–2.81 h) and DHA (4.03 h) but was better than AM and AE in trials (Figure 1, bottom). This indicates that the rapid effect of QHS capsules was not as good as oral AS and DHA even given at three- to sixfold higher doses [19–21, 29]. The patients treated with oral QHS showed 13.95 h of \( P_{50}\) and the 1464.4% h/\( \mu l \) of AUIC (Table 1). The absorption of QHS capsules with a 1.21 h half-life was slower than the absorptions of AS and DHA drugs, suggesting that the slow reduction of parasitemia may have resulted from slow absorption and lower antimalarial potency. Compared with oral AS and DHA study, oral QHS appeared to have very low bioavailability of 30% [33] and low antimalarial potency with cultured \( P. falciparum \) [34].

2.5 Intramuscular artemether (AM)

PK and PD profiles in plasma following AM intramuscular administration in sesame oil of 3.2 mg/kg on day 1 and then 1.6 mg/kg daily on day 2-5 can be seen in Figure 2 (bottom, left). The mean peak plasma concentration was reached at 74.9 ng/ml and then declined with an elimination half-life calculated at 7.83 h (Table 1), indicating that this formulation had the lowest peak of drug concentration when compared to the other four artesinin drugs. A mean AUC was estimated at 1230 ng h/ml [35, 36]. At the same dosage regimen, the time of lag phase in the parasitemia curve was 7.26 h, which was the second longest lag time compared with the other three drugs except for AE, indicating that the effect of the AM intramuscular formulation had a very low and prolonged absorption from muscle injection sites [37].

Parasitemia counts early after dosing did not decrease due to the low peak concentration of AM, but increased markedly to 110% at 4 h (parasitemia was set at 100% of the zero dosing time). This observation may explain why the lag time was longer at 7.26 h with no parasite decrease after injection. Similarly, there was
very slow clearance of parasites producing a mean PC$_{50}$ time of 15.6 h (Figure 1, bottom), which was also the longest PC$_{50}$ time compared to the other three drugs except AE (Table 1). The AUIC of 1613.4% h/μl also revealed that this drug given as an intramuscular regimen was not efficacious in reducing parasitemia [35]. Although intramuscular AM was not fast enough to kill parasites in patients, the long-lasting exposure level of AM (7.83 h elimination half-life) could reduce parasitemia at an acceptable rate. Computer modeling estimated the E$_{max}$ at 0.003% parasitemia in this clinical trial. The MPC (E$_{max}$) was only a little more than oral AS in the first-day modeling, but much less than oral DHA, oral QHS, and intramuscular AE (Table 1).

2.6 Intramuscular arteether (AE)

PK and PD profiles in plasma following AE intramuscular administration in sesame oil of 4.8 mg/kg at 0 h and 1.6 mg/kg at 6 h on day 1 and then daily 1.6 mg from day 2–5 are illustrated in Figure 2 (bottom, right). The mean peak plasma concentration was reached at 110.1 ng/ml and then declined with an elimination half-life calculated at 22.7 h (Table 1), indicating that this formulation has a low peak of drug concentration when compared to AS, DHA, and QHS. Mean AUC was estimated at 4702 ng h/ml [38]. At the same dosage, the lag time in the parasitemia curve was 8.89 h, which was the longest lag time and the highest AUC value compared with the other four drugs, indicating that the effect of the AE intramuscular formulation had a very low and prolonged absorption from muscle injection sites [37].

Parasitemia counts early after dosing did not decrease due to the low peak concentration of AE, but increased to 108% at 6 h (100% parasitemia set at 0 h of the first dosing time). As with AM, this increase may be the reason why the lag time is longer at 8.89 h with no parasite killing after injection. Similarly, a very slow parasite clearance was produced at mean PC$_{50}$ time of 19.68 h, which was the longest PC$_{50}$ time compared to the other four drugs (Table 1). The highest AUIC of 2463.5% h/μl revealed that the drug with the intramuscular regimen was not efficacious in reducing parasitemia [35, 39]. Intramuscular AE was neither able to exterminate parasites rapidly, nor to reduce parasitemia much in patients revealing it to be an inferior antimalarial agent when compared to the other four drugs (Figure 1, bottom). The computer modeling estimated the E$_{max}$ at 0.55% parasitemia in this clinical trial. In spite of two doses on day 1 (4.8 mg/kg at 0 h and 1.6 mg/kg at 6 h), the E$_{max}$ was still the highest value compared to other the four artemisinins (Table 1).

3. Efficacy and potency of artemisinins depending on drug peak concentration

Intravenous and oral AS are the fastest killers of parasites in human malaria treatments out of the five artemisinins, indicating that AS is a superior antimalarial agent in performance of PK/PD. IV-AS provides the highest peak concentration and a very short exposure time, while oral AS can also provide high peak levels and similar short exposure times. The data suggest that the higher peak level has a major role in eliminating parasites rapidly and the short exposure time contributes to the avoidance of fatal neurotoxicity [40, 41] as well as prevention of resistance [42].

Although DHA has similar efficacy to AS in vitro [34], the agent does not have as rapid effect as IV-AS or oral AS, even with twofold higher dosing. The explanations include lower bioavailability [43, 44], which results in a slower absorption phase, and a long lag time which has an effect on activity. However, we believe the principal reason is due to the lower peak concentration observed when compared to oral AS.
Oral artemisinin (QHS) does not compete well in this PK/PD comparison with its relatively low potency against cultured *P. falciparum* [34]. Although high oral doses (three- to sixfolds higher than oral DHA and AS, Table 1) produced higher plasma concentrations (2601 ng h/ml of AUC) and high peak concentrations (588 ng/ml), the relatively low potency [34] and bioavailability [33] significantly limited the efficacy. Intramuscular AM or AE consistently displays low efficacy and slow parasite killing. Due to the sesame oil formulation, AM and AE have a very low and prolonged absorption from muscle injection sites [37]. Initially, parasitemia counts after dosing do not decrease due to the low and delayed peak concentrations (75–110 ng/ml) of AM and AE. This may be the main reason for slow elimination of parasites as the observed lag times of 7.2–8.9 h are the longest of the drugs. Subsequently, they have the slowest clearance rates, with mean PC50 times of 15.63–19.68 h, potentially resulting in inadmissible failures in some of the AE trials (Table 1) [38]. Although drug exposure times of AM and AE are comparatively longer than AS, DHA, and QHS, this long exposure apparently did not improve efficacy. Instead, it seems to induce neurotoxicity [41]; therefore, this formulation should not be encouraged for clinical use to treat acute and severe malaria as safer agents are available.

PK/PD evaluations demonstrate that the rapid efficacy of the artemisinins is principally due to the drug peak concentration (Cmax). This further indicates that AS has superior PK/PD following either oral or intravenous administration. Other pharmacokinetic parameters, such as drug exposure level (AUC) and drug exposure time (half-life), tend to be of minor importance for efficacy [45]. Most clinical observations demonstrate that the fast pharmacodynamic properties of these drugs have been largely addressed with pharmacokinetic findings [38, 45, 46]. Further, low drug exposure of artemisinins may be a cause for observed treatment failures [37, 47, 48]. These studies showed that using a low dose regimen may not provide enough drug exposure to kill the parasites in these patients [49]. In contrast, the clinical cure indicated that the intravenous formulations, like AS injection, are very important in the rapid treatment of malaria with high observed peak concentrations (Cmax), especially in severe and complicated malaria [26, 27].

Evidence shows that higher plasma concentrations (Cmax and AUC), especially peak concentrations (Cmax), greatly enhance the efficacy and clinical therapeutic potentials of the artemisinins. As previously discussed, the severity of the possible complications for *P. falciparum* malaria constitutes a serious medical emergency, and appropriate treatment should be initiated if infection is suspected. Appropriate treatment requires enough high-dose regimens and should be given to provide successful therapeutic efficacy for malaria patients, as it is known that 84% of all malaria related deaths occur within 24 h of hospital admission in African children [50]. As such, first exposure concentrations of artemisinin drugs are critical in the clinical setting.

4. PK/PD evaluation of artemisinin-based combination therapies (ACTs)

In order to avoid a high recrudescence of the monotherapy of artemisinins and to delay or prevent emergence of artemisinin resistance, WHO recommends the use of combination therapies for the treatment of uncomplicated *P. falciparum* malaria. Artemisinin derivatives rapidly decrease the parasite biomass, while the presence of partner antimalarial drugs with a different and slow-acting mechanism reduces the probability of high recrudescence. These therapies include one artemisinin derivative plus a partner, slow-acting, antimalarial drug with a longer half-life [51, 52].
WHO encourages the development of fixed-dose combination (FDC) versions of ACTs, versus cobbled tablets that can be misused to facilitate administration of artemisinin as monotherapy.

Two ACT combinations, artesunate-sulfadoxine/pyrimethamine (AS-SP) and artesunate-amodiaquine (AS-AQ), are used in areas where parasites are susceptible to these drugs. In areas where resistance to sulfonamide-pyrimethamine, chloroquine, and amodiaquine is prevalent, other artemisinin combinations are used such as artemether-lumefantrine (AL) or artesunate-mefloquine (AS-MQ). More recently, dihydroartemisinin-piperaquine (DP) is a promising ACT option that exhibits an excellent efficacy and safety profile and is currently the first-line therapy for uncomplicated malaria in Asia. Currently, artemisinins have been introduced to the market combined with other slow-acting drugs to create fixed-dose ACTs containing amodiaquine, mefloquine, and piperaquine [53].

Artemisinin-resistant *falciparum* malaria has developed on the border between Thailand and Cambodia. The development of artemisinin resistance is likely a consequence of patient treatment with artemisinin monotherapy with substandard, counterfeit, or adulterated drugs for over 40 years. This artemisinin resistance phenomenon is characterized clinically by much slower parasite clearance rates after artemisinin treatment [54]. This artemisinin resistance, defined by a delayed parasite clearance time, has been associated with several genetic mutations.

One hypothesis to explain this phenomenon is delayed parasite clearance derived from a stage-specific decrease in artemisinin sensitivity against circulating young asexual ring-stage parasites. Another hypothesis to explain this phenomenon is dormancy of ring-stage parasites *in vivo*, which would render them resistant to artemisinin treatment. A related hypothesis is that reduced sensitivity to treatment with artemisinins renders the ACT partner drug vulnerable to development of resistance. This very ominous development accompanied with the development of resistance over time in Asia to all of the partner drugs used for ACTs suggests that all of the current ACT regimens would be predicted to fail in Southeast Asia. This phenomenon will lead to malaria recurrence after treatment, and decreased efficacy of artemisinin-based treatment of severe malaria. To assess this question further concerning AS-MQ efficacy, a clinical trial was conducted on the Thai-Cambodian border using this combination to treat 151 subjects infected with uncomplicated *falciparum* malaria. Patients were followed over a 42 day period or until recurrent parasitemia was observed. The PCR-corrected treatment failure rate at 28 days was 13.1%, and the treatment failure rate at 42 days after treatment was 18.8%. These treatment failures were associated with longer parasite clearance times, increased *pfmdr1* copy number, increased initial parasitemia, and elevated mefloquine IC$_{50}$ values. These data demonstrate the combined effects of artesunate resistance and mefloquine resistance in this region [55].

Similar to other drug resistance phenotypes, this resistance can best be understood based on its mechanism of action. More recently, it was demonstrated that artemisinin attacks multiple parasitic targets, suggesting that mutations in drug targets are unlikely to cause high-level artemisinin resistance. These findings will help us to better understand the mechanisms of artemisinin resistance and suggest that how can we continue to use ACTs [51].

There is a very large body of evidence to support the hypothesis that ACTs provide the best possible treatment available today for uncomplicated multidrug-resistant *falciparum* malaria. ACTs provide rapid treatment responses that are well tolerated, provide excellent cure rates with 3-day treatment regimens, provide reductions in gametocyte carriage, and decrease drug resistance by providing protection for combination partner drugs.
Clinical trials in 10 investigational sites in 7 African countries (Burkina Faso, Nigeria, Gabon, Zambia, Uganda, Rwanda, and Mozambique) were performed. About 4116 African children under 5 years of age with uncomplicated P. falciparum malaria were treated with four ACTs: 1226 with AL, 1002 with AS-AQ, 413 with chlorproguanil-dapsone-arthesunate (CDA), and 1475 with DP. The PCR-corrected cure rate on day 63 showed no differences between DP, AL, and AS-AQ, while these three ACTs were statistically superior in comparison with CDA. The PCR-uncorrected cure rate at day 63 indicated that DP was statistically superior to AL, AS-AQ, and CDA [56].

In addition, the efficacy of the Eurartesim® formulation of DP in Thailand, Laos, and India was compared with that of AS-MQ for the treatment of patients aged 3 months to 65 years with uncomplicated P. falciparum malaria in a noninferiority trial conducted in Asia. DP was shown to be a highly efficacious drug for the treatment of uncomplicated P. falciparum malaria in areas where multidrug parasites are prevalent [57].

Several additional trials compared the efficacy of the Artekin® formulation of DP versus AS-MQ in patients with uncomplicated P. falciparum malaria. Most of the trials were conducted in Asia with one trial conducted in Peru, and the majority of trials included both pediatric and adult patients. DP was shown to be highly effective for the treatment of uncomplicated P. falciparum malaria [58].

Antimalarial drug resistance is now well established in both P. falciparum and P. vivax. In southern Papua, Indonesia, where both strains of Plasmodia coexist, a series of studies were conducted to optimize treatment strategies. A randomized trial compared the efficacy and safety of DP with AS-AQ. Of the 334 patients in the evaluable patient population, 185 were infected with P. falciparum, 80 were infected with P. vivax, and 69 were infected with both species. DP was both more efficacious and better tolerated than AS-AQ when used to treat multidrug-resistant P. falciparum and P. vivax infections. The prolonged therapeutic effects of piperaquine appeared to delay the time to P. falciparum reinfection, decrease the rate of recurrence of P. vivax infection, and reduce the risks of both gametocyte carriage and anemia [59].

Other studies have also shown that DP has excellent efficacy for the treatment of uncomplicated malaria. The results showed that DP was superior to AL and AS-AQ for reducing the risk of recurrent parasitemia and recrudescence [60]. DP has consistently been shown to be well tolerated, safe, and efficacious in adults and children in Asia, Africa, and South America, both in children and in adults with uncomplicated malaria due to P. falciparum, P. vivax, or mixed infections with significantly less nausea, vomiting, and dizziness than AS-MQ [58, 61]. DP was also better tolerated, with no clinically significant cardiovascular or metabolic effects [58].

Recently, nine trials compared the efficacy of Eurartesin®, Duocotecxin®, or Artekin® formulations of DP with that of AL in patients with uncomplicated P. falciparum malaria. Most of these trials were conducted in Africa, with one trial conducted in Cambodia. These additional trials demonstrated the efficacy of DP for the treatment of uncomplicated P. falciparum malaria. DP was shown to be superior to AL with respect to other endpoints, including fever and parasite clearance times, reinfection rates, and gametocyte carriage rates [58].

The conclusions of those studies were that DP was shown to be a safe, well tolerated, and highly effective treatment of P. falciparum malaria in Asia and Africa, but the effect on gametocyte carriage was inferior to that of AS-MQ [62].

5. Therapeutic effects of ACTs depending on the half-life of partner drug

Concerning therapeutic benefits, combination therapy minimizes the risk of emergence and spread of parasites resistant to either agent. Preventing the
development of artemisinin resistance is of vital importance given the crucial role artemisinin derivatives play in malaria control and treatment programs. Artesunate resistance has already emerged in western Cambodia [1, 63]; however, ACTs are still capable of achieving cure rates exceeding 90%. Since 2001, WHO guidelines have recommended the use of ACTs to include DP, AL, AS-MQ, AS-AQ, and AS-SP to treat patients with uncomplicated *P. falciparum* malaria. Among those ACTs, DP represents a new and extremely promising fixed-dose combination. Several clinical trials have repeatedly shown that DP is a safe and highly efficacious therapy against uncomplicated *P. falciparum* and the asexual stages of *P. vivax* malaria. The risk of recurrent infections was significantly lower for DP, followed by AS-AQ and then AL, supporting the recent WHO recommendation to consider DP as a valid option for the treatment of uncomplicated *P. falciparum* malaria [64].

These therapies include one artemisinin derivative plus a partner compound, slow-acting, antimalarial drug with a longer half-life [51, 52]. The cumulative risk of parasitological failure was greater in studies of patients treated with AL, AS-MQ, and AS-SP than in patients treated with DP, reflecting the very long half-life of piperaquine. The long half-life of piperaquine is expected to have a major impact in improving the health-care systems of countries in *P. falciparum* malaria endemic areas (Table 2). Piperaquine has a large apparent volume of distribution (greater than 500 l/kg) and a terminal elimination half-life estimated around 5 weeks. With increasing sensitivity of assay techniques, the true terminal half-life is probably similar to that of chloroquine, 1–2 months. The oral bioavailability of piperaquine increases with coadministration with fat [58, 64–67].

In addition, the superior efficacy of DP for the treatment of *P. vivax* in malaria endemic areas versus chloroquine or other ACTs may reflect some measures of chloroquine resistance in areas where trials were conducted or comparison with one of the longer acting ACTs. Of the ACTs, DP has the longest half-life and as such was shown to be highly efficacious at preventing *P. vivax* relapses for up to 56 days following treatment. In a separate study, AS-MQ also provided protection against *P. vivax* parasitemia for up to 63 days. The shorter half-life combinations such as AL, although equally effective at rapidly reducing parasite biomass, were shown to provide comparatively little protection against early relapse [64–67]. Accordingly, the DP combination demonstrably has superior PK/PD qualities compared to all other ACTs recommended by WHO.

<table>
<thead>
<tr>
<th>Antimalarials</th>
<th>Half-life of artesinin derivative</th>
<th>Half-life of partner drug per full adult course (US$)</th>
<th>Regions currently in use</th>
<th>Purchase cost per course (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether-lumefantrine</td>
<td>~3 h</td>
<td>4–5 days</td>
<td>Africa, EM, SE Asia, WP and SA</td>
<td></td>
</tr>
<tr>
<td>Artesunate-mefloquine</td>
<td>&lt;1 h</td>
<td>14–21 days</td>
<td>Africa, SE Asia, WP and SA</td>
<td></td>
</tr>
<tr>
<td>Artesunate-amodiaquine*</td>
<td>&lt;1 h</td>
<td>9–18 days</td>
<td>Africa and EM</td>
<td></td>
</tr>
<tr>
<td>Dihydroartemisin-piperazine</td>
<td>45 min</td>
<td>~5 weeks</td>
<td>Africa, SE Asia</td>
<td></td>
</tr>
<tr>
<td>Artesunate-pyronaridine</td>
<td>&lt;1 h</td>
<td>16 days</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Chloroquine†</td>
<td>NA</td>
<td>1–2 months</td>
<td>Africa, EM, SE Asia, WP and SA</td>
<td></td>
</tr>
<tr>
<td>Sulfadoxine-pyrimethamine</td>
<td>NA</td>
<td>~4 days (S) or ~8 days (P)</td>
<td>Africa, EM (IPT in Africa, EM and WP)</td>
<td></td>
</tr>
</tbody>
</table>

*This refers to the *t*½ of the active metabolite monodesethylamodiaquine; the *t*½ of amodiaquine is ~3 h.

†These former first-line antimalarials are included as a reference. EM, eastern Mediterranean; IPT, intermittent preventive treatment; NA, not applicable; P, pyrimethamine; S, sulfadoxine; SA, South America; SE Asia, Southeast Asia; *t*½, half-life; WP, Western Pacific.

Table 2.
Plasma half-lives of the partner drugs used in artemisinin-based combination therapies (ACTs) [58, 64–67].
6. Conclusion

Artemisinins have been used clinically in the treatment of malaria for over 40 years, during which time their mechanism of action and pharmacokinetic properties have been elucidated. Empirical judgments concerning efficacy and optimal administration have been influenced by their impressive parasite clearance kinetics, which are superior to many commonly used alternatives. Among the five artemisinins in current use, the PK/PD profiles of AS are the best.

This report has also discussed the fact that the rapid efficacy of artemisinins is principally driven by peak concentration ($C_{\text{max}}$) from the first drug exposure. Other factors in the pharmacokinetic parameters, such as drug exposure level (AUC) and drug exposure time (half-life), appear to be of lesser importance. By the fundamental and reliable measures of efficacy in cure and mortality rates for uncomplicated and severe malaria, it is demonstrated that current artemisinins (AS, AM, and DHA), performing in roles as ACT or monotherapy, provide a clear-cut advantage over other antimalarials in some geographical locations. The most recent advances in the decrease of the mortality (34.7%) were shown with the use of IV-AS, as compared to IV quinine.

Although the artemisinins are poorly efficacious at achieving 100% cure in malaria when used as monotherapies, this shortage has been overcome using oral ACTs and IV-AS sequentially with a slower acting partner drug such as mefloquine or piperaquine. Previous arguments for the long-term benefits of combination and sequential therapies for preventing resistance and recrudescence still stand. The rapid action and subsequent decrease in mortality show that the artemisinins have a great advantage over other antimalarials when used as ACTs for uncomplicated malaria and in sequential therapy with AS injection in cases of severe and complicated malaria.

As a result of the long half-life of oral piperaquine, DP has excellent PK/PD potential when compared to all other ACTs. Importantly, WHO guidelines for the treatment of malaria expanded to include DP as an ACT option for the “first-line treatment of uncomplicated $P. falciparum$ malaria worldwide” [53]. This was categorized as a “Strong Recommendation” and was added due to “High Quality Evidence.”

Acknowledgements

This study was supported by the United States Army Research and Materiel Command. The opinions or assertions contained herein are the private views of the author and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>QHS</td>
<td>artemisinin</td>
</tr>
<tr>
<td>AS</td>
<td>artesunate</td>
</tr>
<tr>
<td>DHA</td>
<td>dihydroartemisinin</td>
</tr>
<tr>
<td>AE</td>
<td>arteether</td>
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<tr>
<td>AM</td>
<td>artemether</td>
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<tr>
<td>AL</td>
<td>artelinate</td>
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<tr>
<td>PK</td>
<td>pharmacokinetics</td>
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<tr>
<td>PD</td>
<td>pharmacodynamics</td>
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