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Invited Review

Formulation and pharmacokinetics of artemisinin and its derivatives

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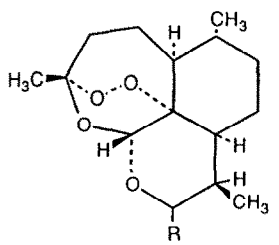
Summary

Artemisinin, the leading compound of a completely deviant class of drugs, might be of incredible importance in the combat of malaria. Although the herb from which it is isolated has been known for more than 2000 years, and over 2000 patients have been successfully treated in clinical studies, no pharmacokinetic data are available, and thus empirical formulations are used. In this review the available literature on formulation and kinetic aspects of artemisinin and its derivatives is reinterpreted and discussed in order to determine the kinetic requirements for a rational and optimal design of artemisinin formulations.

Introduction

Artemisinin (Chinese: Qinghaosu) (Fig. 1a) is a sesquiterpene lactone with a characteristic peroxide bridge. It is isolated from the herb *Artemisia annua* L. (Qinhao), a member of the Compositae family (Asteraceae). This herb has been in use in China for more than 2000 years in the treatment of fever. In the twentieth century it became clear that its antipyretic activity is confined to the treatment of malaria. After the isolation of the active principle artemisinin by Chinese scientists in 1972, this substance appeared to be a potent blood schizontocide, the peroxide group, unique in nature, being essential for its activity. Artemisinin is the leading compound of a completely deviant



a) R:	=O	artemisinin
b)	-OH	dihydroartemisinin
c)	-O-(C=O)$(CH_2)_2$COONa	sodium artesunate
d)	-O-CH3	artemether
e)	-O-CH_2CH_3	arteether
f)	-O-$CH_2C_6H_4$COONa	sodium artelinate

Fig. 1. Structure of artemisinin and some of its derivatives.

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class of drugs, which might be of significant importance in the combat of malaria. A detailed review on the history, isolation and structure elucidation was published by Klayman (1985).

The parasite and fever clearance rates with artemisinin and its derivatives are higher than with any other antimalarial drug (Qinghaosu antimalaria coordinating research group, 1979; Jing-Bo Jian et al., 1982; Li et al., 1985). Excellent results have been reported in the treatment of *Plasmodium vivax* and *P. falciparum* infections in patients, including the cerebral form, with both chloroquine-sensitive and chloroquine-resistant strains (Qinghaosu antimalaria coordinating research group, 1979; Luo and Shen, 1987; Myint and Shwe, 1987; Myint et al., 1989). Artemisinin resistance could be induced in vitro (Inselburg, 1985; Li et al., 1986). Until now no resistance has been described in patients. Cross-resistance with other antimalarials is limited.

In this article the available literature on formulation and kinetic aspects of artemisinin and its derivatives is reviewed, in many cases reinterpreted and discussed. These data are related to information on the fever and parasite clearances in order to determine the kinetic requirements for an optimal and rational artemisinin formulation design.

Artemisinin Derivatives

Artemisinin can be hydrogenated at the C-10 keto group to the hemiacetal dihydroartemisinin (Fig. 1b). The resulting hydroxy group can be used for further derivatisation. Many experimental derivatives have been prepared of which only a few are used in practice (Luo and Shen, 1987). The most important derivatives are currently artesunate, the water-soluble sodium salt of the succinic acid ester (Fig. 1c), and the lipophilic esters artemether and arteether (Fig. 1d and e).

The usage of artesunate is limited by its hygroscopy and poor stability in aqueous solution, due to hydrolysis of the ester linkage. It is therefore distributed in a dual package, powder with solvent. Recently, more stable water-soluble compounds have been developed, in which a carboxylic acid chain is joined by an ether linkage (Lin et al., 1987). The sodium salt of artelinic acid (Fig. 1f) is the most promising of this class of drugs, but is not yet in use.

Formulation and Pharmacokinetics

Artemisinin

Intravenous administration Concentration-time profiles of artemisinin in man after intravenous injection are not available because of the low solubility in water and lack of a suitable solvent for i.v. use. The pharmacokinetics after i.v. injection have been determined in rats (Niu et al., 1985), but information on the formulation is lacking. Probably, a micronized aqueous suspension was used in that study.

Each of the seven points in the curve was obtained from three rats, 21 in total. The distribution and elimination are very rapid and the distribution volume is large. The parameters calculated from these data were $t_{1/2}$, $\alpha = 2.66$ min, $t_{1/2}$, $\beta = 30$ min and $V_\beta = 4.1$ l/kg. These data can only be seen as rough estimates of the true population means in rats, due to methodological and statistical shortcomings of the study.

Intramuscular administration The intramuscular route of administration is most frequently used. About 2000 patients were successfully treated in China during the 1970s (Qinghaosu antimalaria coordinating research group, 1979; Li G.-Q. et al., 1982). The i.m. formulation consisted of a suspension in oil or water. The applied dosage scheme is 800–1200 mg divided over 3 days, e.g. 600 mg on day 1 and 300 mg on days 2 and 3, administered as a single daily dose. Precise data on the formulation such as suspension vehicle, concentration, viscosity, etc. have not been given or discussed.

The pharmacokinetics in humans have been determined after i.m. administration of suspensions in oil and aqueous suspensions (Titulaer et al., 1990). Ten healthy male volunteers received 400 mg artemisinin as a suspension in olive oil or in 0.5% HPMC and 0.9% NaCl. The i.m. injection was placed in the upper outer quadrant of the buttock. In Fig. 2 the concentration-time profiles

are shown. In Table 1a the calculated pharmacokinetic parameters are summarized.

A striking difference was observed between the aqueous suspension and the suspension in oil. The mean peak concentration after i.m. administration of the suspension in oil resembles that after oral administration of the same dose, though maxima occur at a later time. After i.m. injection of an aqueous suspension low and variable concentrations were observed. This is probably caused by the fast aqueous solvent absorption and subsequent particle aggregation, in contrast to the case of oil as vehicle.

The profiles of the suspension in oil show a large variation in peak concentrations and the time that zero concentrations are reached again. This obvious variation in absorption rate might be caused by differences in the shape of the depot and/or in the activity of the volunteer and subsequent bloodflow in the muscle.

Oral administration Concentration-time profiles of artemisinin after oral administration, as depicted in Fig. 3, have been determined by Zhao (1987) and Titulaer et al. (1990). In Table 1b the calculated pharmacokinetic parameters from the second study are summarized.

Artemisinin is quickly absorbed with peak concentrations occurring at about 1 h, but the bioavailability relative to the i.m. injection of a suspension in oil is only 32% (Titulaer et al., 1990).

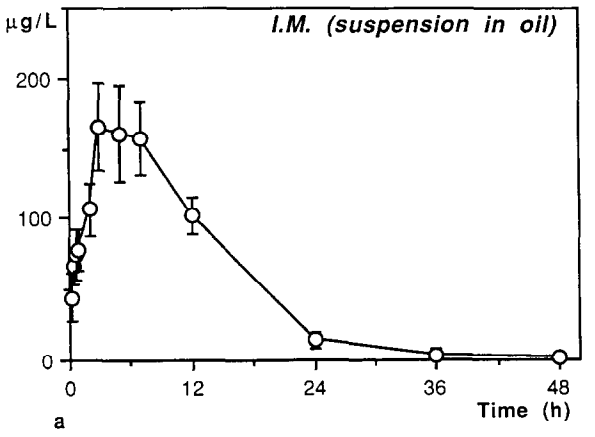
The study of Zhao (1987) had the character of a preliminary experiment, since the data were collected from only one volunteer. The results differ considerably from the results of the study of Titulaer et al. (1990). The peak concentration was found at about 4 h and the concentrations were much higher over the whole time period. Artemisinin was given in the study of Titulaer et al. after an overnight fasting period, but in the study of Zhao artemisinin was administered 30 min after a light breakfast. An explanation might be therefore that the absorption of artemisinin is influenced by concomitant food intake. Drugs with a high first-pass metabolism, such as artemisinin, are often susceptible to the influence of food on absorption and bioavailability (Beerman, 1979; Merkus, 1984).

Rectal administration Artemisinin, rectally administered in suppositories, is tested in large clinical trials in China (Li et al., 1985). Fig. 4b shows an artemisinin concentration-time curve of a human volunteer after administration of 10 mg/kg as a suppository (Zhao, 1987). The peak concentration is much lower than after oral administration, being found at about 7–9 h after administration. Information about the formulation (sup-

TABLE 1

Pharmacokinetics after administration of 400 mg artemisinin (data from Titulaer et al., 1990)

	C_{max} (μg/l)	t_{max} (h)	AUC (μg h l^{-1})	MAT (h)	$t_{1/2}$, abs (h)	$t_{1/2}$, el (h)	k_{el} (h^{-1})	MRT (h)
(a) Suspension in oil, i.m.								
Min	91	0.75	993	1.10	0.76	4.16	0.07	7.2
Max	331	7	3945	3.56	2.47	15.96	0.17	25.2
Mean	209	3.4	2419	2.30	1.59	7.44	0.11	10.6
SD	97	2.0	1055	0.20	0.51	3.83	0.04	5.8
n	10	10	10	8	8	8	8	8
(b) Aqueous suspension, oral								
Min	159	0.75	574	0.49	0.14	1.0	0.24	0.26
Max	440	2	1018	1.79	0.93	2.9	0.67	3.9
Mean	260	1	819	0.78	0.54	1.9	0.41	3.4
SD	94	0.5	190	0.41	0.29	0.6	0.14	0.7
n	10	10	8	8	8	8	8	8



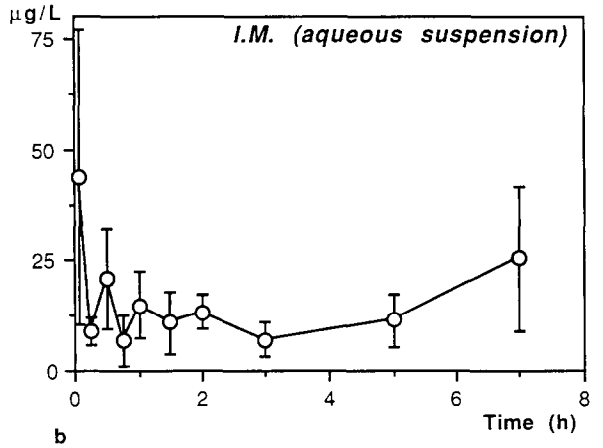


Fig. 2. Artemisinin concentration-time curves after i.m. administration of 400 mg artemisinin; (a) suspension in oil, (b) aqueous suspension ($n = 10$, bars indicate SE. From Titulaer et al., 1990).

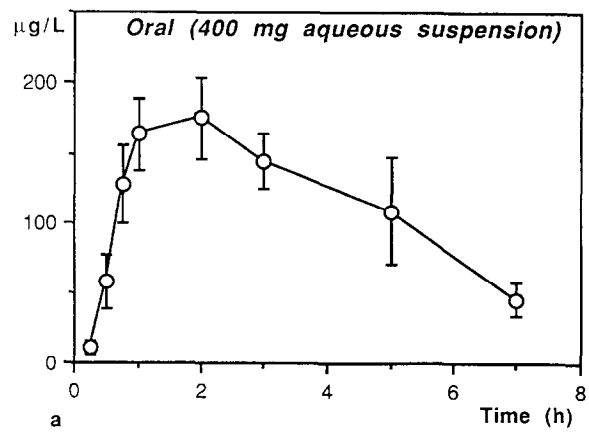
pository base and size, particle size) is lacking. It might be assumed that the suppositories available in China containing micronized artemisinin and a polyethylene glycol-stearate base with polysorbate, were used. The above-mentioned study has the character of a pilot study.

Fig. 4a shows concentration-time profiles after rectal administration of 400 mg artemisinin as a micro-clysma to 10 healthy volunteers (Titulaer et al., 1990). Artemisinin appears to be poorly absorbed from this formulation. An explanation might be that artemisinin is solubilized better in polyethylene glycol derivatives than in water and that the latter is not rectally absorbed, remaining available as solvent during the absorption process.

Kinetics of artemisinin derivatives

Artesunate Sodium artesunate is in use in China for i.v. and i.m. administration. Li G.Q. et al. (1982) reported the use of slowly i.v. injected artesunate, 20 mg/ml 5% GNS or GS and i.m. injections of artesunate, 100 mg/ml distilled water. A loading dose of 200 mg, followed by 100 mg on days 2 and 3 was used.

Pharmacokinetic data in man are not available. Artesunate is rapidly distributed in rabbits, rats



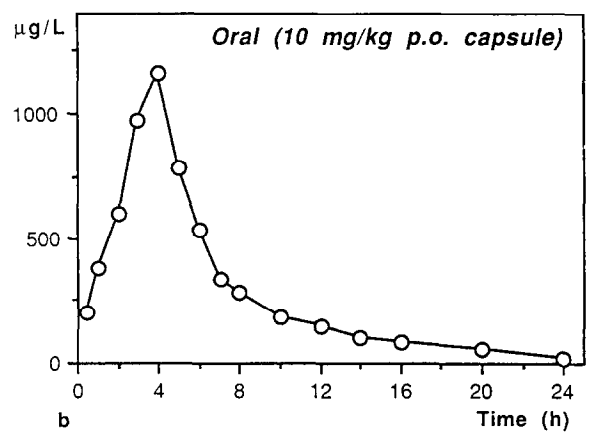


Fig. 3. Artemisinin concentration-time curves after oral administration of artemisinin. (a) Aqueous suspension 400 mg ($n = 10$, bars indicate SE. From Titulaer et al., 1990). (b) Capsule 10 mg/kg ($n = 1$. Redrawn after Shishan Zhao, 1987).

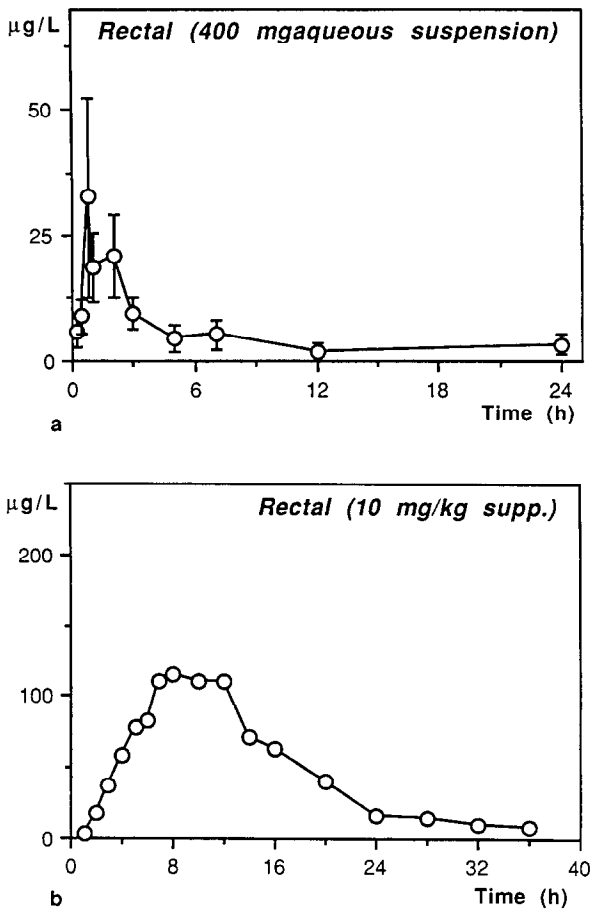


Fig. 4. Artemisinin concentration-time curves after rectal administration of artemisinin. (a) 400 mg in a micro-clysma ($n = 10$, bars indicate SE. From Titulaer et al., 1990). (b) 10 mg/kg in a suppository ($n = 1$. Redrawn after Shishan Zhao, 1987).

and dogs. It is hydrolyzed to dihydroartemisinin by blood esterases with a half-life of about 1.7 min (Zhou et al., 1987) or 4 min (Edlund et al., 1984), respectively. The hydrolysis half-life in dogs is about 0.45 h (Zhao et al., 1986). Artesunate can therefore be conceived as being the prodrug of dihydroartemisinin. Dihydroartemisinin is rapidly eliminated with a half-life of about 2.5 h as determined from studies in dogs (Theoharides et al., 1988). The dihydroartemisinin concentration decreases to the detection limit in about 2 h in rats (Edlund et al., 1984).

Artesunate penetrated the blood cells of rats with a low distribution rate. Dihydroartemisinin, however, is preferentially accumulated in the *Plasmodium falciparum* infected erythrocyte in vitro, showing a 2-fold concentration in the uninfected erythrocyte as compared to 300-fold in the infected red cell (Gu et al., 1984). This is probably connected with the altered membrane structure of infected erythrocytes (Ye et al., 1986) and/or extensive binding to parasite substrates. The protein binding of artesunate is reported to reach an extent of 59% and, more relevantly, that of dihydroartemisinin 43% (Luo and Shen, 1987).

Artesunate has been reported to be percutaneously absorbed and to clear the parasitaemia after administration in an ointment to hairless mice (Xuan et al., 1988). At this moment the relevance of this finding is not easy to interpret.

Artemether Artemether is in use in China a solution in oil for i.m. administration in humans. Li G.-Q. et al. (1982) reported the following dosing scheme: artemether oil preparation, 80 mg/ml: day 1, 320 mg; days 2 and 3, 160 mg.

Fig. 5 shows mean concentrations of artemether in plasma after a dose of 6 and 10 mg/kg, respectively, to three volunteers (Zhou et al., 1988). The t_{max} is found at about 6 h. The half-life of absorption was 2–2.6 h.

The half-life of elimination cannot be calculated with enough accuracy from this study, due to

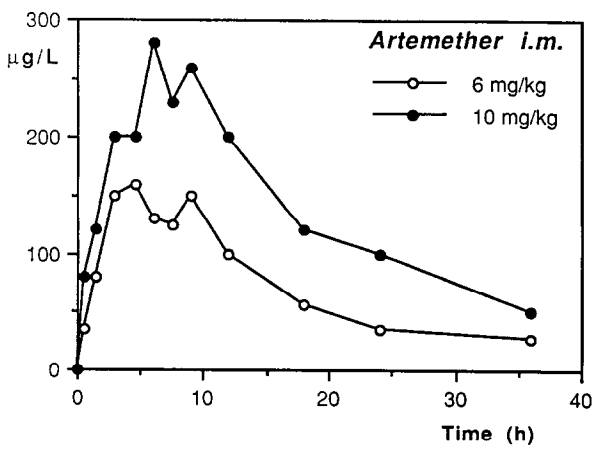


Fig. 5. Artemether concentration-time curve after the intramuscular administration of 6 mg/kg and 10 mg/kg ($n = 3$. Redrawn after Zhou et al., 1988).

the sustained absorption. The authors suggested elimination half-lives from about 7 to 11 h. The period during which the concentrations are higher than the effective concentration is claimed to be about 50 h after a dose of 6 mg/kg. This means that the artemether injection is a long-acting preparation and should allow once daily dosing. However, the power of a study with three volunteers is low. An estimation of the risk of unprotected intervals between two dosages needs a larger scale study.

The bioavailability of artemether intramuscularly injected as a solution in oil is reported to be 37–50% (China cooperative research group on qinghaosu and its derivatives as antimalarials, 1982). However, these results might be biased by the limited observation time of 72 h. If this finding is true, this is a serious drawback compared to the artemisinin suspension injection in oil (Titulaer et al., 1990).

Artemether is strongly bound to plasma proteins (76%) and distributes rapidly over the blood cells and brain (Li et al., 1982; Luo and Shen, 1987). In contrast to artesunate the biotransformation into dihydroartemisinin is slow.

Artemether has, as artesunate, been reported to be percutaneously absorbed after administration in an ointment to hairless mice (Klayman, 1985).

Fundamental pharmacokinetic properties of artemisinin

Absorption Artemisinin is rapidly but incompletely absorbed after oral administration (Titulaer et al., 1990). The mean absorption time (MAT) is 0.78 h and the bioavailability relative to the i.m. injected suspension in oil 32%. Because no i.v. formulation of artemisinin is available yet, future studies must reveal the absolute bioavailability. The low bioavailability after oral administration could be explained from the results of former in vitro studies and pharmacokinetic experiments in rats and dogs (Niu et al., 1985; Zhao et al., 1986). After in vitro incubation of artemisinin in stomach and ileum preparations of the rat, artemisinin appeared to be stable, but a high metabolic clearance was demonstrated in rat liver slices (Niu et al., 1985), indicating that the incomplete absorption after oral administration can at least partially be ascribed to a high first-pass clearance in the liver.

Distribution and protein binding The tissue distribution was determined after i.v. administration of 150 mg/kg artemisinin in rats (Niu et al., 1985). The highest concentrations are found in the lungs, also quite high in the kidneys, lower in heart, brain and liver and low in muscles, fat, spleen and fetus. After oral administration of 900 mg/kg the highest concentrations are found in the liver. The distribution is very rapid. The distribution (α-) phase ends within 20 min. The concentrations are much higher at 5 min than at 30 min after injection. From the high concentrations in the brain it appears that artemisinin passes the blood-brain barrier in rats.

By combining the data on oral and intramuscular administration in oil from the study of Titulaer et al. (1990) and supposing that the absorption from the latter is complete, a volume of distribution of about 5 l/kg can be estimated. From many antimalarial drugs it is known that the volume of distribution and other kinetic parameters are altered in patients. Information on artemisinin with respect to these parameters is currently lacking.

Artemisinin passes the rat placenta but more slowly than the distribution processes over the other organs. The concentrations in the rat fetus were higher at 30 min as compared to 5 min after injection. No information is available on artemisinin excretion into breast milk.

Protein binding of 64% has been reported (Luo and Shen, 1987). Artemisinin is excreted in human saliva (Zhao, 1987). The plasma/saliva ratio was fairly constant, being about 8.0 ± 2.7 (mean $\pm$ SD). Normally, the reciprocal value, saliva/plasma ratio, is given in the literature. In this case, this is about equal to 0.12, which is less than the free fraction in serum and is indicative of an intermediate salivary clearance rate (Zuidema and Van Ginneken, 1983).

Metabolism and excretion In rat experiments the liver appears to be the main site of metabolism (Niu et al., 1985). Reduction of the peroxide bridge is the most important step in the metabolic pathway. Four metabolites were extracted from urine after an oral dose of artemisinin to volunteers. The metabolites all lack the peroxide moiety and

are therefore devoid of antimalarial activity. The kidneys and the lungs contribute to the metabolism to a much lesser degree.

The half-life of elimination in humans is very short, of the order of magnitude of 1–2 h after oral administration (Titulaer et al., 1990). The apparent elimination half-life after i.m. administration is much longer due to interference with the now low absorption rate.

Only a very small fraction of the administered dose is excreted in unchanged form in feces and urine, regardless of the route of administration.

TABLE 2

Formulation and clinical aspects

Formulation	Clearance of		Recrudescence rate (1 month) (%)	Number of patients
	Fever (h)	Parasites (h)		
p.o. [a]	21–46	18–61	31–85	247
i.m. (oil) [b]	21–36	28–48	13–21	212
i.m. (aqueous) [c]	31–46	30–73	9–28	369
Rectal [d]	21	53	47	100

Majority of infections, *P. falciparum*; others, *P. vivax*.
[a] Tablets or suspension (nasal feeding), total 2–3.2 g in 3 days.
[b,c] Suspension, total 0.8–1.2 g in 3 days.
[d] Suppository, total 2.8 g divided in 3 days, twice daily. (Data from: Qinghaosu antimalaria coordinating research group, 1979; Li G.-Q. et al., 1982, 1985).

Implications of Pharmacokinetic Properties for Therapeutic Use

Dose and therapeutic range

The mechanism of action of artemisinin is not fully understood but differs from that of other antimalarials. No folic acid antagonism has been demonstrated. It has been suggested that artemisinin or a peroxy metabolite acts as an initiator in a free radical chain process (Ames et al., 1985; Krungkrai and Yuthavong, 1987). Some effects on nucleic acid and protein synthesis have been reported (Ellis et al., 1985; Luo and Shen, 1987; Xuan Wenyi et al., 1988) and an effect on polyamine biotransformation has been described (Whaun et al., 1985). The primary target of attack is possibly protein synthesis. A minimal inhibitory concentration of 10^{-7} M is estimated for artemisinin (Luo and Shen, 1987). A membrane-stabilizing effect of *Plasmodium*-infected erythrocytes and some modulating effects on red cell immunity have been reported for artemether (Li et al., 1986).

Table 2 summarizes the most frequently used routes of administration, i.e. dosing schemes. Useful treatments of patients appeared to be an artemisinin aqueous or oily suspension of 1.2 g, intramuscularly injected over 3 days (e.g. 600, 300 and 300 mg). As an oral dose 10 mg/kg body weight per day is mostly recommended. Rectally, 2.8 g (600 mg at $t = 0$ and 4 h; 2×400 mg on days 2 and 3) in 3 days has been used in clinical trials. From studies in mice it appears that the intramuscular injection of artemisinin in oil is more active than in water (China cooperative research group on qinghaosu and its derivatives as antimalarials, 1982).

As can be derived from Table 2, fever and parasite clearance rates are higher with i.m. suspensions in oil than with the i.m. aqueous suspension. The rates after oral and rectal administration are comparable with that of i.m. artemisinin suspension in oil. These facts are easily understood from the artemisinin bioavailability data of these formulations and their pharmacokinetic profiles described above (Niu et al., 1985; Titulaer et al., 1990).

Recrudescence rate

The recrudescence rate with artemisinin and related compounds is relatively high and dependent on the formulation, dosing scheme and duration of therapy (Jiang et al., 1982; Li et al., 1984). Oral and rectal formulations, the formulations with a short mean residence time, are afflicted with a higher recrudescence rate than parenteral formulations (Luo and Shen, 1987), as shown in Table 2.

The high recrudescence rate is probably caused by two factors. The activity of artemisinin and its derivatives is confined to the blood schizonts (the plasmodia in the erythrocytic phase, especially in their early stage, the rings) and the rather short elimination half-life. It is obviously important that between two dosage times artemisinin remains

present in sufficiently high concentrations. It can be supposed that newly formed erythrocytes, the reticulocytes, are sensitive to infection when they are not rapidly protected by sufficient drug delivery, especially since the younger population is more susceptible to an attack of *P. falciparum* (Boonpucknavig et al., 1984).

Discussion

Important aspects for therapy are a rapid onset of action and a relatively long duration of action. From Table 2, it can be concluded that the fever and parasite clearances are low following the very slowly absorbed i.m. aqueous suspension but that absorption rates as found for the oral and i.m. suspension in oil do not differ markedly. From recent Chinese data it can be seen that the intravenous administration of artesunate also does not result in a more rapid fever and/or parasite clearance.

It appears, however, to be very important that artemisinin is dosed in such a frequency that a constant supply of sufficient drug is guaranteed to prevent an excessively high recrudescence rate. This means that a sustained release formulation with a sufficiently high initial release has the highest potential for recrudescence prevention.

Moreover, formulations with a high bioavailability and low production costs are essential as artemisinin is costly and available on the market in limited quantities only.

At present, only the intramuscular suspension in oil meets all the requirements. A disadvantage, however, is the high variability in absorption rate. More research is needed (and is now in progress) to determine the optimal manner of administration and most appropriate formula.

The once daily dosage schemes as currently applied with the available preparations and as mentioned in this article are sensitive to recrudescence. All preparations run the considerable risk of much shorter durations of active protection than 24 h. Experimental therapy with parenteral depot formulations and longer duration of therapy are needed for adapting dosage forms and dosage schemes in a close relationship to an optimum therapy and prevention of recrudescence. At this time it is still necessary to use other antimalarial drugs after fever and parasitemia have subsided to prevent the residual recrudescence.

Toxicity of artemisinin seems to be negligible even at high doses. A slight reticulocytopenia and a reversible pyrogenic reaction have been observed (Anonymous, 1987). Artemisinin and its derivatives are embryotoxic in laboratory animals (China cooperative research group on qinghaosu and its derivatives as antimalarials, 1982).

Titulaer et al. (1990) reported the absence of pain at the site of injection with i.m. formulations and the absence of other side-effects after oral and rectal administration in their experiments.

Pharmacokinetic drug interactions have not been reported but are likely to occur, as artemisinin

TABLE 3

Formulation and pharmacokinetics

Route	Dose	No. of subjects	C_{max} (μg/l)	t_{max} (h)	AUC (μg h l^{-1})	$t_{1/2,el}$ (h^{-1})
Oral	10 mg/kg	1	1150	4	8103	2.4 [b]
	400 mg	10	260	1	819	1.9 [c]
i.m. oil	400 mg	10	209 [a]	3.4 [a]	2419 [a]	7.44 [c] [a]
i.m. aqueous	400 mg	10				
Rectal	10 mg/kg	1	115	8	1062	6.5 [b]
	10 mg/kg	6	10 [a]	6.65 [a]	– [a]	– [d] [a]
	400 mg	10				

[a] Not determined due to large variability and poor absorption. [b] Zhao (1987). [c] Titulaer et al. (1989). [d] Shen (1986).

is a high clearance drug. More research is needed on this aspect.

Potentiation and additive effects have been reported for many artemisinin combinations with antimalarial drugs (Chawira and Warhurst, 1987; Chawira et al., 1986a,b, 1987). Antagonism, however, may occur with pyrimethamine and with chloroquine in combination with artemisinin against *P. falciparum* in the field.

Summary

Artemisinin is a sesquiterpene lactone with a unique peroxide moiety in its structure. It is the leading compound of a new class of antimalarials. Besides artemisinin, its derivatives sodium artesunate and artemether are experimentally applied in the clinic. Artemisinin and derivatives are very fast acting blood schizontocides, especially suited for the treatment of severely ill patients. Artemisinin has been dosed most frequently by intramuscular injection. The suspension in oil results in a rapid absorption and relatively high peak concentrations. An aqueous suspension results in a more sustained release with a low onset and low concentrations. Artemisinin is completely absorbed, in the strict sense, after oral administration, but a high first pass metabolism results in relatively low bioavailability. Absorption after rectal administration as an aqueous suspension or in suppositories is incomplete. Artemisinin is rapidly distributed over the tissues, passes the erythrocyte wall, the blood brain barrier, the salivary glands and the placenta. It is rapidly excreted by biotransformation, mainly in the liver. Artemisinin shows a relatively high recrudescence rate, probably dependent on formulation characteristics which might be partially prevented by better products and better dosage schemes. The toxicity is low, however teratogenicity was observed in laboratory animals. Kinetic drug interactions are not reported but dynamic interactions occur with several antimalarials.

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