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Halofantrine: a new substance for treatment of multidrug-resistant malaria

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Malaria situation

Malaria is one of the most important causes of morbidity and mortality in tropical countries. The World Health Organization considers the worldwide annual incidence of acute malaria to be 270 million infections and 110 million clinical cases [28]. The number of deaths is estimated at 1–2 million per annum. Contributing to this death rate is the particularly high fatality rate of approximately 2% in multiresistant *Plasmodium falciparum* infections [21].

Since the description of the first chloroquine-resistant *P. falciparum* strains in Thailand in 1959 and Columbia in 1960 [16] the problem of resistance has expanded to more than 50 countries [13]. Furthermore, resistance against the majority of currently available antimalarial agents has developed as well, especially in Africa and Southeast Asia. A 1989 study in Thailand reported that the efficacy of chloroquine was almost 0% and that of sulfadoxine/pyrimethamine less than 10%. Quinine as monotherapy had an efficacy of 60% and mefloquine one of not more than 80% [6] (Fig. 1).

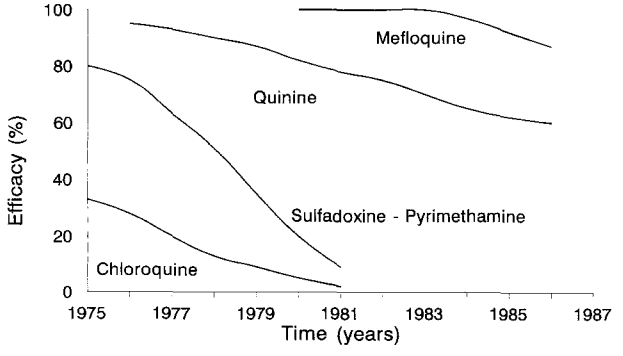

Fig. 1. Increase in resistance to various antimalarials in Thailand (from [6])

In 1986 the established combination of mefloquine with sulfadoxine and pyrimethamine, which had been introduced to delay the evolution of resistance to mefloquine, was effective in 98% of all *P. falciparum* infections. However, in a prospective study conducted in the same area in 1990, the efficacy had already dropped to 71% [14]. This increase in resistance to mefloquine may also increase the resistance to quinine because of structural similarities [24]. Due to this continuously worsening malaria situation there is an urgent need for new and, especially, structurally different antimalarial agents.

Halofantrine

The Walter Reed Army Institute for Research has tested more than 300000 substances within the scope of its antimalarial drug development program; of these, 9000 have shown potential antimalarial activity. Among the substances entering further development was halofantrine, which had been described as (a potential) antimalarial as early as the Second World War [27]. Halofantrine is an amino alcohol and belongs to the class of 9-phenantrenmethanols, which have not yet been used in the treatment of malaria. The risk of cross-resistance to other antimalarials, which in general are aminoquinolones, seems to be minor as the structure of halofantrine is basically different (Fig. 2).

Halofantrine is a blood schizontocide affecting only trophozoites and schizonts in the red blood cells. As with all other blood schizontocides, halofantrine is ineffective against the liver forms of *P. vivax* and *P. ovale*. Thus, additional treatment with a tissue schizontocide such as primaquine is indicated in these infections.

The mechanism of action of halofantrine is not yet completely understood. The substance seems to bind to ferriprotoporphyrin IX in red blood cells affected by plasmodia [3]. Further modes of action which have not yet been observed with other antimalarials may include inhibition of the proton-

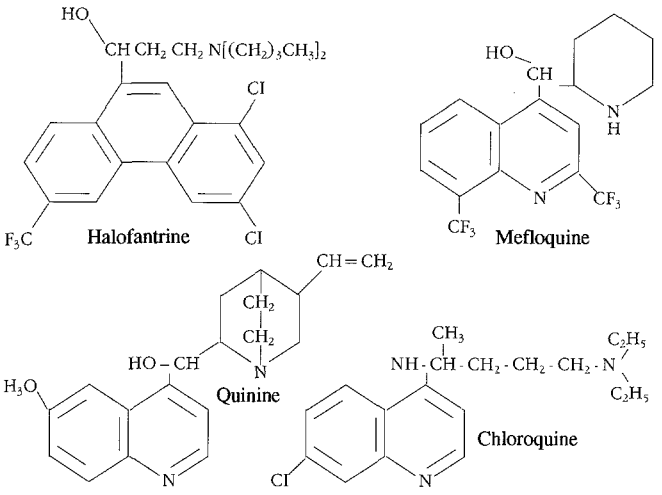

Fig. 2. Structure of various antimalarials

Table 1. In vitro antimalarial activity of drugs against *P. falciparum* isolates from naturally acquired malaria infections in West Africa and Thailand

Mean IC_{50} (ng/ml)				
Country	Chloroquine	Mefloquine	Quinine	Halofantrine
Sierra Leone	4.73	24.50	53.60	3.90
Sierra Leone	6.39	18.71	40.09	3.60
Nigeria	6.91	15.03	40.33	1.26
Nigeria	7.20	11.83	40.80	0.90
Nigeria	8.41	17.06	77.99	4.70
Nigeria	4.73	32.39	91.15	2.40
Sudan	6.39	1.57	10.65	0.33
Indochina	6.91	4.30	90.75	0.45
Thailand[a]	7.20	5.33	165.61	0.68

[a] All cases

pump at the parasite-erythrocyte contact spot [25] as well as an effect on mitochondria and hematozoin vesicles of the *Plasmodium* [17].

The antimalarial efficacy of halofantrine has been demonstrated both in vivo in various rodents and primate species and in vitro. The in vitro tests were performed by determinating the uptake of radioactively labeled hypoxanthine in the erythrocyte stages of chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains. The mean inhibitory concentration for halofantrine was 2.5 and 3.2 ng/ml, respectively, compared to 6.7 and 7.8 ng/ml for mefloquine. For both substances cross-resistance to chloroquine can thus be excluded clinically [20]. The in vitro efficacy of halofantrine has also been verified through clinical isolates of *P. falciparum* cases from Asia and Africa [15, 26] (Table 1).

In vitro comparisons of the mean inhibitory concentrations of halofantrine and mefloquine in 235 clinical *P. falciparum* isolates from various endemic areas did not indicate cross-resistance between the two substances. However, resistance may be induced by incubating *P. falciparum* isolates in increasing mefloquine concentrations. The mean inhibitory concentration of mefloquine thereby increases five fold, whereas the increase with halofantrine is only two fold [20].

Halofantrine is only poorly and incompletely absorbed after oral administration. Although great inter- and intraindividual differences in kinetics are evident, the maximum plasma concentration is consistently reached by about 6 h [5]. Above a single dose of 500–750 mg absorption of the substance does not increase further. Because of this ceiling effect and the great variability in absorption halofantrine cannot be used as single dose. During the dose-finding studies a dosage regime of 3 × 500 mg halofantrine at 6-h intervals was shown to be most effective. However, absorption and pharmacokinetics of halofantrine can be improved with high-fat meals, with the C_{max} being up to six fold [12]. Bioequivalence data of different formulations have revealed that absorption of the suspension is 20% lower than that with tablets and capsules. Again, inter- and intraindividual variations must be taken into account.

The main metabolite of halofantrine is an *N*-desbutylhalofantrine, which also has schizontocidal activity. The elimination half-life of halofantrine is 1–2 days, and that for the equally effective metabolite 3–5 days. Elimination kinetics and especially duration of subtherapeutic substance levels are a major determinant in the development of resistance against antimalarials. Because of the substantially shorter elimination and half-life duration of subtherapeutic levels of halofantrine compared to chloroquine and mefloquine the problem of resistance to halofantrine should be significantly less [1] (Fig. 3). Halofantrine is not suitable for prophylactic use because of its pharmacokinetics, which, again, should delay the development of resistance.

Halofantrine is neither mutagenic nor teratogenic. Because of its embryotoxicity, however, halofantrine is justified during pregnancy only for vital indications and in the absence of an alternative compound. Halofantrine had no negative impact on the major organ systems in the dose ranges tested. Unlike most other antimalarials, halofantrine does especially not interfere with the mechanism of insulin secretion, with the risk of hypogly-

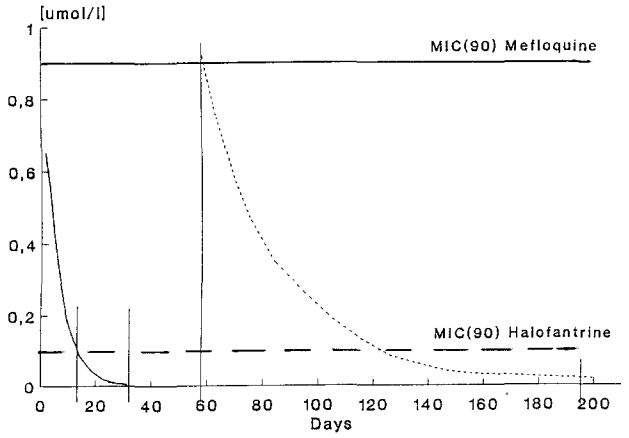

Fig. 3. Pharmacokinetics of mefloquine and halofantrine: duration of subtherapeutic levels. Subtherapeutical Level Halofantrine: Day 13–28; Subtherapeutical Level Mefloquine: Day 57–193. — Halof. + Metab. (C_{max} = 6.4; 0.7) (T0.5 = 38 h; 103 h); --- Mefloquine (C_{max} = 6.0) (T0.5 = 21 d); — Detection Limit

cemic episodes particularly deleterious in cerebral malaria [18].

Studies on halofantrine

Up to now, more than 2000 patients with acute malaria have been treated in clinical studies with halofantrine, 1474 of them according to the optimal dosage scheme of 3 × 500 mg halofantrine at 6-h intervals. Approximately 20% of the patients were children below the age of 5 years. These studies were conducted between 1985 and 1990 mainly in West and East Africa, Southeast Asia, and the Pacific area, thus in areas with high chloroquine and multidrug resistance [9].

Of the 1474 patients 1315 were infected with *P. falciparum*, 122 with *P. vivax*, and the rest with *P. ovale*, *P. malariae* or mixed infections. Included in the studies were patients with a parasite count between 1000 nd 250000 parasites/cm^2. Exclusion criteria were severe or complicated malaria such as cerebral malaria, acute renal failure, acute liver failure, protracted vomiting, pregnancy, and pretreatment with another antimalarial within the previous 14 days. For each study local ethical review committee approval had been obtained; patients gave written or oral, witnessed, informed consent prior to study entry. Parasitemia was cleared within 7 days in all but eight patients (0.5%). The mean fever clearance time was 50.2 h for *P. falciparum* and 49.6 h for *P. vivax* infections. The mean parasite clearance time was 57.9 h and 57.3 h, respectively.

During the observation period of 28 days, the recrudescence of *P. falciparum* parasitemia occurred in 77 patients (6%), mainly nonimmune persons or infants below the age of 2 years. However, it cannot be excluded that some of these parasitemias were in fact new infections, as permanent isolation of the patients over 28 days was practically impossible. In *P. vivax* malaria six recrudescences occurred (5.4%). Thus, the overall efficacy of *halofantrine* for treatment of acute malaria can be considered at least 94%, even in areas with unfavorable resistance and high transmission rate.

Halofantrine was in general well tolerated. Fewer than 5% of the patients experienced mild and transitory diarrhea or irritation of the intestinal tract. Rare events included cough itching, and headache. Laboratory abnormalities such as anemia, thrombocytopenia, and increased transaminases at study entry were considered disease – but not drug – related by the investigators and normalized in parallel to the improvement of the clinical condition. Central nervous symptoms, seizures, or psychotic episodes were not observed in any of the patients during the halofantrine treatment.

Preexisting immunity is one of the major determinants of the therapeutic efficacy of antimalarials. Thus, efficacy in nonimmune patients cannot be deduced from efficacy in the semi-immune [7]. This explains, for example, the higher recrudescence rate in infants, who by definition are considered non-immune.

To evaluate the efficacy of halofantrine in nonimmune individuals we performed a prospective clinical trial in five German institutions specializing in tropical diseases. Included were nonimmune travelers who developed acute malaria after returning from endemic areas with a parasite count of up to 5%. Two different treatments were compared: patients of group A received 3 × 500 mg halofantrine at 6-h intervals on the day of study entry and patients of group B received a second treatment, with the same dosage, 7 days later. We included 80 patients with imported *P. falciparum* or *P. vivax* malaria. In more than half of these patients malaria occurred despite prophylaxis with chloroquine, proguanil, or mefloquine. Halofantrine cleared parasitemia in all 80 patients. The clearance time was 53 h and parasite clearance time 65 h. However, recrudescense occurred in 3 of 27 patients in group A (11%) whereas in group B none of the 53 patients developed further episodes of parasitemia [11]. Similar observations were made in a Swiss study with a similar protocol [4] as well as in two French trials [2, 19].

Thus, in nonimmune patients, in whom the majority of imported malaria cases occur in Europe, a secondary treatment course with 3×500 mg halofantrine on day 7 is indicated in addition to the primary therapy on day 1.

Stand-by therapy

The worldwide increase in antimalarial drug resistance represents a major problem for the increasing tourism to endemic areas. The malaria incidence in nonimmune travelers to endemic areas – for instance in more than 2 million Germans in 1988 [30] – is higher than expected. When traveling to West Africa, the incidence without chemoprophylaxis is as high as 2.4 cases of clinical disease per 100 travelers per month. A survey of more than 11000 travelers to endemic areas indicated that, although most of the travelers were informed about the risk of malaria at their destination, only 55% carried out correct and consequent malaria chemoprophylaxis, and less than 5% correct and consequent exposure prophylaxis [23].

The World Health Organization explicity states that even with correctly performed chemoprophylaxis, complete protection against malaria is not guaranteed [29]. This is especially true for stays in areas with multiple resistance and high transmission rate. In a recent study by the Centers for Disease Control the monthly incidence of *P. falciparum* infection despite correct chloroquine prophylaxis accounted for 2.7 cases per 100 per month in peace corps volunteers in West Africa. Despite consequent mefloquine prophylaxis at biweekly intervals 1/100 nonimmune persons developed acute malaria [10]. In addition, all antimalarials used for chemoprophylaxis are known to induce adverse events in up to 7–45% of travelers, which consequently leads to poor compliance and less protection [22].

Thus, the World Health Organization recommends for the malaria areas B and C that persons take along a curative dose of an antimalarial [29]. The major element of this stand-by concept of the World Health Organization is that travelers to endemic areas carry out a consequent exposure prophylaxis, including the use of impregnated mosquito nets, mosquite repellants, mosquito coils, and appropriate clothing (long sleeves and trousers) [8]. If in spite of these precautionary measures symptoms of malaria occur within 7 days of arrival, and a physician is not immediately available, travelers should take one curative dose of the stand-by drug as self-medication to avoid delaying the start of treatment. In every case, however, a physician must be consulted as soon as possible for confirmation of diagnosis and for possible further treatment. The antimalarial used as stand-by drug must be effective against all forms of malaria, have a low failure rate and a short fever and parasite clearance time, and above all be well tolerated. This is especially important with regard to possible misdiagnosis, as patients may not come to harm by the self-medication. As halofantrine fulfills these requirements, the Working Group on malaria prophylaxis and therapy of the German Society for Tropical Medicine recommends and the Bundesgesundheitsamt (Federal Health Authority) approves halofantrine as first drug for stand-by treatment of acute malaria [8].

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