The Treatment of Animal Models of Malaria with Iron Chelators by Use of a Novel Polymeric Device for Slow Drug Release

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Accepted for publication February 4, 1997

ABSTRACT

The hydrophilic desferrioxamine (DFO) and the lipophilic salicylaldehyde isonicotinoyl hydrazone (SIH) are iron chelators which inhibit in vitro proliferation of Plasmodium falciparum with similar potency (IC_{50} ~20 \mu M in 24- to 48-h tests). The in vivo assessment of these drugs was performed on Swiss mice infected with Plasmodium vinckei petteri with novel modes of drug administration and release. The drugs were delivered postaptently either by multiple i.p. injections or by a single i.p. or s.c. insertion of a drug-containing polymeric device which released most of the drug within 7 days at apparently first-order rates. A regimen of three daily i.p. injections of 5 mg DFO for 3 consecutive days or a 70-mg dose of the drug given as an i.p. or s.c. polymer implant evoked similar delay and reduction in peak parasitemias and reduced mortality with no apparent signs of toxicity. Relatively faster, but otherwise similar results were obtained with the less hydrophilic SIH. In combination, the two drugs apparently potentiated each other. The polymeric devices were particularly useful for treating Plasmodium berghei K173-infected C57Bl/6 mice, a suggested model of cerebral malaria, in which classical methods of DFO delivery were ineffective. The insertion of a 140-mg DFO-containing device on day 6 postinfection (parasitemia ~1%) led to a marked reduction in parasite proliferation, appearance of neurological sequelae and mortality of mice. Our studies indicate that polymeric devices for slow drug release might be highly advantageous for both hydrophilic and lipophilic drugs whose antimalarial efficacy might depend on the maintenance of sustained blood levels. The results obtained with slow-release devices have implications for malaria chemotherapy as well as for iron chelation therapy in iron overload conditions.

Resistance of Plasmodium falciparum to chloroquine, quinine, sulfadoxine, pyrimethamine and mefloquine has created an urgent need for new drugs which are effective against multidrug-resistant strains of malaria (Peters, 1990). Strategies to overcome resistance have relied on the application of drugs of different chemical character and mode of action (Vennerstrom et al., 1991), including iron-chelating agents (reviewed in Cabantchik et al., 1986; Gordeuk et al., 1994). At present the only iron-chelating drug approved for human treatment is DFO, of which the parenteral administration and release. The drugs were delivered postaptently either by multiple i.p. injections or by a single i.p. or s.c. insertion of a drug-containing polymeric device which released most of the drug within 7 days at apparently first-order rates. A regimen of three daily i.p. injections of 5 mg DFO for 3 consecutive days or a 70-mg dose of the drug given as an i.p. or s.c. polymer implant evoked similar delay and reduction in peak parasitemias and reduced mortality with no apparent signs of toxicity. Relatively faster, but otherwise similar results were obtained with the less hydrophilic SIH. In combination, the two drugs apparently potentiated each other. The polymeric devices were particularly useful for treating Plasmodium berghei K173-infected C57Bl/6 mice, a suggested model of cerebral malaria, in which classical methods of DFO delivery were ineffective. The insertion of a 140-mg DFO-containing device on day 6 postinfection (parasitemia ~1%) led to a marked reduction in parasite proliferation, appearance of neurological sequelae and mortality of mice. Our studies indicate that polymeric devices for slow drug release might be highly advantageous for both hydrophilic and lipophilic drugs whose antimalarial efficacy might depend on the maintenance of sustained blood levels. The results obtained with slow-release devices have implications for malaria chemotherapy as well as for iron chelation therapy in iron overload conditions.

Received for publication August 13, 1996.

This work was supported in part by the National Institutes of Health, grant AI20342 (Z.I.C.) and by the Authority for Research and Development of the Hebrew University (J.G.). Plasmodium vinckei petteri was obtained from Prof. L. Leclerc from Pasteur Institute, Paris.

ABBREVIATIONS: CM, cerebral malaria; DFO, desferrioxamine; DMSC, dimethyl sulfoxide; poly(FAD-SA), poly (dimer erucic acid-co-sebacic acid, 22:78); PSA, poly sebacic anhydride; SIH, salicylaldehyde isonicotinoyl hydrazone; PBS, phosphate-buffered saline.

Printed in U.S.A. Vol. 281, No. 3
tion of cleavable groups for augmenting intracellular drug retention and attaining more persistent cytotoxic effects (Capantchik et al., 1996; Tsafack et al., 1996a). Although fast speed of action and persistent inhibition are conferred to drugs by apparently opposite chemical properties, they can be accomplished by use of permeant lipophilic prodrugs which produce intracellular imperative hydrophilic drugs (Tsafack et al., 1996a). However, a major drawback of lipophilic drugs is their poor water solubility, which might limit their in vivo application. An alternative and versatile means of drug administration to animals is based on polymers into which lipophilic or hydrophilic drugs can be encapsulated and released in a controlled fashion (Chasin et al., 1990). Those polymers whose degradation products are both nontoxic and can be completely eliminated from the circulation are particularly useful because they serve both as a safe delivery system and as a vehicle for antimalarial drugs. In vivo, slow-release devices for the antifolate pyrimethamine in rodent malaria are parasite sequestration (MacPherson et al., 1986; Curfs et al., 1989; Eling and Sauerwein, 1995). However, the hallmark of CM in human malaria is parasite sequestration (MacPherson et al., 1985), a property which has also been described recently in a rodent model (Kaul et al., 1994). The chelators were assessed as therapeutic agents via two modes of administration: by multiple i.p. injections and by s.c. or i.p. insertion of a single dose of drug (or combination of drugs) which was encapsulated into biodegradable polymers. The latter were found to be convenient, safe and efficient vehicles for antimalarial drug delivery.

Materials and Methods

Iron Chelators

SIH was prepared as described elsewhere (Baker et al., 1962) and DFO was purchased from Ciba Geigy (Basel, Switzerland) as Desferal.

Animal Models of Malaria

Two plasmodial strains that cause malaria in mice were used: 1) P. vinckei petteri in Swiss mice (females, 35–45 g, 10–12 weeks old) and 2) P. berghei K173 in C57Bl mice (same sex and age) which display neurological disorders. The mice were infected with parasitaemia by i.p. injection of infected blood (diluted with saline) from donor animals in which parasites were maintained by weekly transfer of infected blood. The parasitaemias and body temperatures were measured. A correlation was found between decrease in body temperature (below 30°C) within approximately 24 h before death in the second week and the presence of lesions in the brain as determined post mortem (Polder et al., 1992; Eling and Sauerwein, 1995).

Parasite Development

Parasitaemias were assessed by use of Giemsa-stained blood smears.

Drug Delivery Systems

Devices containing DFO. We used matrices of a bioerodible polymer, poly(FAD-SAA), that releases DFO in vitro for 7 days with first-order kinetics. The matrices were designed to obtain a similar in vitro release profiles for all screened drugs. The matrices used undergo in vivo degradation and elimination within 6 weeks after release of the drugs (Domb et al., 1995). They were prepared first by melting the polymer on a hot plate at 70°C, removing it from the plate and mixing quickly with the drug powder (30–40% by weight). The mixture was then pressed between two metal plates to obtain a film of the appropriate thickness (2 mm) and the polymer was cut to obtain the desired dose. In vitro slow-release tests of the drugs were performed by placing the polymer tablet in 20 ml PBS (0.1 M, pH 7.4) and incubating it at 37°C. The solution, which was replaced daily, was used for drug determination by UV-visible absorption of the iron-hydroxamate complex (at 420 nm) after addition of excess FeCl3. The polymer itself was estimated according to its dry weight.

Devices containing SIH. SIH (100 mg) was dissolved in 2.5 ml of DMSO and added to the polymer solution (114 mg polyethylene glycol 4000, 320 mg PSA and 22.8 mg Tween 80 in 8 ml chloroform). The mixture was stirred thoroughly, the solvents were evaporated by vacuum. Another 160 mg of PSA was added, the mixture was melted with a rotavaporator and traces of DMSO were vaporized with high vacuum. Another 160 mg of PSA was added, the mixture was melted at 80–70°C for complete mixing and was allowed to stand overnight to form tablets of 97.5 mg (about 2 × 3 × 5 mm). Devices loaded with different amounts of SIH were produced similarly by use of proportional amounts of the ingredients. SIH released from the polymer was monitored by placing each polymer sample in 20 ml PBS at 37°C

Fig. 1. Cumulative release of DFO (upper) or SIH (lower) from polymers into salt solutions. The polymers poly(FAD-SAA) contained 30 or 40% DFO or 30% SIH and the indicated amounts of the drugs.
and determining the amount released into the PBS by UV absorption at 333 nm.

The matrices containing given amounts of drug were implanted s.c. or i.p. in infected mice. The devices were dipped in 70% ethanol for sterilization and inserted through an incision in the lower abdominal region of ether-anesthetized mice. The implanted devices were retrieved from the implant site of some of the treated animals, and the drug content was quantified to determine total drug release (Domb, 1994).

**Experimental Design**

Chelators were either injected at a frequency of three times a day for 2 or 3 consecutive days, or administered as polymeric devices on day 2, 3 or 4 after infection. Each experiment was performed at least three times (usually with 5–6 mice/group). Statistical analysis was conducted for each individual experiment. This approach was adapted because of variability between results obtained in different experiments caused by variations inherent in the biological systems. These include mice and experimental factors, such as the stage in the life cycle of the plasmodia in the infective inoculum. However, all individual experiments lead to the same qualitative conclusions. Consequently, we depicted a graphically representative set of results for each type of experiment and conducted statistical evaluation of two parameters: the parasitemia 2 days after drug administration (decreased values indicate a delay in parasite development) and the highest value of parasitemia (peak parasitemia). Significance is defined in terms of α(2), the two paired probability according to Mann-Whitney’s test (with values above .05 indicating no statistically significant difference between experimental and control groups).
Mice that recovered from malaria were followed for an additional month to monitor possible recurrence of parasitemia. In some experiments, mice were challenged after this period with viable plasmodia to assess the acquisition of immunity.

**Results**

*In vitro* release of DFO and SIH. The iron chelators used for these studies were selected on the basis of their performance as growth inhibitors in *in vitro* cultures (Tsafack *et al.*, 1996b). A series of preliminary experiments were conducted to evaluate the *in vitro* release of the iron chelators from drug-loaded polymers of poly(FAD-SA). The two factors considered were drug dose and the weight ratio of drug/polymer which determine the rate of drug release. The higher the ratio of the hydrophilic drug to the polymer, the faster the release of drug, and *vice versa*, for lipophilic drugs (Domb, 1994). Different doses of drug were obtained by weighing a given preparation of the drug-containing polymer. Figure 1 displays the cumulative drug-release profiles for various drug/polymer formulations. Although a 30% DFO-containing polymer (wt/wt) released the 70-mg dose continuously during a 7-day period, a 40% polymer containing the same DFO dose released the drug at about 25% faster speed during the first 2 days (fig. 1A). We selected the 40% polymers for all the reported studies with animals. The release of the lipophilic SIH from 40% polymers was linear for the first 3 days for the various doses used (5–50 mg). In a 6-day period, 65 to 95% of the drug was released from the polymers which were selected for further experiments (above 20 mg, fig. 1B). The experiments were performed in triplicates and...
repeated at least three times. For each individual experiment the standard deviation exceeded no more than 10% of the mean value.

**In vivo effects of DFO.** The effects of DFO on an animal model of malaria were assessed in relation to the mode of administration: i.p. injections of DFO (fig. 2A) and s.c. or i.p. implants of the polymer containing DFO (fig. 2B). Swiss mice infected with *P. vinckei petteri* (3 x 10^6 parasitized erythrocytes) by i.p. injection of infected blood were treated starting from day 2 postinfection, at which point the first parasites were detected in peripheral blood (parasitemia = 0.01%, herewith defined as onset of patency). The treatment comprised either i.p. injections of DFO (2.5- or 5-mg DFO doses in 50 μl saline, three times per day for 3 days) or a single s.c. insertion of the drug-containing device. Analysis of a dose-response profile of the injected DFO revealed that although 2.5 mg doses were ineffective, 5-mg doses led to marked reduction in parasitemias and total elimination of mortality. A peculiar feature displayed by some animals treated with 2.5 mg DFO was an unexplained death at 3 to 5 days after cessation of treatment and after a demonstrable clearance of parasites from the peripheral blood (fig. 2A). The s.c. insertion of a single polymeric tablet containing 70 or 140 mg DFO also conferred protection to infected mice (fig. 2B). This was manifested as a reduction in parasitemia, a delay in peak parasitemia and a reduction in mortality. After peak parasitemia, there was an abrupt clearance of parasites in DFO-treated animals, as manifested by the parasitemias. The presence of the polymer, with or without drug, was apparently well tolerated by the mice and there were no indications of adverse reactions or toxicity. The antimalarial effect of the DFO tablet was essentially identical whether the polymer was inserted s.c. or i.p. (data not shown).

**In vivo effects of SIH.** A dose-response effect was obtained after SIH i.p. injections three times per day for only 2 days. Additional i.p. injections of SIH were generally avoided, particularly with relatively high doses of drug, because of toxic and occasional lethal effects of prolonged treatments. Although 2-mg SIH injections (in DMSO, 50 μl) had virtually no effect on the course of the infection, 4-mg injections (in DMSO, 50 μl) produced a fast attenuation of the infection and prevented death in most of the animals (fig. 3A). It should be noted that although SIH was initially dissolved in DMSO for injection into animals, the SIH-containing polymer was rendered mostly free of DMSO. A result analogous to that produced by DFO was obtained with polymeric inserts of SIH. The drug released from a single 36-mg SIH-polymer insert significantly delayed the parasite infection, and most of the animals survived at a dose of 65 mg (fig. 3B). The data shown in figures 2 and 3 revealed similar performances of DFO and SIH. This includes also an abrupt decrease in parasite survival after reaching peak parasitemia values. However, a closer inspection of the data obtained during the first 2 days of treatment which started at patency (when parasitemia was about 0.01%) reveals a marked difference in the onset of inhibition of parasite proliferation by both drugs (table 1). The treatment, which commenced 2 days after infection, included multiple injections of either SIH (3 x 2 mg/mouse/day) or DFO (3 x 2.5 mg/mouse/day) or implants of SIH (35 mg) or DFO (70 mg). Although the dose of SIH was relatively lower or equal to that of DFO, at day 3 of infection (day 1 of treatment), the inhibition of parasite proliferation was already 60% and 72% for SIH administered by injection and by polymer implants, respectively, whereas for DFO the values were 15 and 29%, respectively. At day 4, SIH was still more effective than DFO when given by injection, but equally effective when given by polymer. It should be stressed that the speed of action of SIH was faster despite the fact that it was used at relatively lower iron-chelating doses than DFO, because DFO binds iron at 1:1 stoichiometry whereas SIH binds it at 2:1 stoichiometry (Baker et al., 1992).

To further assess the efficacy of the antimalarial treatment in controlling progression of the disease, we examined the polymer-drug implants on animals that had reached fulminating stages of infection, that is at 1% and 9.5% parasitemia. The results shown in figure 4 indicate that both DFO (70 mg) and SIH (35 mg) were demonstrably effective in attenuating parasite proliferation and reducing mortality of infected animals even at a late stage of the infection. At the relatively lower dose (35 mg SIH vs. 70 mg DFO), SIH gave better protection than DFO, particularly when applied at high (9.5%) parasitemia. However, it should be emphasized that the two agents could not be assessed at the same concentration, either because DFO was inefficient at doses <50 mg/implant, or because of SIH apparent toxicity at doses >50 mg/implant.

**Combined in vivo action of DFO and SIH.** A combination of DFO and SIH added in separate polymers was examined and compared with the individual effects of the two drugs. A 50-mg DFO dose had only a minor effect on the course of infection, whereas a 20-mg SIH dose significantly attenuated it and reduced mortality. However, the combination of the two drugs had a more pronounced effect, particularly in preventing mortality (fig. 5).

**Effect of DFO on a rodent model of CM.** The effect of a DFO-containing polymer was also examined on C57Bl mice infected with *P. berghei k177*. The treatment commenced at day 6 postinfection, when parasitemias reached about 1%. Preliminary studies indicated that administration of DFO by injection (up to 12 mg x 3 days/5 days) was ineffective in changing the course of the disease (not shown). However, increased drug levels were associated with toxicity. Table 1 shows that for a given infection regimen, either DFO or SIH starting at day 2 postinfection (P < 0.01%) as follows: DFO injections were given i.p. in saline at a dose of 2.5 mg/mouse for 3 days, three times daily (8 h apart) (control = saline only). SIH injections were given in DMSO for 2 days (2 mg/mouse, same regimen as DFO) (control = DMSO only). Polymers (40%) containing either 70 mg DFO or 35 mg SIH were implanted s.c. on day 2 postinfection. Each group of treatment consisted of 10 infected mice, 5 control and 5 treated. P = average % parasitemias (S.E. values were <10%). The inhibition of growth was significantly higher (P < 0.05) for SIH- relative to DFO- treated mice on day 3 (both by injection and by polymer implant: 72% vs. 28% and 60% vs. 16%, respectively) and on day 4 (only by injection: 73% vs. 14%).

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<th>Drug Treatment of Parasitemia</th>
<th>i.p. injection</th>
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<td>Control P</td>
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<tr>
<td>DFO P</td>
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<tr>
<td>% inhibition</td>
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<tr>
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<td>17.5</td>
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<tr>
<td>SIH P</td>
<td>2.2</td>
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<td>% inhibition</td>
<td>60</td>
<td>73</td>
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animals treated with s.c. inserts of polymers containing 140 mg DFO had a significant reduction in parasitemia and relief from CM symptoms (table 2).

**Recurrence of parasitemias in polymer-treated mice.** Mice which recovered after treatment (about 2 weeks after infection, figs. 2–5) were observed for an additional month to monitor possible recurrence of disease. Blood smear examinations (twice a week) revealed no parasites. These mice were challenged after this period with $20 \times 10^6$ parasitized erythrocytes and did not show any parasitemias over a further 2 weeks. This experiment was repeated twice with mice from all the experimental groups, including convalescent mice from control groups. Typical high parasitemias and mortality were demonstrated in control mice which had not been previously exposed to malaria.

**Discussion**

The demand for new chemotherapeutic strategies for the treatment of malaria has increased with the widening spread of parasite drug resistance. This is demonstrated in the case of mefloquine, which is widely used for the treatment of malaria and is the prophylactic drug of choice (Wallace *et al*., 1996). Strategies to overcome resistance have relied on the application of single or pairs of drugs of either different chemical character and mode of action (Vennerstrom *et al*., 1991) or similar mode of action but different cytotoxicity for the various stages of parasite growth. The latter strategy was used primarily with iron chelators in combination with DFO (Golenser *et al*., 1995; Tsafack *et al*., 1995; Cabantchik *et al*., 1996), a clinically approved agent that can only be given...
For animal chemotherapy of malaria based on iron chelators, we considered four factors which might affect the efficacy of the treatment: 1) the proven in vitro record of the drug, such as speed of action and wide action profiles on all blood stages of parasite development; 2) the possibility of parenteral drug treatment based on a single drug application; 3) the possibility of attaining sustained blood levels of the drug by slow-drug release devices; and 4) possible synergistic effects of combination of drugs. The most effective antimalarial iron chelators we have tested in vitro were reversed siderophores of high lipophilic character (Lytton et al., 1994), particularly when used in combination with the hydrophilic DFO (Golenser et al., 1995; Tsafack et al., 1996b). However, the poor aqueous solubility of lipophilic agents limited their animal usefulness because of the need for repeated injections and the mode of action of both types of agents which demanded extended exposure of the parasites. Both limitations could be overcome by use of polymers as possible carriers of lipophilic and hydrophilic drugs and as slow drug release devices.

The polymers we considered were (Domb, 1994; Domb et al., 1995): 1) biodegradable, whose products are eliminated from the organism; 2) implantable as drug carriers (e.g., polysilicones, ethylene-vinyl acetate copolymers, various acrylate-based hydrogels and segmented polyurethane) or as cleavable drug-polymer conjugates; 3) nontoxic, both locally and systemically. Other considerations given were drug loading and uniformity, duration and rate of drug release, pharmacokinetics of polymer degradation products, route of administration, drug stability in the polymer, storage stability and a possibility of terminal sterilization (by γ-irradiation). The selected polymers used were composed of sebacic acid and a dimer of erucic acid, linked by hydrolyzable anhydride bonds. They were produced as s.c. or i.p. implantable tablets, although they can be formulated as injectable microspheres or small pellet inserts (Domb and Maniar, 1993). The test

TABLE 2
Effect of DFO-polymer implants on parasitemia and CM symptoms in a rodent CM model of malaria
Day refers to time after infection (treatment was initiated on day 6; a s.c. implant of DFO (140 mg drug, 40% polymer). P = percent parasitemia; T = body temperature; S = mice survival; ND = not determined.

<table>
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<tr>
<th>Day 8</th>
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<tr>
<td>DFO</td>
<td>7</td>
<td>35.4</td>
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Fig. 5. The effects of SIH, DFO and their combination, administered as polymer implants on *P. vinckei petteri* infections in Swiss mice. Polymers were inserted 2 days after infection, at which point parasitemia was 0.01%. Each line represents parasitemia of a single mouse.
iron chelators selected for this study were the lipophilic SIH and the hydrophilic DFO. The results indicated that the drug-containing tablets fulfilled the above-stated requirements in terms of sterility, lack of toxicity and slow-release properties, which were apparently dictated by the relative amount of drug in the polymer (Domb, 1994). With the hydrophilic DFO, the higher its relative content in the polymer, the higher the overall hydrophilicity of the device and the speed of drug release (fig. 1A). The converse was apparently the case with the lipophilic SIH, as shown in figure IB.

In tests performed in Swiss mice infected with P. vinckei petteri, the polymers containing 70 mg DFO or 65 mg SIH gave results similar to those of three i.p. injections/day/3 days of 5 mg DFO (a total of 45 mg DFO) or three injections/day/2 days of 4 mg SIH (a total of 24 mg SIH) (figs. 2 and 3). These were manifested in delay of peak parasitemia and the lower mortality. Although at comparable polymeric doses, SIH outperformed DFO in terms of speed of action (table 1), the overall performance of both drugs in reducing parasite load and mortality was similar (figs. 2 and 3). Both SIH and DFO polymer insertions were effective even when the initial parasitemias were as high as 9.5% (fig. 4). Combinations of the iron chelators should be considered because they were more efficient than the individual polymers in reducing mortality (fig. 5).

The effect of slow release of iron chelators was also examined on a CM model in mice infected with P. berghei highly resistant to DFO. Six days postinfection, when parasitemias were about 1%, the animals were treated by s.c. insertion of tablets containing 140 mg DFO. The treatments reduced parasitemias and also prevented CM symptoms in most of the mice, whereas repeated injections of DFO were ineffective in this model.

The rapid clearance of parasites from chelator-treated animals that have reached relatively high parasitemia might be indicative of an improved clearance of parasites by the reticuloendothelial system. Such action might be the result of chelator-mediated reduction of toxic iron load which is generated by phagocytosis of infected cells and which might hamper macrophage activities (Schwarz et al., 1992). Thus, this mode of chelator action should be added to the proposed modes of action of iron chelators as antimalarials. These have been focused either on chelator action on intraerythrocytic parasites (reviewed in Gordeuk, 1994; Cabantchik 1994; Cabantchik et al., 1996) or in the prevention of pathological iron-dependent processes (Hunt et al., 1992; Golenser and Chevion, 1994; Mabeza et al., 1996). Drug treatment may affect the course of the disease directly by killing the plasmodia and indirectly by altering the immune responses (e.g., by changing cytokine response). Recent retrospective clinical studies support the notion of a possible iron chelator action on immune cell responses (Thuma et al., 1996). This also strengthens the suggestion that chemotherapy should be complementary to vaccination (Tanner and Evans, 1994).

Taking in toto the results of this study and the clinical record of DFO (Gordeuk et al., 1994; Mabeza et al., 1996), we propose that iron chelators delivered by slow-release polymeric devices can be advantageous for malaria therapy. They can be particularly useful when used as combinations of drugs that display different speeds of action. Moreover, similar parenteral treatments might be also applicable to iron-overloaded individuals that require frequent iron chelation therapy (Olivieri et al., 1995; Porter, 1996).

Acknowledgments

We acknowledge the technical assistance of C.C. Hermens from the University of Nijmegen.

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