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Thuma, Philip; Olivieri, N. F.; Mabeza, G. F.; Biemba, G.; Parry, D.; Zulu, S.; Fassos, F. F.; McClelland, R. A.; Koren, G.; Brittenham, G. M.; and Gordeuk, V. R., "Assessment of the Effect of the Oral Iron Chelator Deferiprone on Asymptomatic Plasmodium Falciparum Parasitemia in Humans" (1998). *Biology Educator Scholarship*. 160.

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ASSESSMENT OF THE EFFECT OF THE ORAL IRON CHELATOR DEFERIPRONE ON ASYMPTOMATIC *PLASMODIUM FALCIPARUM* PARASITEMIA IN HUMANS

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Abstract. While the parenteral iron-chelating agent desferrioxamine B has anti-malarial activity in humans, the usefulness of an orally active chelator for this indication has not been investigated previously in vivo. We conducted a prospective, double-blind, placebo-controlled, cross-over trial of deferiprone (L1; CP20; 1,2-dimethyl-3-hydroxypyridin-4-one) in 25 adult Zambians with asymptomatic *Plasmodium falciparum* parasitemia. Deferiprone was administered daily for three or four days in divided doses of 75 or 100 mg/kg of body weight, dosages that are effective for treating iron overload. No reduction in asexual intra-erythrocytic parasites was observed during or after deferiprone treatment. The mean peak plasma concentration of deferiprone ($108.9 \pm 24.9 \mu\text{mol/L}$) achieved was within the range demonstrated to inhibit the growth of *P. falciparum* in vitro, but the systemic exposure as determined by the 24-hr plasma concentration-time curve would not be predicted inhibit growth in vivo. No evidence of deferiprone-associated hematological toxicity was noted in this short-term study of these subjects, all of whom had clinical evidence of normal body iron stores. Because of the risk of neutropenia and other adverse effects with higher doses or prolonged use of the chelator, additional trials of deferiprone as a sole anti-malarial agent would not seem to be justified. In contrast, further efforts are needed to develop other orally active iron-chelating agents specifically for their anti-malarial action.

Malaria remains a major hazard to the health of people in the developing world, and the emergence of strains of *Plasmodium falciparum* that are resistant to existing anti-malarial drugs emphasizes the importance of the development of new therapeutic approaches. Iron-chelating drugs inhibit the growth of the erythrocytic phase of *P. falciparum* in vitro as well as in experimental animals.^{1,2} Recent studies in humans have shown that, as a single agent, the iron-chelating drug desferrioxamine B enhances parasite clearance and reduces symptoms in adults with mild-to-moderate *P. falciparum* malaria.³⁻⁵ Furthermore, when given together with quinine, desferrioxamine B increases the rate of recovery of full consciousness and of parasite clearance in children with cerebral malaria.⁶ While desferrioxamine B has anti-malarial activity in humans, it is not the ideal iron-chelating agent for use in malaria. The rate of penetration of desferrioxamine B into the parasitized erythrocyte is slow,⁷ the absorption from the gastrointestinal tract is poor, necessitating parenteral therapy, and the half-life in the circulation is short, requiring continuous administration for optimal effectiveness.⁸ Due to these considerations, efforts to investigate the anti-malarial effect of new, orally active iron-chelators appear to be indicated.

The orally active iron-chelating agent, deferiprone (L1; CP20; 1,2-dimethyl-3-hydroxypyridin-4-one) has been used in human trials for the treatment of transfusional iron overload.⁹ When deferiprone is administered to iron-loaded patients in divided doses three times daily of 75 mg/kg/day, peak serum concentrations of 94–125 $\mu\text{mol/L}$ are achieved.¹⁰ Deferiprone also has activity against *P. falciparum*. Continuous exposure to deferiprone concentrations in the range of 5–100 $\mu\text{mol/L}$ has resulted in 52–100% inhibition of the growth of *P. falciparum* cultured in erythrocytes in vitro.¹¹⁻¹³

While these studies suggest that the administration of deferiprone to humans at doses currently used in trials in patients with iron overload might produce an anti-malarial ef-

fect, the results of the single reported study of deferiprone treatment of malaria in animals proved to be negative. A deferiprone dose of 300 mg/kg/day in three divided doses administered intraperitoneally for 13 days did not suppress *P. berghei* infection in six female Wistar rats.¹¹ The lack of effectiveness of deferiprone in this animal model, as compared with the studies in vitro, was attributed to the intermittent attainment of effective anti-malarial plasma concentrations. The relatively low lipophilicity of deferiprone, compared with other hydroxypyridinones, may have limited access to the intra-erythrocytic parasite under these circumstances.¹¹ Because the pharmacokinetics of deferiprone in humans would be expected to differ substantially from those in rats and because deferiprone is an orally active iron-chelating agent with a record of investigational clinical use in humans, we wished to determine if the oral administration of this agent had an effect on parasitemia in humans. While effective anti-malarial concentrations might be achieved only intermittently, we postulated that the chelator might nonetheless affect the balance of plasmodial growth and lead to a reduction in parasitemia in semi-immune adults living in an endemic area.

SUBJECTS AND METHODS

Approval for the study was obtained from the Ethics and Research Committee of the University of Zambia School of Medicine, and the Clinical Investigation Committees of both Pennsylvania State University College of Medicine and The Hospital for Sick Children in Toronto, Canada. The study was conducted between September and December 1993 at the Macha Mission Hospital in southern Zambia, an area where malaria is highly endemic, where R3 chloroquine resistance is a known problem, and where the intensity of clinically symptomatic malaria is highest during the rainy season from November through April. During the other months of

the year, many residents have low levels of parasitemia with no signs or symptoms of acute malarial infection and are considered to be semi-immune to malaria. This trial was designed to detect at least an 80% reduction in parasitemia in the treatment group as compared with the placebo group.

Preparation of deferiprone and placebo. Deferiprone was synthesized at the University of Toronto Lash Miller Laboratories by the direct reaction in aqueous solution of methylamine and the natural plant product maltol or ethyl maltol in a one step process.¹⁴ Assurance of 99% purity was established as previously described.¹⁰ Capsules containing 300 mg of deferiprone were prepared by Novopharm, Ltd. (Toronto, Canada). Identical placebo capsules containing only starch were prepared by the Department of Pharmacy at The Hospital for Sick Children, (Toronto, Canada).

Subjects. Healthy asymptomatic adult male volunteers more than 18 years of age were screened for the presence of *P. falciparum* parasites by obtaining thick blood smears from a peripheral blood sample and staining with Giemsa; those having asexual forms of the parasite were invited to participate. Informed consent was obtained from all individuals who took part in the study. A medical history was obtained and a physical examination was performed. Baseline laboratory studies performed on each individual included a full blood count, blood glucose, and urinalysis. A total of 31 individuals were enrolled, and the study was carried out in three parts.

Pharmacokinetics. Six subjects were enrolled in the pharmacokinetic study, but one was removed after 24 hr because of very low parasite counts. The remaining five individuals were given 75 mg/kg/day of deferiprone divided into doses given every 8 hr for 72 hr. The subjects took no food for 1.5 hr before or after ingesting the study drug. They were kept in an inpatient facility. A thick blood smear was obtained for estimation of parasites every 8 hr and a full blood count was performed daily.

Pharmacokinetic studies on plasma and urine were carried out. Three of the subjects were studied after receiving three doses (24 hr) of therapy while two of the subjects were studied after receiving only two doses (16 hr) of therapy. Venous blood was drawn into a vacutainer containing lithium heparin just before the next dose was due and labeled as Time 0. The next deferiprone dose was then taken by the subjects, and further venous blood samples were obtained in lithium heparin vacutainers at 30-min intervals up to 2 hr and then hourly intervals at intervals up to 8 hr after the dose. The blood was centrifuged immediately after collection, and the plasma was frozen at -70°C and analyzed within two months.

Complete urine collections were obtained from each of the five individuals for a 24-hr period. After complete bladder emptying just before the next dose of deferiprone, all urine passed for the next 8 hr was collected. At the end of the 8-hr period, the bladder was again emptied and the total volume of urine passed for the previous eight hour period was recorded. Two subsequent urine collections were obtained for the next two 8-hr periods. An aliquot from each 8-hr collection was stored at -70°C and analyzed within two months.

Placebo-controlled cross-over trial of deferiprone at 75 mg/kg/day. Thirteen subjects were enrolled, but one was removed after 24 hr when he was found to have very low

parasite counts; the remaining 12 completed the nine-day study period. Both deferiprone and placebo were given sequentially to each volunteer in a prospective, randomized, double-blind, cross-over fashion. Deferiprone, 75 mg/kg/day divided into doses given every 8 hr, or placebo was administered for an initial 72-hr period, followed by three days of no drug. This was then followed by a cross-over to the alternate study agent, placebo or deferiprone, for the remaining three-day period. The subjects were kept in an inpatient facility, with vital signs, review of systems, and a fingerstick blood sample for a thick malaria smear being obtained every 4 hr for the initial 24-hr period of each agent, then every 8 hr thereafter. A full blood count and glucose level was obtained every day from venous blood. During the three days of receiving no study drug, a daily assessment was performed and a thick blood smear was obtained. Study subjects were evaluated one week after discharge from the study, at which time a history was obtained and a physical examination was performed, as well as a full blood count and thick smear for estimation of malaria parasites.

Placebo-controlled cross-over trial of deferiprone at 100 mg/kg/day. Twelve additional subjects were enrolled for a nine-day study period. Two subjects dropped out early for personal reasons; one at three days and one at seven days. Deferiprone in a dose 100 mg/kg/day or placebo was given orally every 6 hr for a period of 96 hr, followed by a 24-hr period of no drug; each subject then received either deferiprone or placebo for another 96-hr period. Monitoring was carried out as in the 75 mg/kg/day study, except that systems review was done every 6 hr and vital signs were recorded every 12 hr. Thick malaria smears were obtained every 6 hr hours for the entire nine-day period. All other aspects of the study were as in the trial examining deferiprone at 75 mg/kg/day.

Laboratory techniques. Malaria parasite concentrations were estimated by determining the number of ring forms per 200 white blood cells in a Giemsa-stained peripheral smear, and then multiplying by the most recent white cell count. If there were fewer than 10 parasites per 200 white blood cells, then the number of organisms per 500 white blood cells was determined. The smears were read in a blinded fashion by two different laboratory technicians and the result was recorded as the mean of the two readings. White blood cell and platelet counts were determined using a counting chamber, and the white cell differential was determined manually after staining with Giemsa. Hematocrit was measured with a microcentrifuge.

Analysis of plasma deferiprone concentrations was performed using a high-performance liquid chromatography method giving a detection limit of 0.5 mg/ml of deferiprone, as previously described.¹⁵ Levels of deferiprone-glucuronide, the major metabolite of deferiprone, were determined as follows. Following overnight incubation at 37°C with glucuronidase, to completely remove the glucuronide moiety from the parent molecule, deferiprone levels were measured again and the difference was calculated to determine the quantity of plasma metabolite levels. Elimination half-life ($t_{1/2}$) and area under the plasma concentration-time curve (AUC) were computed by use of the ADAPT program.¹⁶

Statistical analysis. Malaria parasite concentrations showed a log normal distribution and were transformed log-

TABLE 1

Pharmacokinetic data on five subjects receiving deferiprone, 25 mg/kg by mouth every 8 hr (75 mg/kg/day)

Kinetic parameters*	Results (mean ± SD)
Plasma deferiprone	
24-hr AUC (mg min/L)	7,747.26 ± 1,509.6
Half-life ($t_{1/2}$) (min)	92.38 ± 6.54
Apparent clearance (L/min/kg)	0.010 ± 0.002
Apparent volume distribution (L/kg)	1.34 ± 0.27
Renal clearance (L/min)	0.038 ± 0.023
C _{max} (μg/ml)	15.15 ± 3.47
(μmol/L)	108.85 ± 24.92
C _{min} (μg/ml)	0.70 ± 0.28
(μmol/L)	5.02 ± 2.01
C _{ss} (μg/ml)	3.37 ± 0.22
(μmol/L)	24.24 ± 1.62
Time to deferiprone peak (min)	84.00 ± 32.86
Plasma deferiprone-glucuronide	
24-hr AUC (mg min/L)	1,070.73 ± 618.71
C _{max} (μg/ml)	2.73 ± 2.36
Renal clearance (L/min)	0.022 ± 0.015
Time to peak (min)	180.0 ± 103.92

* C_{ss} = steady state concentration; AUC = area under the plasma concentration-time curve.

arithmically for statistical analysis. Changes in parasite concentrations over time were examined with repeated measures analysis of variance. Demographic and clinical features of the participants at enrollment were compared between treatment groups by Student's *t*-test. During treatment with deferiprone or placebo, hematologic parameters were compared by the paired *t*-test and reported side effects were compared between treatment groups using Fisher's exact test. The Bonferroni correction was applied for multiple comparisons.

RESULTS

Pharmacokinetic study. The results of deferiprone pharmacokinetics are shown in Table 1 and Figure 1. Five subjects studied had a mean peak plasma deferiprone level of 108.9 μmol/L (15.15 μg/ml) at 84 min, a $t_{1/2}$ of 92.4 min, and a mean 8-hr AUC of 2,582 mg.min/L, with a calculated mean 24-hr AUC of 7,747 mg.min/L.

Demographic and clinical features. Demographic and presenting clinical features of the 25 subjects enrolled in the cross-over study are shown in Table 2. There were no significant differences at the start of the study between subjects who received deferiprone first or placebo first in any of the parameters measured. Urinalyses were normal in all except two subjects, one with *Schistosoma haematobium* infection and one with low-grade pyuria.

Effect of deferiprone at 75 mg/kg/day on parasitemia. Mean peripheral blood asexual parasite counts in the 12 subjects who completed both the initial treatment period and the cross-over treatment period are presented in Figure 2. There was no significant decrease in parasites for subjects given either deferiprone or placebo in the initial or cross-over periods.

Effect of deferiprone at 100 mg/kg/day on parasitemia. The mean peripheral parasite concentrations in the 10 subjects who completed both the initial and cross-over treatment

Deferiprone pharmacokinetic data
(5 subjects)

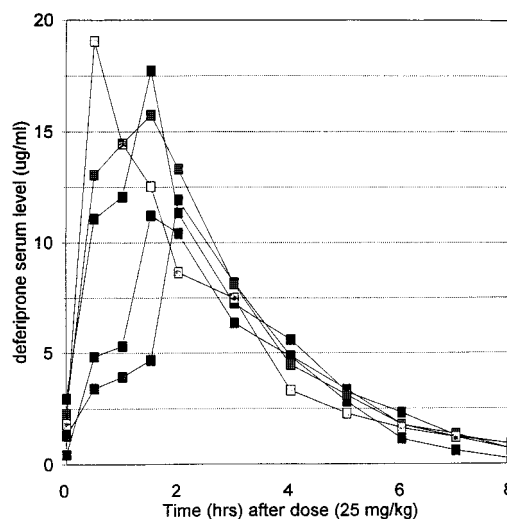


FIGURE 1. Plasma deferiprone concentrations in five subjects receiving deferiprone 25 mg/kg orally.

periods are shown in Figure 3. No significant decreases in parasites were observed for subjects given either deferiprone or placebo in the initial or cross-over periods.

Toxicity and side effects. White blood cell counts, absolute neutrophil counts, platelet counts and hematocrits were assessed during the study, and no significant differences were found when these parameters were compared at the start and the end of therapy in either the deferiprone or placebo groups. Possible side effects were obtained by open questioning during the review of systems. All complaints were transient in nature, and no subject chose to withdraw from the study as a result of his symptoms. After applying the Bonferroni correction, there was no significant difference in the side effects reported by subjects while receiving deferiprone as compared with those while receiving placebo.

TABLE 2

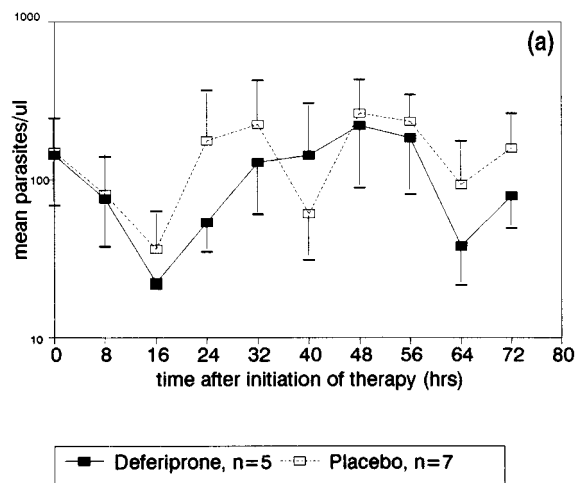
Demographic and clinical features of study subjects, according to whether deferiprone or placebo was given in the first period of the study*

Deferiprone at 75 mg/kg/day	Deferiprone 1st (n = 6)	Placebo 1st (n = 7)
Age (mean ± SD)	18.8 ± 0.7	18.9 ± 1.1
Parasites/μl†	102 (52–202)	149 (91–244)
Hematocrit % (mean ± SD)	44 ± 3	44 ± 2
WBC × 10 ⁹ /L (mean ± SD)	5.5 ± 1.3	6.0 ± 1.6
Platelets × 10 ⁹ /L (mean ± SD)	195 ± 43	179 ± 34
Deferiprone at 100 mg/kg/day	Deferiprone 1st (n = 6)	Placebo 1st (n = 6)
Age (mean ± SD)	28.5 ± 9.0	23.3 ± 3.6
Parasites/μl†	248 (112–552)	124 (70–219)
Hematocrit % (mean ± SD)	42 ± 3	44 ± 2
WBC × 10 ⁹ /L (mean ± SD)	5.1 ± 0.8	4.9 ± 0.8
Platelets × 10 ⁹ /L (mean ± SD)	185 ± 24	189 ± 33

* There were no significant differences between those receiving deferiprone or placebo first. WBC = white blood cells.

† Geometric mean parasites with SEM range.

Deferiprone 75 mg/kg/day Initial Treatment Period



Deferiprone 75 mg/kg/day Crossover Treatment Period

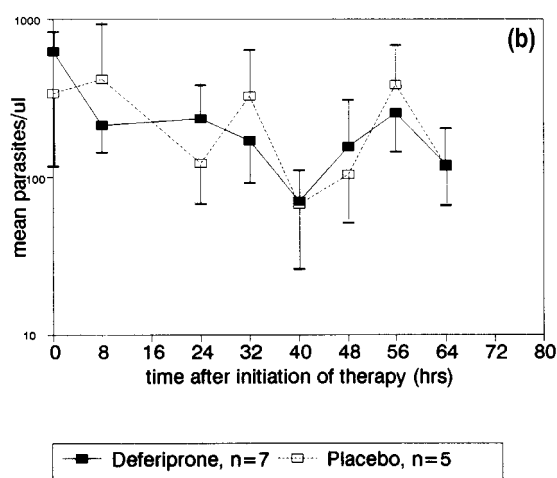


FIGURE 2. **a**, mean and SEM peripheral blood asexual parasite concentrations in 12 subjects who received deferiprone, 75 mg/kg/day, or placebo during the initial study period of 72 hr. Mean parasite concentrations did not differ significantly over time between the two study groups. **b**, mean and SEM peripheral blood asexual parasite concentrations in 12 subjects who received deferiprone, 75 mg/kg/day, or placebo during the cross-over study period of 72 hr. Mean parasite concentrations did not differ significantly over time between the two study groups.

DISCUSSION

Parenteral desferrioxamine B, in doses of 50–100 mg/kg/day administered by continuous infusion, has anti-malarial activity in humans,^{3–6} but no orally active iron-chelator has heretofore been examined for a clinical anti-plasmodial effect. In the present study, we examined whether the orally active iron-chelating agent, deferiprone, has clinically detectable anti-malarial activity in humans. The purpose was

not solely to find a drug that is a potent anti-malarial as a single agent, but also to consider a compound that may have activity in enhancing parasite clearance^{3,5} or in protecting tissues from damage threatened by ischemia and hemorrhage,⁶ and which could conceivably be beneficial in combination with other anti-malarials.⁶

Our results showed no clinically detectable effect of deferiprone on asexual peripheral blood *P. falciparum* parasites when the chelator was given in doses of 25 mg/kg every 6–8 hr to male subjects with mild parasitemia. The trial was designed to look for an 80% reduction in parasite density when comparing the deferiprone with the placebo group. Power calculations using an alpha of 0.05 and a power of 80% indicate that given the parasite densities present in the current study, to reliably show even a 40% reduction in parasites in the 75 mg/kg group would have required eight subjects in each arm of the study, with 11 subjects needed in each arm of the 100 mg/kg study to show the same reduction. Thus, given the low number of subjects in this study, it is possible that the anti-plasmodial effect of deferiprone was not found due to a type II error.

Our pharmacokinetic study indicated that the subjects achieved a mean peak plasma deferiprone level of 108.9 $\mu\text{mol/L}$ after a dose of 25 mg/kg, which is within the range of concentrations that result in 85–100% inhibition of parasite growth in vitro.^{11–13} While the peak deferiprone levels were in the range expected for effective anti-plasmodial activity, the drug was administered every 6–8 hr during the study and the $t_{1/2}$ was only 92 min. Considering the findings of other investigators,^{11,12} these pharmacokinetic results suggest that plasma concentrations of deferiprone with effective anti-malarial activity were maintained only for intermittent brief periods during the therapy. For example, deferiprone levels of 5–15 $\mu\text{mol/L}$ produced only 38–52% inhibition of parasite growth in vitro.^{11,12} Thus, the findings serve to emphasize that sustained exposure to effective concentrations of an iron-chelating agent is required for an anti-plasmodial effect.

Together with the brief period of exposure, the lack of a clinical anti-malarial effect may also be related to the low partition coefficient of deferiprone when compared with some of the other orally active hydroxypyridinone chelators. Although desferrioxamine is considerably less lipophilic than deferiprone, it has equivalent or superior anti-parasitic activity with continuous exposure in vitro,¹² and some investigators have suggested that desferrioxamine may have access to the erythrocytic trophozoite by means of a parasitophorous duct, thus bypassing the red blood cell membrane and cytoplasm.¹⁷ While it should be noted that the entrance of drugs into the red blood cell and into the erythrocytic parasite itself is a complex issue, the action of the hydroxypyridinone class of chelators on the erythrocytic phase of *P. falciparum* is apparently related to the ability to penetrate the red blood cell, and derivatives with higher lipophilicity have greater anti-parasitic effect in vitro.¹⁸ Although the relatively low lipophilicity of deferiprone results in less ability to penetrate red blood cells than other oral iron chelators,¹² this agent was the only such chelator with sufficient human experience to warrant its testing in subjects with malaria. The fact that deferiprone is a bidentate chelator rather than an hexadentate chelator may also have had an influence on

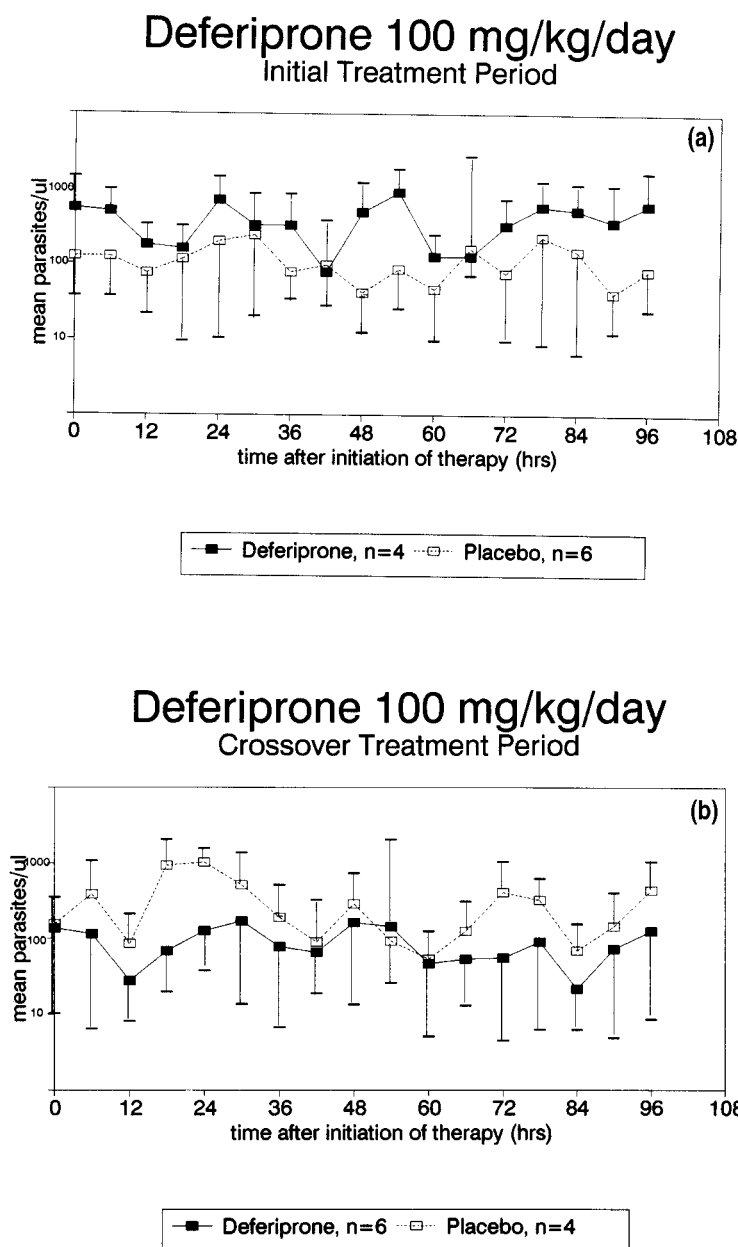


FIGURE 3. **a**, mean and SEM peripheral blood asexual parasite concentrations in 10 subjects who received deferiprone, 100 mg/kg/day, or placebo during the initial study period of 96 hr. Mean parasite concentrations did not differ significantly over time between the two study groups. **b**, mean and SEM peripheral blood asexual parasite concentrations in 10 subjects who received deferiprone, 100 mg/kg/day, or placebo during the cross-over study period of 96 hr. Mean parasite concentrations did not differ significantly over time between the two study groups.

the results of the study because a bidentate chelator requires a molar ratio of three-fold more of the compound to have the same chelating activity as an hexadentate chelator such as desferrioxamine B. With a bidentate chelator, the iron chelating effect should decrease more quickly as concentrations are lowered compared with an hexadentate chelator.¹⁹

Deferiprone is an orally active iron chelator that was developed as an agent for chronic therapy of iron overload, whereas effective anti-malarial oral iron-chelating agents might well have different chemical characteristics and different properties of distribution, metabolism and excretion. The present study seemed warranted because of the positive results of trials of desferrioxamine B in malaria, and the

knowledge that deferiprone is the only orally active iron chelator available for human trials, even though it may not be the ideal agent. Adverse effects, most commonly neutropenia with or without thrombocytopenia, have been observed in other studies with deferiprone doses of 75–100 mg/kg/day or more, but only when the agent has been administered to iron-loaded patients over a period of weeks to months.^{20, 21} While no adverse hematologic effects have ever been observed with the administration of deferiprone over a short period of time, it is possible that the hematologic toxicity of this agent may be idiosyncratic. Concern has been raised that subjects without iron overload may be more prone to toxic effects of deferiprone than iron-loaded subjects, but in vitro

data suggest that cellular toxicity may not be directly related to the degree of iron loading.²²

Given the absence of a parasite-lowering effect with the doses used in this trial, and using the pharmacokinetic data obtained in this study, we developed a model to calculate a dosing of deferiprone that would give the equivalent in vivo anti-plasmodial effect to that seen in vitro with a steady state level of 100 $\mu\text{mol/L}$, known to be lethal to parasites. Our model assumed that parasites cultured in vitro over a 48-hr period with a deferiprone concentration of 100 $\mu\text{mol/L}$ (13.9 mg/L) were exposed to the equivalent of a 48-hr AUC of 40,320 mg.min/L. Given this assumption, the calculated mean 48-hr AUC of 15,494 in our subjects was only 38.4% of that necessary in vitro, or a dose factor of 2.6. Using the dose received of 75 mg/kg multiplied by this dose factor, we calculated that a dose of 193.3 mg/kg or essentially 200 mg/kg/day would be necessary. In addition, given that the plasmodicidal concentration of deferiprone in vitro was 100 $\mu\text{mol/L}$, we calculated that during every 8-hr period, only three of our subjects had levels above this for a mean time of only 110 min. Thus, we believe that dosing every 2 hr may be necessary to keep serum levels in the effective range. Because studies in animals have found bone marrow suppression and other severe adverse effects at a dose of 200 mg/kg (Biesemeier JA Laveglia J, unpublished data and Schnebli HP, unpublished data),²³ further trials of deferiprone as a sole agent for human *P. falciparum* infection do not appear to be justifiable. On the other hand, given the large number of people still suffering from malaria throughout the world, efforts to continue the development and eventual human trials of orally active iron chelators, specifically developed for their anti-malarial action, would seem to be warranted.¹⁸

Acknowledgments: We thank the Macha Mission Hospital administration and the Zambian Ministry of Health for allowing us to conduct this study, as well as Simon Armstrong, for the synthesis of the placebo and Dr. Christine McLaren for statistical assistance. We also thank the staff of Macha Hospital and specifically the following individuals without whom we could not have carried out this project: Abram M'hango and David Lusale.

Financial support: This work was supported in part by an Orphan Products Development Grant (FD-R-000975) from the U.S. Food and Drug Administration, by a grant from the Medical Research Council (Canada), by a grant (VO1 A135827) from the International Collaborations in Infectious Disease Research Program of the National Institute of Allergy and Infectious Diseases, and by a grant from the Office of Minority Health to the Cell Biology and Metabolism Branch of the National Institute for Child Health and Human Development. Nancy F. Olivieri and Gideon Koren are Career Scientists of the Ontario Ministry of Health.

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