

Iron-chelating agents for treating malaria (Review)

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[Intervention Review]

Iron-chelating agents for treating malaria

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ABSTRACT

Background

It is still unclear whether iron-chelating agents, such as intravenous desferrioxamine (DFO) and oral deferiprone, given alone or added to standard antimalarial treatment would reduce malaria deaths.

Objectives

To evaluate iron-chelating agents alone or combined with standard antimalarial drugs for treating *P. falciparum* malaria.

Search strategy

In May 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 2), MEDLINE, EMBASE, LILACS, mRCT, and reference lists. We also contacted researchers in the field.

Selection criteria

Randomized controlled trials comparing iron-chelating agents with placebo, or comparing iron-chelating agents plus standard antimalarial drugs with antimalarial drugs alone in adults or children with *P. falciparum* malaria.

Data collection and analysis

We independently applied inclusion criteria and assessed trial methodological quality, and one author extracted data. We contacted trial authors for additional data. We combined dichotomous data using risk ratios (RR) and continuous data with weighted mean differences (MD), and presented both with 95% confidence intervals (CI).

Main results

Seven trials involving 570 participants met the inclusion criteria. Two small trials compared DFO with placebo (plus standard antimalarial drugs in both groups). No evidence of benefit or harm was shown in relation to death, but the trials were small (435 participants). The risk of experiencing persistent seizures was lower with DFO compared with placebo (RR 0.80, 95% CI 0.67 to 0.95; 334 participants, 1 trial), but adverse effects were more common with DFO. One small trial involving 45 adults and children compared deferiprone with placebo (plus standard antimalarial drugs in both groups). Participants in the deferiprone group had significantly faster coma recovery (MD -27 h, 95% CI -34.20 to -19.80) and parasite clearance (MD -24 h, 95% CI -35.27 to -12.73). No adverse effects were reported for this trial.

Authors' conclusions

There are insufficient data to draw any conclusions for DFO and deferiprone. There are nonsignificant trends towards fewer seizures but overall harm (death) with DFO, and results from one small trial of deferiprone suggest shorter coma recovery and parasite clearance.

2008: We do not plan to update this review given the paucity of recent trials in this area and other priorities in malaria treatment research.

PLAIN LANGUAGE SUMMARY

Iron-chelating agents for treating malaria

Malaria is a major health problem that particularly affects people living in sub-Saharan Africa and other tropical parts of the world. It often causes considerable morbidity and high mortality, especially in children under five, and is passed by mosquito bites from infected female mosquitoes. Several drugs are available to treat malaria infections, and there are also additional drugs that can be used to increase effectiveness. Since parasites require iron to reproduce, drugs that withhold available iron (ie iron-chelating drugs) from the parasite could inhibit the parasite reproduction rate and may be used as adjuncts to traditional antimalarial drugs. However, the agents may also reduce the availability of iron to the individual, and this may contribute to or exacerbate anaemia. There are a number of different iron-chelating agents, such as desferrioxamine (DFO) and deferiprone, and all were considered in the review of trials, although DFO has to be given intravenously and so will be of little use in most malarious areas. The drugs may also display adverse effects like headaches, dizziness, muscle pain, and tiredness. The review found seven trials of DFO and deferiprone involving 570 participants. Although the drugs may have helped in part with parasite levels, there seemed to be adverse effects including concerns about possibility of an increase in death. There is insufficient evidence to support the use of iron-chelating agents as adjuncts in the treatment of malaria, and further trials are not expected.

BACKGROUND

Each year one to two million people die from malaria, with half of these deaths occurring among children infected with the *Plasmodium falciparum* malaria parasite in sub-Saharan Africa (Wyller 1992; WHO 2000). Cerebral malaria is the commonest fatal syndrome of *P. falciparum* malaria, and mortality can be as high as 50% (WHO 2000). Death and sequelae occur even in people treated with antimalarial drugs, and researchers are exploring the effects of adding treatments to the main antimalarial regimens in an effort to reduce mortality.

Iron chelation is one potential adjuvant treatment. The biological rationale for iron chelation is that malaria parasites require iron to reproduce, so drugs that withhold available iron from the malaria parasite could inhibit its reproduction rate (Wyller 1992; Mabeza 1996). Other indirect evidence of a potential effect comes from experimental studies that suggest iron supplementation exacerbates malaria infection (Murray 1975; Oppenheimer 1984), and observational studies that have led the authors to conclude that iron deficiency is protective (Murray 1978; Raventos 1982). Theory also

suggests that iron-chelation therapy may accelerate coma recovery by inhibiting iron-induced damage to brain cells, thus protecting against damage to the central nervous system (Mabeza 1996).

Desferrioxamine (DFO) is the standard iron-chelating agent in clinical use. It works by entering malaria parasites and combining (chelating) with available iron (Hider 1994; Lytton 1994; Mabeza 1996). It is generally regarded as a safe drug despite known adverse effects (eg neutropenia, haematological toxicity, transient headaches, dizziness, myalgia, and malaise) and reports of serious auditory and visual neurotoxicities in long-term therapy (Olivieri 1996). However, it is considered of little use in most malarious areas because it is expensive, has to be given intravenously, and penetrates infected red blood cells slowly (Wyller 1992; Hershko 1994).

Other iron-chelating agents are being considered, such as the orally active deferiprone. However, before iron-chelating agents are used as adjuvant treatments for malaria, it is important to assess that their antimalarial action is complementary and not antago-

nistic to standard therapy. In vitro and animal experiments suggest that iron-chelating agents and artemisinin-class antimalarial drugs might be less effective when used simultaneously (Meshnick 1993). Therefore, studies of iron chelator and artemisinin drugs used together will be carefully scrutinized to detect any inhibitory effects of the iron chelator on the action of artemisinin.

OBJECTIVES

To evaluate iron-chelating agents alone or combined with standard antimalarial drugs for treating *P. falciparum* malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children with *P. falciparum* malaria confirmed by a blood slide.

Types of interventions

- Iron-chelating agents versus placebo.
- Iron-chelating agents plus antimalarial drugs versus antimalarial drugs alone.

Types of outcome measures

- Death.
- Coma recovery (time to recover consciousness).
- Persistent seizures (more than three).
- Parasite clearance time (time to 50% clearance).*
- Parasite clearance at day three.*
- Parasitaemia (parasite concentration).*
- Adverse effects: local effects (at site of injection/infusion); systemic effects (toxic effects, nausea, visual disturbance, headache, abdominal pain, other).*

*Measures used for people with asymptomatic malaria.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (May 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 2); MEDLINE (1966 to May 2007); EMBASE (1980 to May 2007); and LILACS (1982 to May 2007). We also searched the metaRegister of Controlled Trials (mRCT) using 'malaria' and 'chelate*' as search terms.

Table 1. Detailed search strategies

Search set	CIDG SR ^a	CENTRAL	MEDLINE ^b	EMBASE ^b	LILACS ^b
1	iron	iron	iron	iron	iron
2	chelate*	chelate*	chelate*	chelate\$	chelate\$
3	1 and 2	1 and 2	1 and 2	1 and 2	1 and 2
4	malaria	deferiprone	deferiprone	deferiprone	deferiprone
5	3 and 4	desferrioxamine	desferrioxamine	desferrioxamine	desferrioxamine
6	-	deferoxamine	deferoxamine	deferoxamine	deferoxamine

Table 1. Detailed search strategies (Continued)

7	-	3 or 4 or 5 or 6	IRON CHELATING AGENTS	IRON CHELATING AGENT	3 or 4 or 5 or 6
8	-	malaria	3 or 4 or 5 or 6 or 7	3 or 4 or 5 or 6 or 7	malaria
9	-	7 and 8	malaria	malaria	7 and 8
10	-	-	8 and 9	8 and 9	-
11	-	-	Limit 10 to humans	Limit 10 to humans	-

^aCochrane Infectious Diseases Group Specialized Register.

^bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Higgins 2006](#)); upper case: MeSH or Emtree heading; lower case: free text term.

We checked the reference lists of all studies identified by the above methods. We also contacted experts and individuals actively involved in malaria research for additional references and unpublished studies, and asked external referees to check the completeness of the search strategy and identify additional unpublished, ongoing, or planned trials.

Data collection and analysis

Selection of studies

We independently assessed the full text of all potentially relevant trials and applied the inclusion criteria. Any disagreement about inclusion of trials was resolved by discussion.

Data extraction and management

H Smith extracted data from the included trials. We contacted trial authors requesting original data; one author supplied a comprehensive account of his studies allowing some quantitative analysis.

Assessment of risk of bias in included studies

We independently assessed the risk of bias in the trials. We assessed the generation of allocation sequence and allocation concealment to be adequate, inadequate, or unclear ([Juni 2001](#)). We classified blinding as double, single, or not blinded, and described who was blinded where this information was available. We considered the inclusion of all randomized participants in the analysis as adequate if greater than 90%, inadequate if less than 90%, or unclear.

Data synthesis

We used [Review Manager 5](#) to analyse data. We assessed the estimates of effect using risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data, and presented both with 95% confidence intervals (CI). We pooled data using a fixed-effect model. We stratified the results by malaria severity – severe malaria, asymptomatic malaria, and symptomatic malaria.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Eligibility

Seven trials involving 570 participants met the inclusion criteria (see '[Characteristics of included studies](#)'). Thuma 1998b reported two cross-over trials, which we treated as two separate trials ([Thuma 1998b-i](#); [Thuma 1998b-ii](#)). [Thuma 1998a](#), conducted at two centres in Zambia, was treated as one for the analysis. One trial was published in reported in two articles with no cross-referencing ([Gordeuk 1992b](#)). Four studies were excluded for the reasons given in the '[Characteristics of excluded studies](#)'.

Location

Mohanty 2002 was conducted in India, and the other trials were conducted in Zambia.

Participants

Thuma 1998a and Gordeuk 1992b looked specifically at children less than six years old with cerebral malaria. Mohanty 2002 studied people aged 13 to 84 years with *P. falciparum* infection and fever. Thuma 1998b-i, Thuma 1998b-ii, Gordeuk 1992a, and Gordeuk 1993 included adults with asymptomatic *P. falciparum* infection; Thuma 1998b-i and Thuma 1998b-ii included adult males only.

Interventions

Four trials compared DFO with placebo. In the two trials in children with cerebral malaria (Gordeuk 1992b; Thuma 1998a), DFO (100 mg/kg/day intravenously for 72 hours) or placebo was added to standard therapy with quinine. Quinine dosage was the same in both trials, but Thuma 1998a gave an initial loading dose of 20 mg/kg. Gordeuk 1992a and Gordeuk 1993, which studied people with asymptomatic malaria, compared DFO (100 mg/kg/day) and placebo (normal saline) administered by continuous subcutaneous infusion over 72 hours via battery-operated pumps.

Three trials compared deferiprone with placebo. Thuma 1998b-i and Thuma 1998b-ii were cross-over trials, but we used only the results from the initial trial periods for the purpose of this review. The intervention group in the Thuma 1998b-i received deferiprone (75 mg/kg/day) divided into doses given every eight hours for an initial 72-hour period. In Thuma 1998b-ii, deferiprone (100 mg/kg/day) was administered every six hours for 96 hours. The participants in Mohanty 2002 received either deferiprone (75 mg/kg/day orally in doses every 12 hours) plus standard quinine and doxycycline therapy or placebo capsules plus the same antimalarial therapy.

Outcome measures

All of the prespecified outcome measures were reported on by at least one of the trials. We also added persistent seizures (more than three) and parasitaemia (parasite concentration) because the included trials provided useful information on these outcome measures.

Gordeuk 1992b and Thuma 1998a reported median time to coma recovery; they treated the data as continuous and implied a skewed data set, which meant that we could not include these in meta-analyses. We contacted the trial authors, and Thuma 1998a provided the mean and standard deviation for survivors; the mean was less than the standard deviation in each treatment group, thus confirming the skewed nature of the data. Time to coma recovery constitutes time-to-event data and should be analysed as such. To pool the results from both trials requires log-hazard ratios, which

give a measure of treatment effect. We contacted the trial authors for this information when the review was first prepared (1999), but we have not received these additional data.

Gordeuk 1992b and Thuma 1998a both reported parasite clearance rate rather than clearance time, and it is unclear how the 'rates' were calculated.

Trials of DFO versus placebo in asymptomatic persons and deferiprone versus placebo reported mean (and standard error of the mean) parasite concentration only.

Risk of bias in included studies

One trial used an adequate method (random-number table) to generate the allocation sequence (Mohanty 2002). The method was unclear in the other trials despite purporting to be randomized. Three trials reported adequate measures to conceal allocation. Participants in Gordeuk 1992b and Thuma 1998a were randomized centrally by pharmacy staff, and Mohanty 2002 used serial numbering. The other four trials did not mention procedures to conceal allocation.

All trials were reported as double blind and used a placebo. Three trials reported that only the pharmacist knew the code to treatment allocation (Thuma 1998a; Thuma 1998b-i; Thuma 1998b-ii), but this was only discovered after communication with the trial author.

The inclusion of all randomized participants in the analysis was adequate in six trials: it was 100% in five trials (Gordeuk 1992a (for the initial period of this cross-over trial analysed in this review); Gordeuk 1992b; Gordeuk 1993; Thuma 1998a; Mohanty 2002); and 92.3% in Thuma 1998b-i. Thuma 1998b-ii included 83.3%, which we consider inadequate, after two participants in this trial of 12 participants withdrew for personal reasons.

Effects of interventions

I. DFO versus placebo (plus standard antimalarial regimen): severe malaria

Gordeuk 1992b and Thuma 1998a compared DFO (100 mg/kg/day) with placebo (both in addition to a standard antimalarial drugs) for children less than six years old.

Death

Both trials reported on deaths, and Thuma 1998a was stopped early on the recommendation of the safety and data monitoring committee since more were reported in the DFO group. While trials stopped early can sometimes introduce bias if due to a trend in the results of a spurious study, in this trial, however, the risk of death was significantly increased in the DFO group (RR 1.70,

95% CI 1.00 to 2.89; 352 participants, [Analysis 1.1](#)), therefore systematic error is unlikely. Overall, the pooled estimate indicates an increased risk of death in the DFO group (435 participants, 2 trials, [Analysis 1.1](#)), but this is not statistically significant.

Coma recovery

Both trials reported the estimated median time to recovery and rate of recovery (see [Table 2](#)). This suggests that the trialists treated time to coma recovery as a continuous variable rather than using survival data methods; and we have not received details of any time-to-event analyses from the trial authors. [Gordeuk 1992b](#) reported an estimated median time to recovery of 20.2 hours (41 participants) in the DFO group and 43.1 hours (42 participants) in the placebo group ($P = 0.38$). The rate of recovery of consciousness was 1.3 times faster in the DFO group in [Gordeuk 1992b](#) and an estimated 1.2 times faster in the DFO group in [Thuma 1998a](#).

Table 2. Desferrioxamine (DFO) vs placebo for severe malaria: coma recovery time

Trial	Outcome description	Rate of recovery ^a	Median time ^b	Notes
Gordeuk 1992b	Time from start of treatment to a sustained coma score 5 (Glasgow Coma Scale); reported as median recovery time (continuous) rather than survival data	1.3 times faster in DFO group than in placebo group (95% CI 0.7 to 2.3)	DFO: 20.2 h (41 participants) Placebo: 43.1 h (42 participants) $P = 0.38$	Adjusted results: deep coma (50 participants) Recovery of full consciousness during the 72-h study period was analysed in all 83 participants
Thuma 1998a	Time from start of treatment to coma score 5 (Blantyre Coma Scale); reported as median recovery time (continuous) rather than survival data	1.2 times faster in DFO group than in placebo group ($P = 0.21$)	DFO: 18.1 h (143 participants) Placebo: 19.0 h (158 participants) 95% CI 0.97 to 1.6	2 study sites used in the trial, but treated as 1 for analysis

CI: confidence interval.

^aRate of recovery of full consciousness. ^bMedian time to recovery.

Persistent seizures

The risk of experiencing persistent seizures was significantly lower with DFO (RR 0.80, 95% CI 0.67 to 0.95; 334 participants, 1 trial, [Analysis 1.2](#)); data provided by the [Thuma 1998a](#) authors upon request.

Parasite clearance

The rate was two times faster with DFO than in the placebo group (95% CI 1.2 to 3.6) in [Gordeuk 1992b](#) (see [Table 3](#)). In contrast, it was faster in the placebo group in [Thuma 1998a](#) (see [Table 3](#)), but this difference was not statistically significant. It is unclear how the trialists calculated these rates.

Table 3. Desferrioxamine (DFO) vs placebo for severe malaria: parasite clearance time

Trial	Outcome description	Rate of clearance	Mean 50% time	Notes
Gordeuk 1992b	Rate of clearance	2.0 times faster in DFO group than in placebo group (95% CI 1.2 to 3.6) Significantly increased with the addition of DFO (P = 0.01)	-	Survival graph provided, but too small to interpret and no information from which hazard ratio could be determined
Thuma 1998a	Rate of clearance reported, but no explanation of 'rate' Trial author provided data for parasite clearance time provided (but treated as continuous data and only mean given (no standard deviation) and parasite clearance on day 3 after correspondence	1.1 times faster in placebo group than DFO group (P = 0.24)	DFO: 24.6 h (145 participants) Placebo: 24.3 h (155 participants)	2 study sites used in the trial, but treated as 1 for analysis

Parasite clearance at day three

There was no statistically significant difference in the number of participants with parasite clearance at day three (300 participants, 1 trial, [Analysis 1.3](#)); data provided by the [Thuma 1998a](#) authors upon request.

Adverse effects

[Gordeuk 1992b](#) stated explicitly that no toxic reaction or side effect could be attributed to DFO. Paresis was observed in two

surviving children at the time of discharge, but both were in the placebo group.

The [Thuma 1998a](#) trial author provided additional data on a range of adverse effects. There were two adverse effects that the trial authors (and external referees) thought were most likely to be directly attributable to DFO treatment, but there was no statistically significant difference compared with placebo: phlebitis (inflammation of the vein wall) (344 participants, 1 trial, [Analysis 1.4](#)); and recurrent hypoglycaemia (334 participants, 1 trial, [Analysis 1.5](#)).

2. DFO versus placebo: asymptomatic malaria

Gordeuk 1992a and Gordeuk 1993 compared DFO (100 mg/kg/day) with placebo in adults with asymptomatic *P. falciparum*. Both trials administered treatments via subcutaneous infusion over 72 hours.

Parasitaemia

Gordeuk 1992a reported significant decreases in geometric mean concentrations of parasites in both the DFO group ($P = 0.0001$; 12 participants) and placebo group ($P = 0.002$; 12 participants) during the initial trial period (see Table 4). The magnitude of the decline in mean parasite concentration with DFO treatment was significantly greater than the decline with placebo ($P = 0.005$).

Table 4. Desferrioxamine (DFO) vs placebo for asymptomatic malaria: parasitaemia

Trial	Outcome description	Change in mean PC ^a	Notes
Gordeuk 1992a	Mean parasite concentration over initial trial period (72 h) (graph) Decrease in geometric mean concentrations of parasites in both treatment groups during the initial trial period	DFO: significant decrease ($P = 0.0001$); 12 participants Placebo: significant decrease ($P = 0.002$); 12 participants Change with DFO compared to placebo: $P = 0.005$	Cross-over trial; initial period only used
Gordeuk 1993	Mean parasite concentration over 72 h (graph)	DFO: significant decrease ($P < 0.001$); 16 participants Placebo: no significant decrease; 21 participants During the week following treatment (days 3 to 10), parasitaemia remained significantly lower in the DFO group ($P = 0.009$)	-

^aChange in mean parasite concentration.

Gordeuk 1993 reported that mean parasite concentrations decreased significantly in the DFO group ($P < 0.001$; 16 participants; see Table 4). Notably, during the week following administration of DFO or placebo (days three to 10), parasite concentrations remained significantly lower in those who received DFO ($P = 0.009$), but mean parasitaemia did not change significantly.

Adverse effects

Gordeuk 1992a noted that no toxicity was detected during the DFO infusions (see Table 5). Participants reported mild swelling and pain at the site of needle insertion in 22/25 subcutaneous administrations of DFO, but only in 10/25 administrations of placebo – a statistically significant difference ($P < 0.05$). Gordeuk 1993 did not report any local or systemic adverse effects, despite reporting that participants were examined and questioned regarding adverse effects twice a day (see Table 5).

Table 5. Desferrioxamine (DFO) vs placebo for asymptomatic malaria: adverse effects

Trial	Outcome description	Local effects	Systemic effects	Notes
Gordeuk 1992a	Adverse effects detected during study period	Mild swelling and pain at site of needle insertion DFO group: 22/25 subcutaneous administrations Placebo group: 10/25 subcutaneous administrations $P < 0.05$	None reported	Participants examined and questioned regarding adverse effects twice daily. Facilities not available in study area for formal ophthalmologic and otologic evaluations
Gordeuk 1993	Adverse effects detected during study period	None reported	None reported	Participants examined and questioned regarding adverse effects twice a day

3. Deferiprone versus placebo: asymptomatic persons

Thuma 1998b-i and Thuma 1998b-ii compared deferiprone (75 mg/kg/day or 100 mg/kg/day respectively) with placebo in adult males with asymptomatic *P. falciparum*.

Parasitaemia

Neither trial reported a significant decrease in parasite concentration in either the deferiprone or placebo groups (see Table 6).

Table 6. Deferiprone versus placebo for asymptomatic malaria: parasitaemia

Trial	Outcome description	Mean at start	Mean at 72 h	Notes
Thuma 1998b-i	Mean parasite concentration over initial trial period (72 h) (graph)	Deferiprone: 102/ μ L (SEM range 52 to 202); 6 participants	Deferiprone: 90/ μ L (SE 15); 5 participants Placebo: 250/ μ L (SE 150);	Cross-over trial; initial period only used

Table 6. Deferiprone versus placebo for asymptomatic malaria: parasitaemia (Continued)

		Placebo: 149/ μ L (SEM range 91 to 244); 7 participants	7 participants	No significant decrease in parasites in either group Trial designed to look for 80% reduction in parasite density (deferiprone vs placebo), but to show even 40% reduction would require 8 participants in each study arm; antiplasmodial effect of deferiprone not found due to a type II error
Thuma 1998b-ii	Mean parasite concentration over initial trial period (72 h) (graph)	Deferiprone: 248/ μ L (SEM range 112 to 552); 6 participants Placebo: 124/ μ L (SEM range 70 to 219); 6 participants	-	Cross-over trial; initial period only used No significant decrease in parasites in either group Antiplasmodial effect of deferiprone possibly not found due to type II error (explanation as in Thuma 1998b-i)

SEM: standard error of measurement.

Adverse effects

Both trials used open questioning of participants to identify possible adverse effects during the study period. Details of five adverse effects were provided. Overall, there was no statistically significant difference (after the trial authors applied the Bonferroni correction) in the number of participants in the two groups experiencing abdominal pain (44 participants, 2 trials, [Analysis 2.1](#)), dizziness (44 participants, 2 trials, [Analysis 2.3](#)), myalgia (20 participants, 1 trial, [Analysis 2.4](#)), and malaise (24 participants, 1 trial, [Analysis 2.5](#)), but the sample sizes were small. There was, however, a significant increase in the number of participants with headache in the DFO group (RR 8.00, 95% CI 1.08 to 59.05; 44 participants, [Analysis 2.3](#)).

4. Deferiprone versus placebo (plus standard antimalarial regimen): symptomatic persons

[Mohanty 2002](#) compared deferiprone (75 mg/kg/day) with placebo (both groups also received a standard antimalarial regi-

men) in 45 participants aged 13 to 84 years with *P. falciparum* infection and fever.

Death

There was no statistically significant difference in the number of deaths between the two groups (45 participants, [Analysis 3.1](#)).

Coma recovery time

Participants in the deferiprone group recovered from coma faster than those in the placebo group (MD -27 h, 95% CI -34.20 to -19.80; 45 participants, [Analysis 3.1](#)).

Parasite clearance time

Mean time to parasite clearance was significantly faster in the deferiprone group (MD -24 h, 95% CI -35.27 to -12.73; 45 participants, [Analysis 3.3](#)).

Adverse effects

The trial authors stated explicitly that deferiprone was reasonably well tolerated in the dose given and had no adverse effects. They also noted that agranulocytosis (a known adverse effect of deferiprone) was not observed during the study.

DISCUSSION

Strength of evidence

We identified only seven trials of iron-chelating agents used in conjunction with standard antimalarial drugs (three trials) or as single agents (four trials). The strength of evidence is affected by the small sample sizes used; any effect would have to be dramatic to detect a difference between the treatment groups. Concealment of allocation was inadequate in four of the included trials, which increases the likelihood of selection bias and exaggerated estimates of treatment effects (Schulz 1995). Poor graphical presentation of continuous data meant interpretation of results for some outcomes was difficult.

Is death less likely in those treated with iron-chelating agents?

The available evidence from one trial of people with severe malaria suggests that DFO is harmful (Thuma 1998a), while the other trial suggests there is no adverse or beneficial effect of DFO (Gordeuk 1992b). To address the inconsistent evidence of the effect of DFO on death will require further large randomized trials of people, but justification for such trials will depend on a belief of potential benefit from iron-chelating agents.

One trial of deferiprone found fewer deaths in the deferiprone group (Mohanty 2002), but the difference was not statistically or clinically significant because of the small number of study participants.

Does adjunctive iron-chelation therapy shorten coma recovery time?

It is inappropriate to comment on the effect of DFO on coma recovery since the available results were reported as continuous data. In one trial of deferiprone for people with symptomatic malaria, coma recovery was significantly faster in the deferiprone group (Mohanty 2002).

Are persistent seizures less likely with adjunctive DFO treatment?

The results from one trial indicate that adjunctive DFO treatment has a significant association with a reduction in the incidence of

persistent seizures in children less than six years old with severe malaria (Thuma 1998a).

Do iron-chelating agents have an effect on parasitaemia?

The results are inconclusive for people with severe malaria. Trialists need to report parasitaemia effects in a consistent way to allow data to be pooled.

In trials of DFO alone versus placebo in people with asymptomatic malaria, means and standard error of the means were reported for parasite concentration. The evidence indicates that participants treated with DFO experienced a significant decrease in mean parasite concentration compared to those taking placebo or no treatment.

Two trials of deferiprone in people with asymptomatic malaria reported means and standard error of the means for parasite concentrations. The results showed no evidence of an effect on parasitaemia. To detect even a 40% reduction in parasites would require at least eight participants in each arm of the 75 mg/kg trial and 11 in each arm of the 100 mg/kg trial (Thuma 1998b-i; Thuma 1998b-ii). The actual numbers used were much smaller. The investigators proposed that, given the low numbers, it is possible the antimalarial effect of deferiprone was not found due to a type II error.

In one trial of deferiprone in people with *P. falciparum* infection and fever (Mohanty 2002), mean time to parasite clearance was significantly faster in the deferiprone group, but it is difficult to determine clinical significance from the small number of study participants.

What are the adverse effects associated with iron-chelating agents?

Hypoglycaemia, phlebitis, and swelling and pain at the site of needle insertion were observed in the DFO trials. All these effects were more common in the participants treated with DFO, but due to the small numbers randomized in the trials we cannot comment on the clinical significance of these results. It should be noted that in one trial, Gordeuk 1992a, participants were questioned regarding adverse effects twice daily, but facilities for thoroughly assessing auditory and visual neurotoxicities were not available. Such effects have been detected in patients receiving long-term DFO therapy (Olivieri 1996), but the trial authors suggested the short-term nature of this trial probably lessens the risk of such complications. Therefore, until further trials can confirm that neurological adverse effects are not associated with DFO therapy, adverse effect data should be regarded as incomplete and interpreted with caution.

Headaches and dizziness occurred more frequently in those receiving deferiprone compared to placebo. Abdominal pain, myalgia, and malaise did not differ significantly between the treatment

groups. Neutropenia has been observed in other studies of deferiprone (75 to 100 mg/kg/day or more), but only in iron-overloaded patients over a long period (Berdoukas 1993). Another adverse effect associated with deferiprone is haematological toxicity, which may be idiosyncratic (Thuma 1998b-i; Thuma 1998b-ii). No data were available for these effects in trials of deferiprone in malaria, which signifies the need to confirm (in future trials) whether or not persons treated with this iron-chelating agent are likely to experience such effects.

Applicability

Trials of iron-chelating agents as adjunctive treatments for malaria were prompted by the fact that cerebral malaria remains a major cause of death in African children despite treatment with standard antimalarial drugs. All trials included in this review, except one small trial in India, were conducted in Zambia. This limits our ability to comment on the wider relevance of iron-chelating agents to populations in other malarious areas.

Trials of DFO in malaria do show positive (but not statistically significant) results; however, it may not be the ideal iron-chelating agent for use in malaria. Parenteral administration is required due to the poor absorption of DFO, so its use is unlikely in uncomplicated malaria or areas where equipment is not readily available. The drug is also expensive and requires continuous administration for optimal effectiveness, limiting its use in most malarious areas of Africa and Asia.

AUTHORS' CONCLUSIONS

Implications for practice

There are insufficient data to draw conclusions about the effect of the DFO or deferiprone iron-chelating agents.

Implications for research

In view of the tendency in one trial for DFO to be associated with more deaths, and given the paucity of recent trials in this area (most recent trial published in 2002) and other priorities in malaria treatment research, new trials in this area are unlikely and we do not plan to update this review.

ACKNOWLEDGEMENTS

We thank D Laloo, H McIntosh, M Molyneux, and P Winstanley for helpful comments; and PE Thuma for kindly supplying original data. This document is an output from a project funded by the Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

REFERENCES

References to studies included in this review

Gordeuk 1992a {published data only}

Gordeuk VR, Thuma PE, Brittenham GM, Zulu S, Simwanza G, Mhangu A, et al. Iron chelation with desferrioxamine B in adults with asymptomatic Plasmodium falciparum parasitaemia. *Blood* 1992;**79**(2):308–12.

Gordeuk 1992b {published data only}

* Gordeuk VR, Thuma PE, Brittenham G, McLaren C, Parry D, Backenstose A, et al. Effect of iron chelation therapy on recovery from deep coma in children with cerebral malaria. *New England Journal of Medicine* 1992;**327**(21):1473–7.
Hershko C, Gordeuk VR, Thuma PE, Theanacho EN, Spira DT, Hider RC, et al. The antimalarial effect of iron chelators: studies in animal models and in humans with mild falciparum malaria. *Journal of Inorganic Biochemistry* 1992;**47**(3–4):267–77.

Gordeuk 1993 {published data only}

Gordeuk VR, Thuma PE, Brittenham GM, Biemba G, Zulu S, Simwanza G, et al. Iron chelation as a chemotherapeutic strategy for falciparum malaria. *American Journal of Tropical Medicine and Hygiene* 1993;**48**(2):193–7.

Mohanty 2002 {published data only}

Mohanty D, Ghosh K, Pathare AV, Karnad D. Deferiprone (L1) as an adjuvant therapy for Plasmodium falciparum malaria. *Indian Journal of Medical Research* 2002;**115**:17–21.

Thuma 1998a {published data only}

Thuma PE, Mabeza GF, Biemba G, Bhat GJ, McLaren CE, Moyo VM, et al. Effect of iron chelation therapy on mortality in Zambian children with cerebral malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1998;**92**(2):214–8.

Thuma 1998b-i {published data only}

Thuma PE, Olivieri NF, Mabeza GF, Biemba G, Parry D, Zulu S, et al. Assessment of the effect of the oral iron chelator deferiprone on asymptomatic Plasmodium falciparum parasitemia in humans. *American Journal of Tropical Medicine and Hygiene* 1998;**58**(3):358–64.

Thuma 1998b-ii {published data only}

Thuma PE, Olivieri NF, Mabeza GF, Biemba G, Parry D, Zulu S, et al. Assessment of the effect of the oral iron chelator deferiprone on asymptomatic Plasmodium falciparum parasitemia in humans. *American Journal of Tropical Medicine and Hygiene* 1998;**58**(3):358–64.

References to studies excluded from this review

Bunnag 1992 *{published data only}*

Bunnag D, Poltera AA, Viraan C, Looareesuwan S, Harinasuta KT, Schindlery C, et al. Plasmodicidal effect of desferrioxamine B in human vivax or falciparum malaria from Thailand. *Acta Tropica* 1992;**52**(1):59–67.

Gordeuk 1990 *{published data only}*

Gordeuk VR, Thuma PE, Brittenham GM, Backenstose AR, Vargas L, McKinley E, et al. Reduced duration of coma in children receiving adjunctive desferrioxamine for cerebral malaria (Abstract). *Clinical Research* 1990;**38**(3):866.

Looareesuwan 1996 *{published data only}*

Looareesuwan S, Wilairatana P, Vannaphan S, Gordeuk VR, Taylor TE, Meshnick SR, et al. Co-administration of desferrioxamine B with artesunate in malaria: an assessment of safety and tolerance. *Annals of Tropical Medicine and Parasitology* 1996;**90**(5):551–4.

Traore 1991 *{published data only}*

Traore O, Carnevale P, Kaptue-Noche L, M'Bede J, Desfontaine M, Elion J, et al. Preliminary report on the use of desferrioxamine in the treatment of Plasmodium falciparum malaria. *American Journal of Hematology* 1991;**37**(3):206–8.

Additional references**Berdoukas 1993**

Berdoukas V, Bentley P, Frost H, Schnebli HP. Toxicity of iron chelator L1. *Lancet* 1993;**341**(8852):1088.

Hershko 1994

Hershko C, Cabantchik ZI. Control of malaria by drug-mediated iron deprivation. *Israel Journal of Medical Sciences* 1994;**30**(11):840–5.

Hider 1994

Hider RC, Epemolu O, Singh S, Porter JB. Iron chelator design. *Advances in Experimental Medicine and Biology* 1994;**356**:343–9.

Higgins 2006

Higgins J, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Appendix 5b. www.cochrane.org/resources/handbook/hbook.htm (accessed 1 May 2007).

Jüni 2001

Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303):42–6.

Lytton 1994

Lytton SD, Mester B, Libman J, Shanzer A, Cabantchik ZI. Mode of action of iron (III) chelators as antimalarials: Evidence for differential effects on parasite iron-dependent nucleic acid synthesis. *Blood* 1994;**84**(3):910–5.

Mabeza 1996

Mabeza GF, Biemba G, Gordeuk VR. Clinical studies of iron chelators in malaria. *Acta Haematologica* 1996;**95**(1):78–86.

Meshnick 1993

Meshnick SR, Yang YZ, Lima V, Kuypers F, Kamchonwongpaisan S, Yuthavong Y. Iron-dependent free radical generation from the antimalarial agent artemisinin (qinghaosu). *Antimicrobial Agents and Chemotherapy* 1993;**37**(5):1108–14.

Murray 1975

Murray MJ, Murray NJ, Murray AB, Murray MB. Refeeding malaria and hyperferræmia. *Lancet* 1975;**1**(7908):653–4.

Murray 1978

Murray MJ, Murray AB, Murray MB, Murray CJ. The adverse effect of iron repletion on the course of certain infections. *British Medical Journal* 1978;**2**(6145):1113–5.

Olivieri 1996

Olivieri NF, Buncic JR, Chew E, Gallant T, Harrison RV, Keenan N, et al. Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. *New England Journal of Medicine* 1996;**314**(14):869–73.

Oppenheimer 1984

Oppenheimer SJ, Gibson FD, Macfarlane SB, Moody JB, Hendrickse RG. Iron supplementation and malaria. *Lancet* 1984;**1**(8373):389–90.

Raventos 1982

Raventos-Suarez C, Pollack S, Nagel RL. Plasmodium falciparum: inhibition of in vitro growth by desferrioxamine. *American Journal of Tropical Medicine and Hygiene* 1982;**31**(5):919–22.

Review Manager 5

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

WHO 2000

Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000;**94**(Suppl 1):1–90.

Wylter 1992

Wylter DJ. Bark, weeds, and iron chelators -- drugs for malaria. *New England Journal of Medicine* 1992;**327**(21):1519–21.

References to other published versions of this review**Smith 2000**

Smith HJ, Meremikwu M. Iron chelating agents for treating malaria. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD001474]

Smith 2003

Smith HJ, Meremikwu M. Iron chelating agents for treating malaria. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD001474]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gordeuk 1992a

Methods	Cross-over trial Generation of allocation sequence: not specified Allocation concealment: unclear Blinding: double blind Inclusion of all randomized participants: 100% (28/28) for the initial period used in this analysis; 3/28 withdrawn after first 72 h
Participants	Number: 28 Description: adults aged 15 to 56 years; partially immune with asymptomatic <i>P. falciparum</i>
Interventions	Iron-chelating agent vs placebo 1. DFO B (100 mg/kg/day) 2. Placebo (normal saline) Subcutaneous infusion over 72 h, then cross-over; initial period only used in this analysis
Outcomes	1. Mean parasite concentration 2. Rate of parasite clearance (graph) 3. Side effects
Notes	Location: Zambia Date: February to August 1990 Sources of support: Ciba-Geigy donated DFO

Gordeuk 1992b

Methods	Generation of allocation sequence: not specified Allocation concealment: central randomization by pharmacy staff Blinding: double blind Inclusion of all randomized participants: 100%
Participants	Number: 83 children Description: < 6 years; cerebral malaria; <i>P. falciparum</i> parasitaemia; unrousable coma
Interventions	Iron-chelating agent plus antimalarial drugs vs placebo plus antimalarial drugs 1. DFO mesylate (100 mg/kg/day) 2. Placebo (5% dextrose) Continuous infusion over 72 h; added to standard quinine and sulfadoxine-pyrimethamine treatment
Outcomes	1. Mortality 2. Time to recovery of full consciousness (Glasgow Coma Scale: 5) 3. PCT (ring form decrease to < 22/mm ³) 4. Rate of parasite clearance (graph)

Gordeuk 1992b (Continued)

Notes	Location: Macha Mission Hospital, S. Province, Zambia Date: 1990-1 Sources of support: Ciba-Geigy donated DFO; Macha Mission Hospital pharmacy prepared the placebo Paired sequential design used for first 30 participants enrolled; study too small to detect reduction in mortality
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Gordeuk 1993

Methods	Generation of allocation sequence: not specified Allocation concealment: unclear Blinding: double blind Inclusion of all randomized participants: 100%
Participants	Number: 37 Description: adult rural Zambians with asymptomatic <i>P. falciparum</i>
Interventions	Iron-chelating agent vs placebo 1. DFO B (100 mg/kg/day) 2. Placebo (normal saline) Continuous subcutaneous infusion over 72 h
Outcomes	Mean parasite concentration (graph)
Notes	Location: Macha, S. Province, Zambia Date: Aug 1990 to Feb 1991 Sources of support: Ciba-Geigy provided DFO First 10 days of study used, day 11 participants with persisting parasitaemia offered DFO (not randomized)

Mohanty 2002

Methods	Generation of allocation sequence: random-number table Allocation concealment: serial numbering Blinding: double blind Inclusion of all randomized participants: 100%
Participants	Number: 45 Description: aged 13 to 84 years with <i>P. falciparum</i> infection and fever
Interventions	Iron-chelating agent plus antimalarial drugs vs placebo plus antimalarial drugs 1. Deferiprone (75 mg/kg/day in 12 hourly divided doses) plus antimalarial regimen for 10 days 2. Placebo capsules plus antimalarial regimen for 10 days Antimalarial regimen: standard quinine and doxycycline therapy plus supportive therapy
Outcomes	1. Mortality 2. Coma recovery 3. Parasite clearance

Mohanty 2002 (Continued)

Notes	Location: KEM hospital, Mumbai, India Date: 1996-7
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Thuma 1998a

Methods	Generation of allocation sequence: not specified; block randomization Allocation concealment: centrally randomized by pharmacy staff Blinding: double blind (only pharmacist knew code) Inclusion of all randomized participants: 100%
Participants	Number: 352 Description: Zambian children aged < 6 years; asexual forms of <i>P. falciparum</i> ; unrousable coma (Blantyre Coma Scale < 5); normal cerebrospinal fluid
Interventions	Iron-chelating agent plus antimalarial drugs vs placebo plus antimalarial drugs 1. DFO B (100 mg/kg/day) 2. Placebo (5% dextrose) Continuous IV infusion over 72 h; added to standard quinine treatment (7-day regimen); also used a quinine loading dose of 20 mg/kg
Outcomes	1. Mortality 2. Coma recovery (time to Blantyre Coma Scale: 5) 3. Parasite clearance time (ring form decrease to < 20/cubic mm) 4. Fever clearance time (temperature decrease to 37.8 °C) 5. Parasite clearance day 3 6. Adverse effects
Notes	Location: Macha Mission Hospital, S. Province (rural) and University Teaching Hospital, Lusaka (urban), Zambia Date: 1992-4 Sources of support: Ciba-Geigy donated DFO Initially to include 600 children but stopped by safety committee

Thuma 1998b-i

Methods	Cross-over trial Generation of allocation sequence: not specified; block randomization Allocation concealment: unclear Blinding: double blind (only pharmacist knew code) Inclusion of all randomized participants: 12/13; 13 enrolled, 1 removed after 24 h (12 completed trial period)
Participants	Number: 13 Description: adult (male) Zambians; asymptomatic <i>P. falciparum</i> parasitaemia
Interventions	Iron-chelating agent vs placebo 1. Deferiprone (75 mg/kg/day) 2. Placebo

Thuma 1998b-i (Continued)

	Administered sequentially every 8 h for 72 h; 3 days wash out, then cross-over; initial trial period only used in review
Outcomes	1. Mean parasite concentration (graph) 2. Toxicity and side effects
Notes	Location: Macha Mission Hospital, Zambia Date: September to December 1993 Sources of support: University of Toronto synthesized deferiprone; Novopharm Ltd, Toronto prepared capsules; Pharmacy Dept, Hospital for Sick Children, Toronto prepared placebo capsules 1 of 2 trials (along with Thuma 1998b-ii) reported in 1 publication

Thuma 1998b-ii

Methods	Cross-over trial Generation of allocation sequence: not specified; block randomization Allocation concealment: unclear Blinding: double blind (only pharmacist knew code) Inclusion of all randomized participants: 10/12; 12 enrolled, 2 dropped out (1 at 3 days, 1 at 7 days), 10 completed the study
Participants	Number: 12 Description: adult (male) Zambians; asymptomatic <i>P. falciparum</i> parasitaemia
Interventions	Iron-chelating agent vs placebo 1. Deferiprone (100 mg/kg/day) 2. Placebo Given orally every 6 h for 96 h; 24 h wash out then, cross-over; initial trial period only used in review
Outcomes	1. Mean parasite concentration (graph) 2. Toxicity and side effects
Notes	Location: Macha Mission Hospital, Zambia Date: September to December 1993 Sources of support: University of Toronto synthesized deferiprone; Novopharm Ltd, Toronto prepared capsules; Pharmacy Dept, Hospital for Sick Children, Toronto prepared placebo capsules 1 of 2 trials (along with Thuma 1998b-ii) reported in 1 publication

DFO: desferrioxamine; *P. falciparum*: *Plasmodium falciparum*.

Characteristics of excluded studies *[ordered by study ID]*

Bunnag 1992	Open pilot study
Gordeuk 1990	Correspondence with first author confirmed that this abstract describes preliminary research conducted prior to Gordeuk 1992b , which is included in this review
Looareesuwan 1996	In an initial toxicity check, 13 patients were treated with artesunate alone (2.4 mg/kg by intravenous, then 1.2 mg/kg by intravenous every 12 h for 8 doses) or the same regimen of artesunate plus desferrioxamine (DFO) continuous infusion over 72 h. Once it was clear little toxicity was occurring, another 18 patients were treated similarly in a randomized single-blind trial. However, because the initial 13 patients had similar baseline characteristics to the subsequent 18 patients, the results were combined. Thus 2 data sets are combined, but 1 is the result of a nonrandomized study
Traore 1991	Pilot trial with just 3 patients as controls

DATA AND ANALYSES

Comparison 1. Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	435	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.89, 2.18]
2 Persistent seizures (> 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Parasite clearance at day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Phlebitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Recurrent hypoglycaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Deferiprone vs placebo: asymptomatic malaria

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abdominal pain	2	44	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.38, 4.35]
2 Headache	2	44	Risk Ratio (M-H, Fixed, 95% CI)	8.0 [1.08, 59.05]
3 Dizziness	2	44	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.63, 39.65]
4 Myalgia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Malaise	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Deferiprone vs placebo (plus standard antimalarial regimen): symptomatic malaria

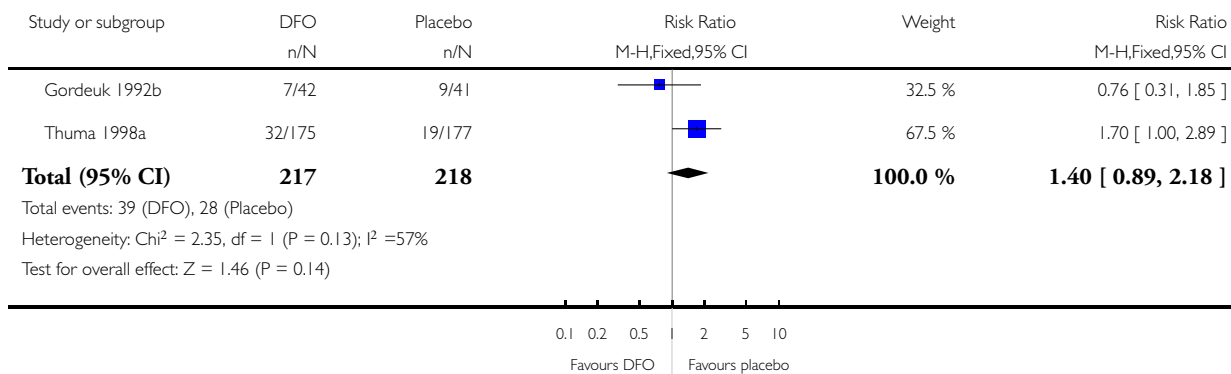
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Coma recovery time	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Parasite clearance time	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria, Outcome 1 Death.

Review: Iron-chelating agents for treating malaria

Comparison: 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria

Outcome: 1 Death

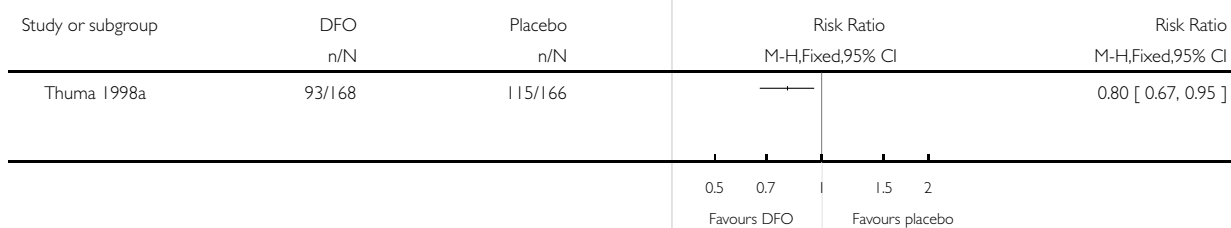


Analysis 1.2. Comparison 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria, Outcome 2 Persistent seizures (> 3).

Review: Iron-chelating agents for treating malaria

Comparison: 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria

Outcome: 2 Persistent seizures (> 3)

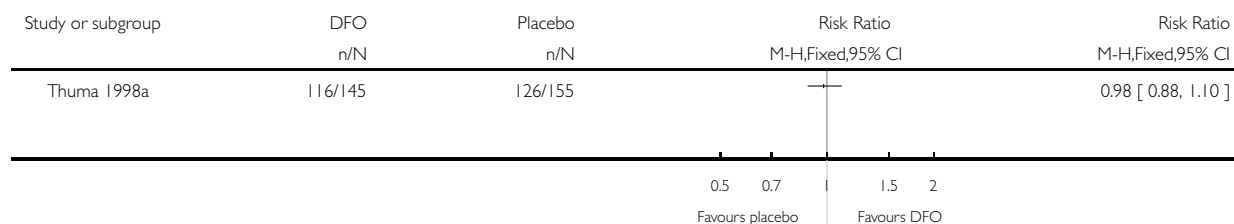


Analysis 1.3. Comparison 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria, Outcome 3 Parasite clearance at day 3.

Review: Iron-chelating agents for treating malaria

Comparison: 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria

Outcome: 3 Parasite clearance at day 3

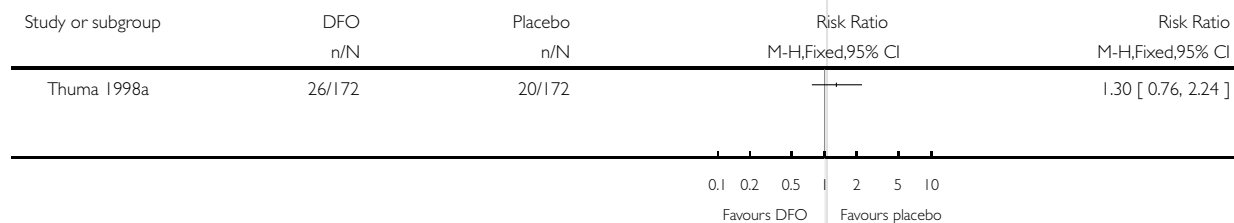


Analysis 1.4. Comparison 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria, Outcome 4 Phlebitis.

Review: Iron-chelating agents for treating malaria

Comparison: 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria

Outcome: 4 Phlebitis

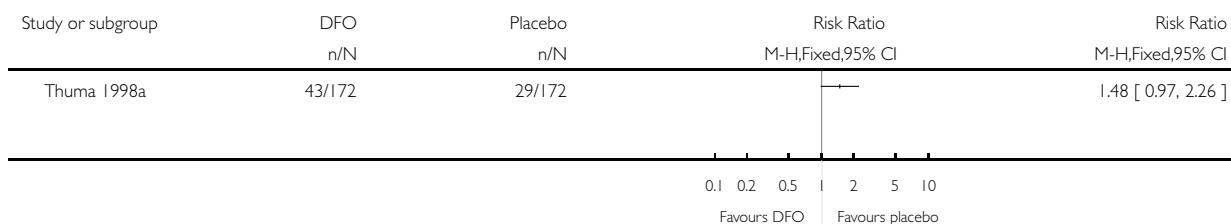


Analysis 1.5. Comparison 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria, Outcome 5 Recurrent hypoglycaemia.

Review: Iron-chelating agents for treating malaria

Comparison: 1 Desferrioxamine (DFO) vs placebo (plus standard antimalarial regimen): severe malaria

Outcome: 5 Recurrent hypoglycaemia

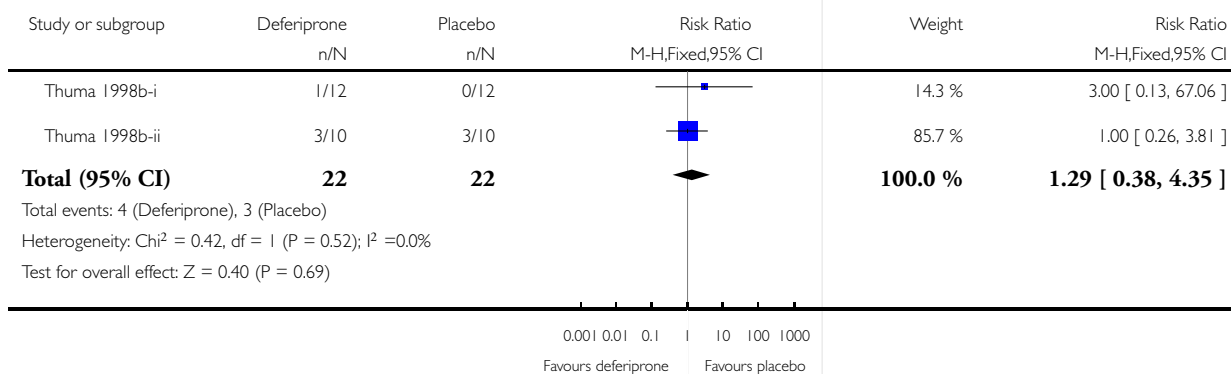


Analysis 2.1. Comparison 2 Deferiprone vs placebo: asymptomatic malaria, Outcome 1 Abdominal pain.

Review: Iron-chelating agents for treating malaria

Comparison: 2 Deferiprone vs placebo: asymptomatic malaria

Outcome: 1 Abdominal pain

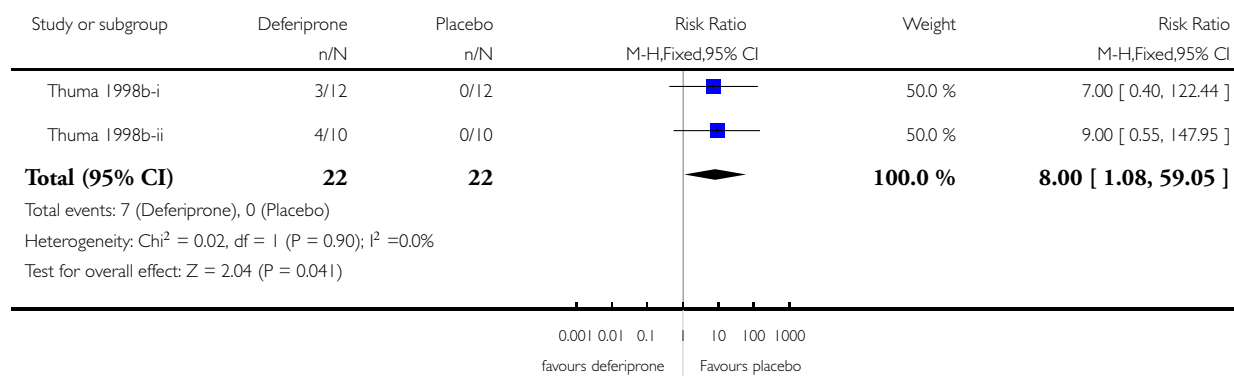


Analysis 2.2. Comparison 2 Deferiprone vs placebo: asymptomatic malaria, Outcome 2 Headache.

Review: Iron-chelating agents for treating malaria

Comparison: 2 Deferiprone vs placebo: asymptomatic malaria

Outcome: 2 Headache

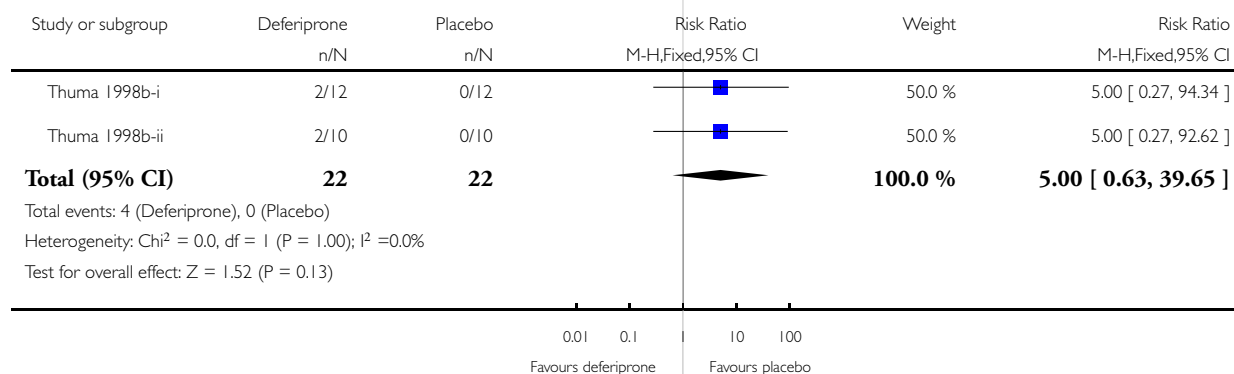


Analysis 2.3. Comparison 2 Deferiprone vs placebo: asymptomatic malaria, Outcome 3 Dizziness.

Review: Iron-chelating agents for treating malaria

Comparison: 2 Deferiprone vs placebo: asymptomatic malaria

Outcome: 3 Dizziness

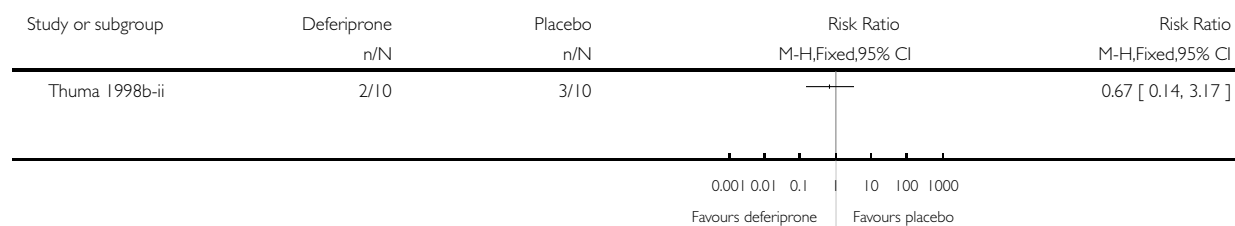


Analysis 2.4. Comparison 2 Deferiprone vs placebo: asymptomatic malaria, Outcome 4 Myalgia.

Review: Iron-chelating agents for treating malaria

Comparison: 2 Deferiprone vs placebo: asymptomatic malaria

Outcome: 4 Myalgia

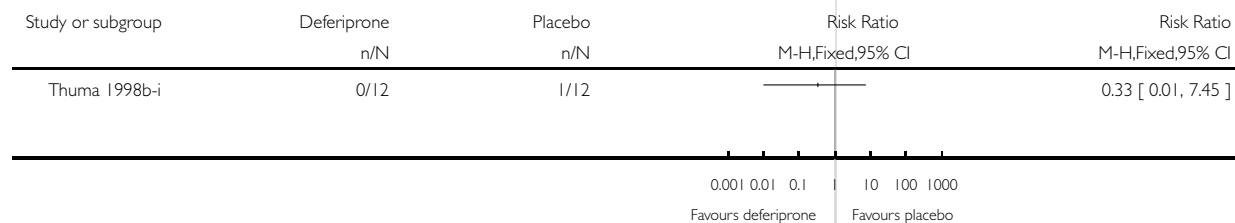


Analysis 2.5. Comparison 2 Deferiprone vs placebo: asymptomatic malaria, Outcome 5 Malaise.

Review: Iron-chelating agents for treating malaria

Comparison: 2 Deferiprone vs placebo: asymptomatic malaria

Outcome: 5 Malaise

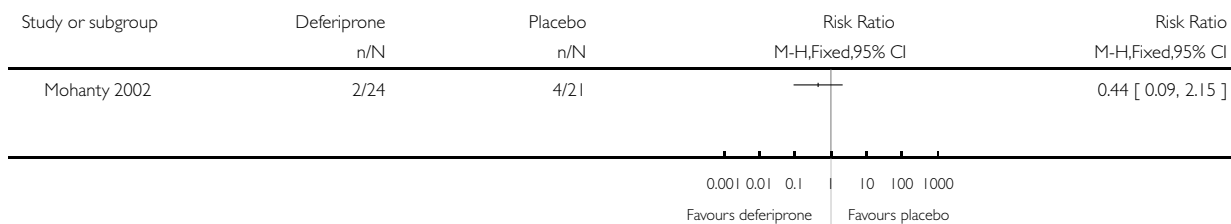


Analysis 3.1. Comparison 3 Deferiprone vs placebo (plus standard antimalarial regimen): symptomatic malaria, Outcome 1 Death.

Review: Iron-chelating agents for treating malaria

Comparison: 3 Deferiprone vs placebo (plus standard antimalarial regimen): symptomatic malaria

Outcome: 1 Death

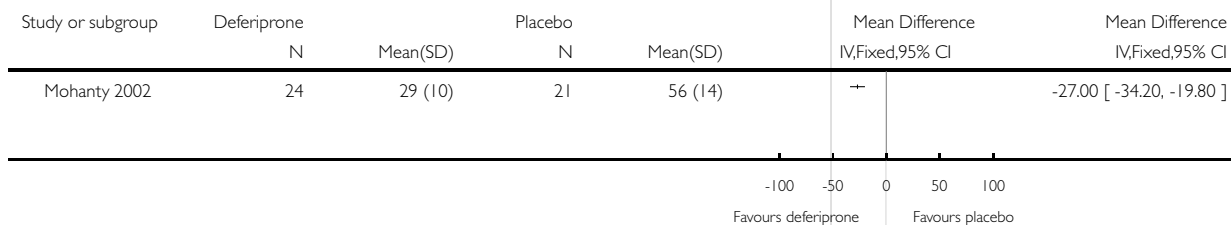


Analysis 3.2. Comparison 3 Deferiprone vs placebo (plus standard antimalarial regimen): symptomatic malaria, Outcome 2 Coma recovery time.

Review: Iron-chelating agents for treating malaria

Comparison: 3 Deferiprone vs placebo (plus standard antimalarial regimen): symptomatic malaria

Outcome: 2 Coma recovery time



Analysis 3.3. Comparison 3 Deferiprone vs placebo (plus standard antimalarial regimen): symptomatic malaria, Outcome 3 Parasite clearance time.

Review: Iron-chelating agents for treating malaria

Comparison: 3 Deferiprone vs placebo (plus standard antimalarial regimen): symptomatic malaria

Outcome: 3 Parasite clearance time

Study or subgroup	Deferiprone		Placebo		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
Mohanty 2002	24	48 (17)	21	72 (21)	→→	-24.00 [-35.27, -12.73]

-100 -50 0 50 100
Favours deferiprone Favours placebo

WHAT'S NEW

Last assessed as up-to-date: 16 February 2003.

16 July 2008	Review declared as stable	We do not plan to update review since it is unlikely that this topic will be considered a priority for further research. Converted to new review format with minor editing.
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HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 4, 1999

22 August 2007	Amended	1 study awaiting assessment (Gordeuk 1990) excluded after correspondence with the first author; review edited and methods clarified.
14 May 2007	New search has been performed	Search updated and no new trials found.
17 February 2003	New citation required and conclusions have changed	Smith 2003 : 1 new trial identified (January 2003) and included (February 2003); we amended the background, search strategy, description of studies, methodological quality of included studies, results, and discussion.

CONTRIBUTIONS OF AUTHORS

We independently applied inclusion criteria, assessed trial methodological quality, and extracted data. H Smith entered data into Review Manager, analysed the data, and co-wrote the review. M Meremikwu helped analyse the data and co-wrote the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (UK), UK.
- European Commission (Development Directorate XII, Grant IC 18 CT 96 0086), Belgium.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*therapeutic use]; Chemotherapy, Adjuvant; Iron Chelating Agents [*therapeutic use]; Malaria, Cerebral [drug therapy]; Malaria, Falciparum [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans