Rectal administration of artemisinin derivatives for the treatment of malaria
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CRD summary
This review of rectally administered artemisinin derivatives for malaria treatment concluded that they demonstrated acceptable therapeutic efficacy, including in severe illness. The reliability of this conclusion was unclear as some aspects of the review, including the synthesis and validity assessment, were poorly reported and potentially inappropriate.

Authors' objectives
To review the pharmacokinetic, efficacy and safety of rectally administered artesunate, artemisinin, dihydroartemisinin and artemether for the treatment of malaria. This abstract will deal only with efficacy and safety.

Searching
The following databases were searched without language restrictions up to December 2006: MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, Global Health and Web of Science. Search terms were reported. Pharmaceutical companies were contacted, conference proceedings and regulatory applications reviewed and references of retrieved articles checked.

Study selection
Studies which assessed rectal administration of an artemisinin derivative in healthy volunteers or patients of any age, regardless of malaria (Plasmodium) parasite species or clinical status, were eligible for inclusion. To be included, participant details had to be clearly specified, with either plasma drug concentrations or parasite clearance assessed using serial blood smears taken at least every 6 hours. Primary outcomes were malaria parasite density as a percentage of baseline at 12 and 24 hours, and time to 50% reduction in parasitaemia. Secondary outcomes were total parasite clearance time, mortality and adverse events.

Controlled studies used comparators of parenteral quinine, artemether or artesunate. Approximately half the included studies were in children, others enrolled only adults or both children and adults. The severity of malaria ranged from uncomplicated to severe. A range of doses and regimens of artemisinin derivatives were employed.

Two reviewers independently selected the studies for inclusion.

Assessment of study quality
Studies were independently assessed for validity by two independent reviewers using the 11 items of the Maastricht-Amsterdam score list which relate to internal validity. Studies which fulfilled at least 6 of the criteria were considered to be high quality.

Data extraction
Parasite densities at 12 and 24 hours as a percentage of baseline were extracted or calculated, using graphical data presentations were necessary. Means or medians (for non-normal data distributions) and standard deviations were employed in calculations. Measures of central tendency and variance were extracted as stated in the primary studies.

The authors did not report how many reviewers carried out the data extraction.

Methods of synthesis
Weighted means were calculated for each agent. A narrative synthesis grouped by the agent and dose employed and, where appropriate, severity of illness treated was also provided. Other differences between studies were discussed in the text and were further apparent from the evidence tables. No formal assessment of statistical heterogeneity was reported.

Results of the review
Thirty-nine studies were included in the review (n = 1,224).

Artesunate (19 studies, n=643): Parasite clearance during the first 12 hours was generally slower in studies using doses below 5 mg/kg than in those using higher doses. Six patients (1.7%) died in studies of severe malaria and two (0.7%) in studies of moderately severe infection.

Artemisinin (10 studies, n=350): In six studies which reported time to 50% reduction in parasitaemia, the mean or median time ranged from 7 to 11.3 hours. Weighted mean mortality was 12.9%.

Dihydroartemisinin (two studies, n=180): One of the two studies clearly reported parasite clearance data, density rose to 30% above baseline at 12 hours and fell to 70% at 24 hours. No deaths were reported in either study.

Artemether (one study, n=51): The single small study found a parasite clearance time of 54.2 hours and a mortality rate of 11.7%.

Comparative studies (eight studies): Studies showed that rectal artesunate was associated with greater reductions in parasitaemia than parenteral quinine (one study) and greater reductions in parasite density compared to intramuscular artemether (one study) but there was no significant difference in other outcomes. Other studies showed significantly faster parasite clearance associated with artemisinin suppositories compared to intravenous or intramuscular quinine (three studies), and more rapid total parasite clearance time with dihydroartemisinin suppositories compared to intravenous quinine (one study). Studies showed no significant treatment differences for other outcomes. One study reported no significant differences between rectal artemether and intravenous quinine for any outcomes.

Authors’ conclusions
Despite marked inter-individual variability in bioavailability, rectal preparations appear to have acceptable therapeutic efficacy for the treatment of malaria, including in severe illness.

CRD commentary
The review question and inclusion criteria were clear. The authors searched a number of relevant databases and other sources without language restrictions, thereby reducing the chances of language or publication bias, as well as of relevant studies being excluded. Rigorous review methodology was reported for the selection of studies and the assessment of validity, but not for the extraction of data. An appropriate validity assessment was carried out but the results of the assessment were not reported, nor were they used to inform the synthesis. Some aspects of the synthesis itself were poorly reported and it did not appear that statistical heterogeneity between studies was assessed. In view of this, and the noted clinical heterogeneity between studies, it is unclear whether the statistical pooling of studies was appropriate. Given concerns about the appropriateness of the synthesis and the poor reporting of some aspects of the review, the reliability of the authors’ conclusions is unclear.

Implications of the review for practice and research
Practice: The authors stated that rectal artemisinin should be prescribed as recommended in current WHO guidelines, with use restricted to pre-transfer treatment when oral and injectable treatments are not possible, followed promptly by definitive treatment.

Research: The authors stated that further research is required to evaluate the following aspects of rectal artemisinin drugs: direct comparison of different formulations and doses; pharmacokinetic analysis; and comparison of rectal versus intravenous artesunate in well-defined severely ill patients.

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Bibliographic details
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.