A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria


Authors' objectives
The primary objective was to compare quinine and artemether in the treatment of severe malaria, with respect to mortality. The secondary aims were the comparison of the two treatments with respect to neurological sequelae, parasite clearance, fever clearance and coma recovery.

Searching
The trials were identified using three methods: discussion with an international panel of malaria clinical investigators; a search of MEDLINE; and reference to trials identified previously by the Cochrane Collaboration. The principal investigators were contacted for details of any other relevant trials they knew of or were involved in. All investigators were offered full collaboration as part of the Artemether-Quinine Meta-analysis Study Group.

Study selection
Study designs of evaluations included in the review
The meta-analysis included individual patient data (IPD) from randomised controlled trials. The included studies used open label or double-blind design. The review also included further published data from randomised (single-blind and open label) and non-randomised trials (patients paired, and patients paired according to age, gender and complications).

Specific interventions included in the review
The interventions were quinine and artemether. The included studies used a loading dose of 20 mg/kg quinine and a maintenance dose of 10 mg/kg. For artemether, the loading dose ranged from 3.2 to 160 mg/kg, while the maintenance dose ranged from 1.6 to 80 mg/kg.

Participants included in the review
Participants with severe malaria. All included studies had participants with 'P. falciparum' parasitaemia. The entry criteria used by the included studies, in terms of age, ranged from greater than 3 months to greater than 16 years. Only patients who survived to discharge were analysed for the outcome measure sequelae. Only patients with an initial Glasgow coma score below 11 or a Blantyre coma score below 4 were included in the analysis of coma clearance. Only patients with a raised initial temperature were included in the analysis of fever clearance.

Outcomes assessed in the review
The five end points studied were death, neurological sequelae, parasite clearance, coma clearance and fever clearance. The authors also defined a derived 'adverse outcome' variable, which combined death and neurological sequelae. Death was defined as any death attributable to the current episode of malaria infection. The definition of neurological sequelae varied between studies but was uniform within each study, and patients were only compared directly within studies. There was considerable variability between the trials in the definition of 'time-to-event' variables (coma recovery, fever and parasite clearance time). These measures were re-derived for each patient from the raw data in accordance with uniform definitions, which were given in the text. All 'time-to-event' measurements were taken from the time of randomisation.

How were decisions on the relevance of primary studies made?
The principal investigators of the individual trials were contacted with a request for collaboration.

Assessment of study quality
Randomisation checks were carried out to ensure that even allocation to treatment took place across the week and across the whole accrual period. The individual data were also checked for transmission errors and general quality. It was not stated how the decision on whether to include or exclude the studies was undertaken.
Data extraction
IPD from the original databases were requested (from the principal investigators) for an extensive set of clinical and laboratory variables. These variables were defined a priori by the Advisory Committee of the Group following discussions at a preliminary meeting of the clinical investigators. A wide range of admission variables, categorical outcome variables, and raw original measurements of coma score, temperature and parasite counts, were included. The data reported for each included study were: country; inclusion criteria including age group; study drug dose regimen; years of accrual; trial design; the number of participants randomised; and the number of participants excluded.

Methods of synthesis
How were the studies combined?
For binary end points (death, sequelae), the summary odds ratios (ORs) were calculated using the method of Peto-Mantel-Haenszel (see Other Publications of Related Interest no.1). For 'time-to-event' analysis (parasite, fever and comma clearance), the hazard ratio (HR) estimates for each trial were calculated using Cox regression, and an overall estimate was calculated using stratified Cox regression (see Other Publications of Related Interest no.2). All analyses were undertaken on an intention to treat basis.

How were differences between studies investigated?
Heterogeneity of treatment effect between groups of patients with differing baseline characteristics (in terms of demographic and clinical presentation) was explored using subgroup analyses. The predefined patient subgroups were age, severe anaemia, renal failure, low blood-pressure, cerebral malaria, hypoglycaemia and jaundice. A statistical test for heterogeneity was performed using the method based on the event difference (observed minus expected) and variance for binary end points (see Other Publications of Related Interest no.1), and Cox regression models for time-to-event end points (see Other Publications of Related Interest no.2). The results of the separate trials and overview, with 99% confidence intervals (CIs) and 95% CIs, respectively, were presented graphically for each end point in forest plots.

Results of the review
Eleven trials with 2,264 patients were included. IPD were obtained for 7 trials (1,947 patients), one of which was double-blind and the remainder were open label.

In the 7 trials providing IPD, 88 patients were excluded from the original analysis, 60 of whom were included in the overview (n=1,919). Tests for heterogeneity revealed no significant heterogeneity between the 7 studies, between the 2 regions (Africa and Asia), or between adults and children for mortality, sequelae, time to coma clearance or time to parasite clearance. However, for fever clearance, significant heterogeneity did exist between studies, regions and age-groups (all P<0.001).

Overall, there were 136 deaths (14%) among 961 patients treated with artemether, compared with 164 (17%) in the 958 treated with quinine (OR 0.8, 95% CI: 0.62, 1.02, P=0.08).

There was no difference between the two groups in terms of coma recovery (n=1,421, HR 1.09, 95% CI: 0.97, 1.22, P=0.12), fever clearance times (n=1,302, HR 1.01, 95% CI: 0.90, 1.15, P=0.81), or the development of neurological sequelae (n=172, OR 0.82, 95% CI: 0.59, 1.15, P=0.24). The median times to recovery from coma were 24 and 23 hours for artemether and quinine, respectively, and for fever clearance, 42 and 48 hours; neurological sequelae were observed in 81 of the 807 patients in the artemether group and in 91 of the 765 in the quinine group. However, the combined 'adverse outcome' was significantly less common in the artemether group (217 events) than in the quinine group (255 events); the OR was 0.77 (95% CI: 0.62, 0.96, P=0.02). In addition, treatment with artemether was associated with significantly faster parasite clearance (n=1,542, HR 0.62, 95% CI: 0.56, 0.69, P<0.001); the median time was 20 hours for artemether and 32 hours for quinine.

In the subgroup analysis, artemether was associated with a significantly lower mortality than quinine in adults with multisystem failure.
Authors' conclusions
In the treatment of severe falciparum malaria, artemether was at least as effective as quinine in terms of mortality, and was superior to quinine in terms of the overall serious adverse events. There was no evidence of clinical neurotoxicity or any other major side-effects associated with its use.

CRD commentary
This was a reasonably well-conducted review of IPD. The objectives were clearly stated. The literature search was not extensive in that only one database was searched. However, the search was supported by personal contact with clinical investigators and researchers in the field. The trial investigators were contacted to request collaboration, but it was not stated if the authors communicated with the trialists to check the eligibility of each trial for inclusion. It was unclear how decisions on the inclusion or exclusion of studies were made. No exclusion criteria were reported, but it appears that only those studies for which IPD were not obtained were excluded from the meta-analysis.

The data were checked for accuracy and to ensure that an even allocation of treatment had taken place. The authors note that the data were analysed on an intention to treat basis; however, twenty-eight patients that were excluded from the original trials were not included in the meta-analysis. IPD were not obtained for four published studies, which were excluded from the meta-analysis. The authors, however, reported that three of these were unlikely to have used proper randomisation and that all four studies revealed a significant morbidity result in favour of artemether.

The authors concluded that, in terms of mortality, artemether is as good as quinine. However, the results indicated that there were no statistically-significant differences between the two drugs. This does not prove that they are equal.

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Implications of the review for practice and research
The authors did not state any implications for further research and practice.

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