

Publication

Artemether-lumefantrine treatment of uncomplicated Plasmodium falciparum malaria : a systematic review and meta-analysis of day 7 lumefantrine concentrations and therapeutic response using individual patient data

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Achieving adequate antimalarial drug exposure is essential for curing malaria. Day 7 blood or plasma lumefantrine concentrations provide a simple measure of drug exposure that correlates well with artemether-lumefantrine efficacy. However, the 'therapeutic' day 7 lumefantrine concentration threshold needs to be defined better, particularly for important patient and parasite sub-populations.; The WorldWide Antimalarial Resistance Network (WWARN) conducted a large pooled analysis of individual pharmacokinetic-pharmacodynamic data from patients treated with artemether-lumefantrine for uncomplicated Plasmodium falciparum malaria, to define therapeutic day 7 lumefantrine concentrations and identify patient factors that substantially alter these concentrations. A systematic review of PubMed, Embase, Google Scholar, ClinicalTrials.gov and conference proceedings identified all relevant studies. Risk of bias in individual studies was evaluated based on study design, methodology and missing data.; Of 31 studies identified through a systematic review, 26 studies were shared with WWARN and 21 studies with 2,787 patients were included. Recrudescence was associated with low day 7 lumefantrine concentrations (HR 1.59 (95% CI 1.36 to 1.85) per halving of day 7 concentrations) and high baseline parasitemia (HR 1.87 (95% CI 1.22 to 2.87) per 10-fold increase). Adjusted for mg/kg dose, day 7 concentrations were lowest in very young children (<3 years), among whom underweight-for-age children had 23% (95% CI -1 to 41%) lower concentrations than adequately nourished children of the same age and 53% (95% CI 37 to 65%) lower concentrations than adults. Day 7 lumefantrine concentrations were 44% (95% CI 38 to 49%) lower following unsupervised treatment. The highest risk of recrudescence was observed in areas of emerging artemisinin resistance and very low transmission intensity. For all other populations studied, day 7 concentrations ≥ 200 ng/ml were associated with >98% cure rates (if parasitemia <135,000/ μ L).; Current artemether-lumefantrine dosing recommendations achieve day 7 lumefantrine concentrations ≥ 200 ng/ml and high cure rates in most uncomplicated malaria patients. Three groups are at increased risk of treatment failure: very young children (particularly those underweight-for-age); patients with high parasitemias; and patients in very low transmission intensity areas with emerging parasite resistance. In these groups, adherence and treatment response should be monitored closely. Higher, more frequent, or prolonged dosage regimens should now be evaluated in very young children, particularly if malnourished, and in patients with hyperparasitemia.

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