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Slow parasite clearance rates in response to artemether in patients with severe malaria

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We recently reported artemisinin-resistant, uncomplicated *Plasmodium falciparum* malaria in Pursat, western Cambodia.¹ Artemisinin resistance manifests as a slow parasite clearance rate (ie, a long parasite clearance half-life). A concern is that parasite clearance rates might be slower in patients with severe malaria² who receive artemisinin monotherapy parenterally³ until they can take an artemisinin-based drug combination orally. To investigate this possibility, in 2010 we assessed parasite clearance in 30 patients with severe malaria in Pursat, with use of a protocol (ClinicalTrials.gov identifier: NCT00341003) approved by Cambodia's National Ethics Committee for Health Research and the National Institute for Allergy and Infectious Diseases Institutional Review Board. Adults or parents of child participants gave written informed consent.

The appendix shows patient characteristics. 87% (26/30) of patients were men and the median age was 25 years (inter-quartile range 20–32 years). 70% (21/30) of patients had at least one erythrocyte polymorphism. 33% (10/30) of patients had *P falciparum* gametocytaemia and 10% (3/10) had *Plasmodium vivax* parasitaemia. Most patients had prostration, repetitive vomiting, or cessation of eating and drinking, or a combination of these manifestations. Two patients had severe anaemia or renal insufficiency; none had cerebral malaria or died. The median haemoglobin concentration was 140 g/L (interquartile range 120–150 g/L). The initial parasite density (median 141 744 parasites per μ L, interquartile range 88 873–264 631 parasites per μ L) was higher than it was in our recent study of patients with uncomplicated malaria (n=168, 50 498 parasites per μ L, interquartile range 27 940–123 276 parasites per μ L, $p<0.0001$).¹

After initial parasite density was counted, patients received intramuscular artemether (3.2 mg/kg on day 0, then 1.6 mg/kg on days 1–4) and orally administered mefloquine (25 mg/kg over days 5 and 6). Parasite densities were counted from thick blood films every 6 h until parasites were undetectable¹ and the data were used to create parasite clearance curves.⁴ The parasite clearance half-life was calculated with use of the Worldwide Antimalarial Resistance Network online parasite clearance estimator.⁵ The parasite clearance time

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See **Online** for appendix

For the **online parasite clearance estimator** see <http://www.wwarn.org/toolkit/data-management/parasite-clearance-estimator>

(median 96 h, interquartile range 66–116 h) was longer than that in our recent study of patients with uncomplicated malaria (n=167, 78 h, interquartile range 60–90 h, p=0.007)¹ and ranged from 48 h to 150 h. One patient with an initial parasite density of 528 000 parasites per μL received artemisinin–piperaquine (Artequick, Artepharm Co, Guangzhou, China) at 168 h and cleared her parasitaemia at 204 h. As was expected, the parasite clearance time correlated with the initial parasite density (Spearman's rank $r=0.501$, p=0.005). The parasite clearance half-life (geometric mean 5.90 h, 95% CI 5.02–6.93) was similar to that in patients with uncomplicated malaria in our recent study (n=168, 5.85 h, 95% CI 5.54–6.18, p=0.781)¹ and did not correlate with age, haemoglobin type, haemoglobin concentration, or initial parasite density.

In this letter, we report baseline parasite clearance rates in patients with severe malaria in western Cambodia. Similar half-life values in patients with severe or uncomplicated malaria suggest that artemether treatment for severe malaria does not accelerate parasite clearance rates compared with artesunate treatment for uncomplicated malaria. Future efforts should monitor parasite clearance and recrudescence rates in patients with severe malaria harbouring large parasite biomasses, which may be more likely to yield artemisinin-resistant parasites.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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