Artesunate Dosing in Severe Falciparum Malaria

To the Editor—In the past 6 years the largest ever randomized controlled trials in severe falciparum malaria have been reported [1, 2]. Compared with quinine, parenteral artesunate reduced mortality by 22.5% (from 10.9% to 8.5%) in African children (N = 5425) and by 35% (from 22% to 15%) in Southeast Asian patients (N = 1461, of whom 202 were children). The artesunate dose evaluated in the AQUAMAT and SEAQUAMAT trials and now recommended by the World Health Organization (WHO) was 2.4 mg/kg, given twice on the day of admission, followed by 2.4 mg/kg once daily. The 2.4 mg/kg intravenous artesunate dose corresponds approximately to the widely used oral dose of 4 mg/kg per day, which gives maximal parasite clearance rates against sensitive parasites [3]. Kremsner et al [4] now report a comparison of a once daily 4 mg/kg intravenous artesunate dose with the WHO-recommended regimen in African children hospitalized with malaria. Despite the

title of their article, Kremsner at al [4] did not study severe malaria (mortality, 1.1%; 2 of 177 children enrolled). Nevertheless, based on similar parasite clearance measures between treatment arms, the authors conclude that "a simple 24-hour, 3-dose regimen should be further studied and developed to licensure for treating severe malaria in children." We think that this conclusion is not valid and that it could be dangerous.

A recommendation to consider changing dosing in a lethal disease cannot be based on a small study in moderately ill patients using a weak and unvalidated surrogate endpoint. Parasite clearance times correlate poorly with disease outcome. Earlier large trials comparing intramuscular artemether with quinine in African children with severe malaria showed more rapid parasite clearance with artemether but no difference in case fatality. With parenteral artesunate, parasite clearance rates are not different in patients dying from severe malaria compared to survivors (RJ Maude et al, submitted). The omission of the 12-hour artesunate dose might be dangerous in the small subgroup of patients with highly synchronous infections harboring mature schizonts and early ring-form parasites, which are relatively refractory to artemisinins [5]. Because of their rapid elimination, therapeutic drug levels of dihydroartemisinin (the principal active metabolite of artesunate) may not extend beyond 8 hours after drug administration. With once daily administration, this leaves some 16 hours during which drug concentrations cannot prevent surviving parasites maturing further and thus sequestering in the microcirculation of vital organs—the lethal pathophysiological process in severe falciparum malaria. The second dose is thus a "safety net" to ensure adequate treatment of this subgroup of patients. The current small trial in moderately ill children cannot exclude such a possibility.

The suggested 40% reduction in costs with the daily dosing regimen also seems unlikely. As recommended in the WHO treatment guidelines, patients can switch to oral treatment as soon as they are able to take food reliably. In children with severe malaria, this is after a mean of 3 doses, which at the time of the AQUAMAT trial cost US $3.3, comprising only 4.9% of the malaria inpatient treatment costs [6]. Minor cost savings should be set against lives saved. The critical question is whether this new regimen would offer any overall benefit to children with severe malaria, and there is nothing in this non-inferiority comparison of parasite clearance rates in children hospitalized with moderate severity infections to suggest that it would.

Notes

Disclaimer. This correspondence reflects the opinions of the authors only. The funders and other organizations had no role in the preparation of the manuscript.

Financial support. The authors are funded by the Wellcome Trust of Great Britain (www.wellcome.ac.uk, grant number 077166/Z/05/Z).

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Arjen M. Dondorp,[1,2] Richard J. Maude,[1,2] Ilse C. E. Hendriksen,[1] Nicholas P. Day,[1,2] and Nicholas J. White[1,2,a]

[1]Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Rajthevee, Bangkok, Thailand; and [2]Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, CCVTM, University of Oxford, United Kingdom

References

1. Dondorp A, Nosten F, Stepniewska K, Day NWhite NJ. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet **2005**; 366:717–25.
2. Dondorp AM, Fanello CI, Hendriksen IC, et al Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet **2010**; 376:1647–57.
3. Angus BJ, Thaiaporn I, Chanthapadith K, Suputtamongkol Y, White NJ. Oral artesunate dose-response relationship in acute falciparum malaria. Antimicrob Agents Chemother **2002**; 46:778–82.
4. Kremsner PG, Taylor T, Issifou S, et al A simplified intravenous artesunate regimen for severe malaria. J Infect Dis **2012**; 205:312–9.
5. ter Kuile F, White NJ, Holloway P, Pasvol G, Krishna S. *Plasmodium falciparum*: in vitro studies of the pharmacodynamic properties of drugs used for the treatment of severe malaria. Exp Parasitol **1993**; 76:85–95.
6. Lubell Y, Riewpaiboon A, Dondorp AM, et al Cost-effectiveness of parenteral artesunate for treating children with severe malaria in sub-Saharan Africa. Bull World Health Organ **2011**; 89:504–12.

Received 5 January 2012; accepted 27 March 2012; electronically published 25 June 2012.

[a]Professor White is co-chair of the WHO Global Malaria Programme malaria treatment guidelines committee.

Correspondence: Nicholas J. White, Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, 420/6 Rajvithi Rd, Rajthevee, Bangkok 10400, Thailand (nickw@tropmedres.ac).

The Journal of Infectious Diseases 2012;206:618–9

DOI: 10.1093/infdis/jis389