

QUININE (Comment)

Should quinine be used if artesunate is available ?

Those who stress the importance of ensuring that medicine is evidenced based are cautious about recommending anything that has not been tested in a placebo controlled trial and, for this reason, the advice given in the systematic review referred to in the current *Formulary* monograph on quinine¹ merely said, until very recently, that Quinine was “probably effective” in the treatment of severe life-threatening malaria. That was because when it became clear in the 1630’s that cinchona bark from Peru, and its active constituent quinine, could cure malaria randomised trials had not yet developed as the most reliable way to advance medical knowledge. That quinine worked was so obvious that a randomised trial would have been difficult to justify, and would now be totally unethical. There is, in fact, overwhelming evidence that use causes a two fold reduction in mortality when it is made available to the children of Africa. Without such treatment nearly half the children suffering a severe attack used to die, and it is important to remember that 90% of all the deaths in the world from malaria occur to children in Africa.

The challenge is that, although the WHO now recommends treatment with artesunate,² and there is unequivocal evidence that treatment with artesunate is even more effective than treatment with quinine, regulatory authorities remain reluctant to approve the sale of this drug in the developed world. This is because almost all the world’s supplies currently come from the Guilin Pharmaceutical Company in China, and it has not yet been agreed that this widely used product meets international GMP standards. In the largest trial ever conducted into the management of severe life-threatening malaria (which recruited 1259 adult patients, and 202 children more than 2 years old), 14% of those given IV artesunate made by this company died, whereas 23% in those given IV quinine died.³ Given the magnitude of this difference the Australian authorities have since agreed to make the Chinese product widely available,⁴ arguing that possible minor imperfections in the tested formulation can not conceivably be held to outweigh the significance of this demonstrated difference in mortality. Other advisory groups have been more timid,⁵ and currently refuse to recommend the use of an obviously effective but currently ‘unlicensed’ drug.

Optimum oral treatment in the young child seems to be 4 mg/kg once a day for three days, along with at least one other anti-malarial drug in order to minimise the risk of resistant parasites becoming prevalent in the community. Treatment using a single 8 mg/kg suppository seems at least as effective as treatment with IM artemether,⁶ but here are, as yet, no published studies of parenteral treatment in very young children. In the SEAQUAMAT trial referred to above children and adults were given a 2.4 mg/kg bolus dose IV on admission and then again 12 and 24 hours after admission. Further doses were then given daily for a total of 7 days (although further treatment was always given by mouth as soon as this was possible). The relatively small studies published to date have not found any evidence that treatment with artesunate is hazardous in pregnancy.⁷

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3. South East Asia Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 2005;**366** :717–25. [RCT]
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5. Laloo DG, Shingadia D, Pasvol G, *et al*. The HPA Advisory Committee On Malaria Prevention in UK Travellers: UK malaria guidelines. *J Infect* 2007;**54**:111–21.
6. Karunajeewa HA, Reeder J, Lorry K, *et al*. Artesunate suppositories versus intramuscular artemether for treatment of severe malaria in Papua New Guinea. *Antimicrob Agents Chemother* 2006;**50**:968–74.
7. McGready R, Ashley EA, Moo E, *et al*. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. *J Infect Dis* 2005;**192**:84653. [RCT]