Editorials

Oral quinine for the treatment of uncomplicated malaria

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Is ineffective in outpatients and should be used only in rare cases

Artemisinin combination therapy is the first line treatment for uncomplicated malaria in nearly all malaria endemic countries in sub-Saharan Africa. This treatment is relatively expensive, but it kills parasites faster than any other method and has few adverse effects.**1** The combination artemether-lumefantrine (Coartem) is co-formulated, can be taken in a convenient schedule over three days, and is popular with patients and healthcare providers.**2** The linked study by Achan and coworkers (doi:10.1136/bmj.b2763) confirms the excellent cure rate (all patients were cured after adjusting for reinfection) of this drug in children with uncomplicated malaria in Uganda.**3**

However, oral quinine is often used to treat uncomplicated malaria either because artemisinin combinations are not available,**4** or on the assumption that it must be effective because it is still the drug of choice for severe malaria in African children (although it is now known to be inferior to artesunate in Asian adults**5**). But although strains of *Plasmodium falciparum* in sub-Saharan Africa remain susceptible to quinine,**6 7 8 9** this may not translate into drug effectiveness. To complete the treatment regimen, Coartem should be taken twice daily for three days, whereas quinine must be taken three times daily for seven days. The bitter taste of quinine and its unpleasant side effects may leave caregivers struggling with their children, hoping that the full seven days of treatment are not needed and deciding to stop treatment after a few days as the fever subsides.

In their open label effectiveness study, Achen and colleagues planned to treat 302 children randomised to a three day course of Coartem or a seven day course of oral quinine. The safety monitoring board

stopped the trial after 178 patients had been recruited, however, because although cure rates at day seven were similar between the treatment arms, after 28 days of follow-up more than a third of children (35%) treated with quinine were parasitaemic compared with only 4% of children treated with Coartem (all of whom were later found to have new infections). Both drugs were given at home and adherence was assessed after three and seven days; by day three (the end of Coartem treatment) adherence was not significantly different between the treatment arms, but it then declined progressively in the quinine arm so that by day seven almost half (44%) of the children taking oral quinine were no longer adherent.

These findings show that a full seven day course of oral quinine is needed to cure malaria. The quinine content of the trial drug was not measured, although its source had been checked to the satisfaction of Ugandan authorities, so poor drug quality is an unlikely but possible alternative explanation. The key finding is that oral quinine was ineffective under conditions that closely resembled those in routine care.

Inadequately treated malaria carries a high risk of morbidity and mortality,[10] and World Health Organization guidelines (2006) do not recommend the use of unsupervised oral quinine as monotherapy. These guidelines recommend its use only in combination with clindamycin or a tetracycline (which are rarely available and tetracyclines are unsuitable for children or pregnant women) for the rare treatment failures that follow a course of artemisinin combination therapy or for uncomplicated malaria in the first trimester of pregnancy. Even then, the use of an alternative artemisinin combination is recommended before using quinine-clindamycin in children.[11] Unfortunately, these recommendations have not found their way into many national guidelines, and more than half of the national malaria control programmes in Africa still recommend monotherapy with oral quinine as second line treatment. In routine practice the use of oral quinine as a first line treatment seems to be widespread.

National guidelines need to be reviewed and updated, and health staff need to be made more aware that unsupervised oral quinine is not an effective treatment for malaria. Careful planning should prevent stock-outs (running out) of artemisinin combinations, and weak distribution networks need to be strengthened. Alternative artemisinin combinations also need to be stocked for the rare cases of treatment failure with a first line combination; the choice of these should be directed by evidence from clinical trials. For the rare occasions when oral quinine must be used in children, the availability of a paediatric preparation with a less bitter taste would probably improve treatment adherence.

The much bigger question is what clinicians will do if artemisinin combinations cannot be relied on as a class of drugs? A strain of *P falciparum* with decreased susceptibility to artemisinin derivatives has been reported in southeast Asia.[12] If this resistance spreads to sub-Saharan Africa, there may be few alternatives to oral quinine. Because of the time needed to develop and license drugs, time and money must be spent now to develop alternative antimalarial drugs.

Notes

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Footnotes

- Research, doi:10.1136/bmj.b2763
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