



Randomised controlled trial

Intermittent preventive treatment of infants with mefloquine reduces risk of clinical malaria in areas of moderate malaria transmission and high resistance to sulphadoxine–pyrimethamine, but safety and tolerability issues need consideration

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Commentary on: **Gosling RD, Gesase S, Mosha JF, et al.** Protective efficacy and safety of three antimalarial regimens for intermittent preventive treatment for malaria in infants: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009;**374**:1521–32.

Resistance to the combination sulphadoxine–pyrimethamine (SP) is increasing.^{1–3} This is the favoured compound for intermittent preventive treatment (IPT; administration of an antimalarial at prespecified intervals to prevent malaria). Gosling and colleagues report on the failure of IPT in infants (IPTi) with SP (–6.7%; 95% CI –45.9% to 22.0%) in Northern Tanzania in the same issue of a journal in which the combination is endorsed by a meta-analysis.⁴

In this double-blind placebo-controlled trial of IPTi in areas of low and moderate malaria intensity, infants aged 8–16 weeks were assigned to age-based doses of SP, chlorproguanil–dapsone (a short-acting antimalarial), mefloquine (a long-acting antimalarial) or placebo administered with second and third immunisations for diphtheria, pertussis, tetanus (DPT) and polio 2 at about 2 months; DPT and polio 3 at 3 months; and measles at 9 months of age. The primary endpoint was protective efficacy against clinical malaria in infants aged 2–11 months.

Clinical malaria was defined as a history of fever in the previous 3 days or axillary temperature >37.5°C plus parasitaemia of any density measured passively and actively before the third IPTi dose. Cases positive by the former definition were treated, but those not fitting the case definition (that is, asymptomatic children with a positive malaria smear) were not specifically mentioned. Effective IPT drugs would prevent microscopic parasitaemia. Parasitaemia can be detected before symptoms, particularly at this vulnerable age. To prevent malaria-related deaths, particularly in the context of studies, these infants should be treated.

The discussion addresses excess dosing, particularly at the third immunisation, when the average dose of mefloquine was 29.9 mg/kg (the standard treatment dose is 25 mg/kg), which unsurprisingly resulted in high rates of vomiting: 8% (141/1731), with an OR compared with placebo of 5.5 (95% CI 3.6 to 8.5). Although the study design incorporated a 3-day course of chlorproguanil–dapsone, no split-dose regimen appears to have been considered for mefloquine, which is unfortunate, as evidence suggests it is better tolerated.^{5–8}

The failure of the trial, particularly in the mefloquine group, to find a protective effect against moderate anaemia, malaria admissions or all-cause hospital

admissions as described by some studies of IPTi with SP was thought to be due to the high level of coverage with insecticide-treated bed nets and close supervision of the children. A change in malaria transmission is also postulated, but no reason for this change is given. The authors detail the uncomplicated malaria treatment protocol, which included introduction of artemisinin combination therapy (ACT) in October 2005, 10 months after the study commenced and more than 2½ years before it was completed. The introduction of ACT has resulted in significant reductions in transmission rates in Asia and Africa.^{9 10}

Pharmacokinetic studies are a necessary component of the IPTi strategy, but few data have been forthcoming.¹¹ For none of these drugs is the pharmacokinetics well established in children, but frequency of dosing will be guided by this knowledge, and nested pharmacokinetic studies should be included in future IPT studies.

This study reinforces the cautious WHO recommendations on SP for IPTi.¹² SP should be considered only in areas of moderate or high transmission and when parasite resistance to SP is low. Gesase and colleagues have since defined the northern Tanzania site as an area of high resistance to SP.¹³ The WHO recommendations were based in large measure on limited data, including a meta-analysis of possibly the six most favourable trials from the IPTi Consortium, which demonstrated a 30% (95% CI 19.8% to 39.4%) overall protection against clinical malaria, a variable reduction in anaemia (<8 g/dl) of 21.3% (95% CI 8.3% to 32.5%) and a 23% reduction (95% CI 10.0% to 34.0%) in all-cause hospital admission⁴ and did not include the evidence of Gosling and co-authors.

Protection from IPTi translates into 35-day protection after each treatment dose of SP, or an overall protective efficacy of 20–30% in infants, which compares with more than 50% protection against clinical malaria from insecticide-treated bed nets and an 18% reduction in mortality, an effect none of the IPTi studies has matched. To date cost-effectiveness analysis of SP IPTi has been limited to cases when the reduction in malaria was highly significant.¹⁴

Controversy surrounds the publication by Gosling and colleagues. The meta-analysis of six trials concluded

that the use of SP for IPTi was effective across a range of transmission settings,⁴ but why did the meta-analysis not wait to include the trial by Gosling and co-authors? The US Institute of Medicine report on SP IPTi endorsed the scaling-up of IPTi programmes,¹⁵ whereas the WHO IPTi technical expert group that reviewed the same data did not¹² because of inconsistencies in the data.¹⁶ It remains unclear how this relates to the enormous investment of \$28 million from the Bill and Melinda Gates Foundation.¹⁷

The major problem for IPTi associated with the Expanded Programme on Immunization (EPI) is that the interval between the vaccinations may not be ideal when compared with the prophylactic effect of antimalarial drugs. Mefloquine has potential, but not at the same dosing schedule. A recent trial examined the use of piper-quine and SP in Gabon in children in monthly rounds, but compliance with all three doses was an issue.¹⁸ Using piper-quine for IPT limits its usefulness as a treatment. A major gap remains more than 10 years after the use of SP for IPTi with EPI was reported; no suitable replacement therapy has been identified, and the pharmacokinetics of the drug in infants is unknown.

Competing interests None.

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