The efficacy of malaria chemoprophylaxis

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CRD summary
The authors concluded that atovaquone/proguanil, tafenoquine, primaquine were the most effective regimens for malaria chemoprophylaxis, but tafenoquine and primaquine should not be prescribed to individuals with G6PD deficiency. Given the limitations of the review data and concerns about the methodology and reporting of the review, the authors’ conclusions may not be reliable.

Authors' objectives
To determine the efficacy, safety and tolerability of malarial chemoprophylaxis.

Searching
MEDLINE and CINAHL were searched for full papers written in English and published between 1999 and 2006. Search terms were reported. Internet search engines (Google, Lycos and Altavista) were used to search for further studies. World Health Organisation (WHO) and Center for Diseases Control (CDC) websites were searched.

Study selection
Clinical trials of drugs used for malarial chemoprophylaxis were eligible for inclusion in the review. Studies in pregnant women and children were not eligible for inclusion.

Included studies assessed the following antimalarial agents alone or in combination: atovaquone, proguanil, tafenoquine, primaquine, mefloquine and doxycycline. Most controlled studies compared the intervention drug to placebo. Most included participants were healthy male and female volunteers either from endemic areas or who were from non-endemic areas, but were visiting/now living in areas where malaria was endemic. Half of the studies included children from the ages of 12 years or 16 years; one study was carried out in secondary school children aged 12 to 20 years. Study locations included West Kenya, Afghanistan, Gabon, South Africa, Papua New Guinea, Ethiopia and Zambia, which were endemic mostly for *Plasmodium falciparum*.

The authors stated neither how papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not appear to carry out a formal validity assessment, but they commented on risks to internal and external validity.

Data extraction
The authors stated neither how data were extracted for the review nor how many reviewers performed the data extraction.

Percentage prophylactic efficacy and numbers of withdrawals due to adverse events were extracted where available.

Methods of synthesis
Studies were discussed in a narrative synthesis according to drug intervention.

Results of the review
Eight studies (five randomised controlled trials and three uncontrolled studies) were included in the review. Sample sizes were reported in only three studies (a total of 630 participants) and ranged from 158 to 297. Five studies failed to report whether sample sizes were based on calculations of statistical power. Internal validity was reported as good in two studies and adequate in a further two studies; the internal validity of two other studies was reported as negative or threatened. External validity was reported as good in two studies and adequate in another; however, the remaining studies included participants from endemic or high-risk areas, which suggested that the study findings may not be
Prophylactic efficacy of atovaquone/proguanil was 97% against *P. falciparum* (one study) and 93-95% against all *Plasmodium* species (two studies). Reported adverse events included stomatitis and a flu-like syndrome.

Efficacy of tafenoquine against *P. falciparum* ranged from 68% to 89% dependent on dosage; the most effective regimen was 400mg/day for three days followed by 200mg per week. However, tafenoquine was associated with haemolytic events in patients with G6PD deficiency and mild gastrointestinal disorders.

Efficacy of primaquine against all *Plasmodium* species was 93%. A number of reported adverse events included haemolytic events and toxemia. None of the participants who received mefloquine or doxycycline contracted malaria (one study), but both regimes were associated with gastrointestinal and neurological disorders, amongst other adverse events.

Study withdrawals due to adverse events included: 2/223 with tafenoquine (one study); 2/158 with primaquine (one study); 12.5% with doxycycline (one study); 4.6% with mefloquine (one study); and 3/175 and 4/150 with atovaquone/proguanil (two studies)

**Authors' conclusions**

Atovaquone/proguanil, tafenoquine, primaquine were the most effective regimens, but tafenoquine and primaquine should not be prescribed to individuals with G6PD deficiency. All the regimens were well tolerated; most withdrawals due to adverse events were associated with doxycycline and mefloquine.

**CRD commentary**

This review answered a briefly defined review question, with wide inclusion criteria for interventions and study design. The review also appeared to include the data from trials of children and adolescents, which the authors stated were not eligible for inclusion. Literature searches were limited by date and only full English-language publications were eligible for inclusion in the review. The date limitations may have been reasonable given the likely changes in malarial parasite resistance to chemoprophylaxis over time, but no explanation or justification for the chosen dates was given. The other search limitations, however, may have introduced publication and language biases. There were also concerns about the reliability of the review methods, which were not described in detail. Details of individual study results were not reported, so it was not possible to verify the findings reported in the review. It was difficult to identify which data came from which study as the different studies were not referenced in the text. It appeared that no formal validity assessment was conducted, but some aspects of study quality were discussed. The review included both randomised and uncontrolled data, statistical power is often not assessed and the limited generalisability of the data to other populations, particularly those from non-endemic areas, was of particular concern. The limited number of studies, absence of information about methods used to assess and define treatment efficacy and differences between studies with respect to study design, populations, interventions and the malarial parasite targeted suggested that the review findings may not be accurate. Therefore, given the limitations of the included data and concerns about the review methodology, the authors' conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further more reliable trials were required to investigate the effects of antimalarial drugs in non-immune individuals and to investigate safer regimens for use in high-risk groups including children and pregnant women.

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**Bibliographic details**

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.