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Abbreviated atovaquone-proguanil prophylaxis regimens in travellers after leaving malaria-endemic areas: A systematic review

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ABSTRACT

Background: We evaluated existing data on the prophylactic efficacy of atovaquone-proguanil (AP) in order to determine whether prophylaxis in travellers can be discontinued on the day of return from a malaria-endemic area instead of seven days after return as per currently recommended post-travel schedule.

Methods: PubMed and Embase databases were searched to identify relevant studies. This PROSPERO-registered systematic review followed PRISMA guidelines. The search strategy included terms or synonyms relevant to AP combined with terms to identify articles relating to prophylactic use of AP and inhibitory and half-life properties of AP. Studies considered for inclusion were: randomized controlled trials, cohort studies, quasi-experimental studies, open-label trials, patient-control studies, cross-sectional studies; as well as case-series and non-clinical studies. Data on study design, characteristics of participants, interventions, and outcomes were extracted. Primary outcomes considered relevant were prophylactic efficacy and prolonged inhibitory activity and half-life properties of AP.

Results: The initial search identified 1,482 publications, of which 40 were selected based on screening. Following full text review, 32 studies were included and categorized into two groups, namely studies in support of the current post-travel regimen (with a total of 2,866 subjects) and studies in support of an alternative regimen (with a total of 533 subjects).

Conclusion: There is limited direct and indirect evidence to suggest that an abbreviated post-travel regimen for AP may be effective. Proguanil, however, has a short half-life and is essential for the synergistic effect of the combination. Stopping AP early may result in mono-prophylaxis with atovaquone and possibly select for atovaquone-resistant parasites. Furthermore, the quality of the studies in support of the current post-travel regimen outweighs the quality of the studies in support of an alternative short, post-travel regimen, and the total sample size of the studies to support stopping AP early comprises a small percentage of the total sample size of the studies performed to establish the efficacy of the current AP regimen. Additional research is required — especially from studies evaluating impact on malaria parasitaemia and clinical illness and conducted among travellers in high malaria risk settings — before an abbreviated regimen can be recommended in current practice.

PROSPERO registration number: CRD42017055244.

1. Introduction

Atovaquone-proguanil (AP; marketed as Malarone® or Malanil® or as generic brands such as Atovaquone Plus®) is a convenient choice for malaria drug prophylaxis in short-term travel [1,2]. 'Short-term' is considered to be a travel of three weeks or less [3]. The current approved regimen of AP for malaria chemoprophylaxis is daily administration of one tablet of 250 mg atovaquone/100 mg proguanil hydrochloride beginning one to two days before entry into a malaria-endemic area, continued during exposure, and discontinued seven days after

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leaving the endemic area [1]. This drug is highly effective in preventing clinical malaria episodes, but non-compliance and non-adherence, in a proportion of patients due to (mainly gastrointestinal) adverse events, are major contributors to a reduced effectiveness.

AP is approved for causal prophylaxis against *P. falciparum* and does not prevent the formation of dormant liver stages (hypnozoites) by *P. vivax* and *P. ovale*, as illustrated by several case-reports [4–7]. Presumptive primaquine treatment may be required to eliminate the hypnozoites in order to prevent relapses due to these malaria species.

Atovaquone belongs to the hydroxynapthoquinone class of compounds and inhibits the parasite mitochondrial electron transport and ATP synthesis, whereas the active proguanil metabolite, cycloguanil, inhibits plasmodial dihydrofolate reductase. Proguanil works synergistically with atovaquone, as it lowers the effective concentration of atovaquone needed to collapse mitochondrial potential [8,9]. Both drugs are active against erythrocytic and pre-erythrocytic stages of *Plasmodium* species, and thus AP exhibits causal prophylactic activity against liver stages and activity against plasmodial blood stages [10,11]. Because of this causal prophylactic activity, AP can be discontinued seven days after return from a malaria-endemic area instead of one month in the case of antimalarials with only suppressive prophylaxis against blood stages of malaria.

The elimination half-life of proguanil is only 12–15 h in both adults and children, while the half-life of atovaquone is two to three days in adults and one to two days in children [8]. However, Edstein and colleagues determined the half-life of atovaquone to be 5.9 days in a study with three volunteers [12], thus giving rise to concerns of a drug partners mismatch time window, which has only very rarely been reported to impact the clinical course of patients [13].

Nixon et al. reviewed pharmacokinetic and –dynamic properties of this slow-acting drug (atovaquone) [14]. Molecular surveillance data from Gabon and Ethiopia [15] demonstrated that in the absence of drug pressure, the occurrence of potentially drug resistance-conveying polymorphisms remain an exception. Over 500 samples from treatment failures and other imported isolates to Europe were screened for single-point, potentially resistance-conferring polymorphisms in the *cytochrome b* gene. This showed that the prevalence of those mutations in the European gene pool is well below 1% [16].

AP is well tolerated by the majority of users; however, adverse reactions when used as prophylactic agent against malaria are nausea, vomiting, abdominal pain, headache, and diarrhea [8]. When compared to other antimalarials currently used for malaria prophylaxis, AP has been found to have fewer reported adverse events in randomized trials [17,18].

A recently performed study by Leshem and colleagues did not detect failures among 485 travellers who discontinued prophylaxis one day after return from a malaria-endemic area, mostly in Eastern Africa; however, several methodological shortcomings were acknowledged [19,20]. These included the choice of a region with limited risk of exposure to malaria, insufficient level of evidence that the drugs were taken appropriately, and possible recall bias. Apart from clinical studies, several pharmacological studies also support the proposal to shorten the AP regimen, citing the long half-life properties of atovaquone with schizonticidal effects [11,12]. However, the absence of comprehensive funding opportunities needed to conduct a study of considerable complexity and study subject numbers makes it challenging to provide a comprehensive, definitive recommendation. Very few clinical and pharmacological studies have been performed that have focused on providing evidence for an abridged AP malaria chemoprophylaxis regimen [19].

The objective of this systematic review is to determine the prophylactic efficacy when discontinuing AP in travellers one day after return from a malaria-endemic area instead of after seven days. In order to assess whether the currently available evidence supports shortening post-travel duration of AP, we reviewed and weighed current clinical and pharmacological data with regard to the prophylactic activity and prolonged inhibitory activity or half-life properties of AP. Finally, we suggest a methodologically feasible study approach in order to answer future questions with regard to malaria prophylaxis.

2. Methods

In this systematic review, we evaluate existing data with regard to the prophylactic efficacy of AP, in order to determine whether prophylaxis in travellers can be discontinued on the day of return from a malaria-endemic area instead of seven days later. However, because of the limited research performed on this topic, we also included studies with alternative regimens of AP chemoprophylaxis, whilst in an endemic area, in support of the prolonged antimalarial activity of AP.

2.1. Search strategy and study selection

The electronic PubMed and Embase databases were consulted to identify relevant studies. Because AP was registered in 1998, we included studies published between 1995 and the present. . Relevant studies identified by additional reading/citation were also considered for inclusion. The PROSPERO protocol was registered at http://www.crd.york.ac.uk (CRD42017055244). The PRISMA guidelines for systematic reviews were followed in most aspects [21]. The few deviations from PRISMA guidelines are discussed below.

The search strategy included terms or synonyms relevant to AP combined with terms to identify articles related to prophylactic use of AP, or pharmacokinetic properties of AP. The full search strategy is provided in Appendix 1 and Appendix 2. This search strategy was verified by a clinical librarian. Screening on title/abstract and full text was performed independently by two reviewers. Discrepancies were resolved by discussion. A recent update of the PubMed and Embase search was performed on the 6th of September 2017. No language restrictions were applied, though no studies meeting the inclusion criteria but not written in English were identified.

2.2. Eligibility: inclusion and exclusion criteria

The PICO format was used to determine the inclusion criteria: (P) Participants: travellers to malaria-endemic areas, in which travellers were defined as children and adults (both pregnant and non-pregnant); (I) Intervention: discontinuation of daily administered AP prophylaxis one day upon return from a malaria-endemic area; (C) Comparison: discontinuation of daily administered AP prophylaxis seven days after return from a malaria-endemic area; (O) Outcome: parasitaemia. Studies with focus on alternative regimens of AP, defined as discontinuation one to seven days after return from a malaria-endemic area, or an outcome other than parasitaemia such as adverse events, were also considered for inclusion. The outcomes considered for non-clinical (e.g. pharmacological or experimental) studies were the half-life properties of AP or an outcome related to elimination half-life (i.e. an outcome suggesting the prolonged inhibitory activity of AP).

Criteria for exclusion were: a focus on malaria treatment (except when there was an emphasis on the duration of the prolonged inhibitory activity or half-life properties of AP), a focus on adherence to prophylaxis, a focus on adverse effects, a focus on resistance (patterns), a focus on prescribing patterns, or when no abstract or PDF file was available.

The following study designs were considered for inclusion: randomized controlled trials, prospective cohort studies, retrospective cohort studies, quasi-experimental studies, open-label trials, patient-control studies, cross-sectional studies; case-series, and non-clinical studies. Pharmacological and experimental studies were considered as non-clinical, and only papers with a focus on the prolonged inhibitory activity or half-life properties of AP were considered and included as non-clinical studies.