HHS Public Access

Author manuscript

J Travel Med. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

J Travel Med. 2017 March 01; 24(2): . doi:10.1093/jtm/taw080.

Acute malaria infection after atovaquone–proguanil prophylaxis

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Dear Editor

In their recent article, Lachish *et al.*[1] suggest that a twice weekly atovaquone–proguanil (AP) regimen may be effective malaria prophylaxis for long-term travellers. There are limitations to this study and related papers, and therefore we caution against any change in AP prophylaxis practice. We provide data from the Centers for Disease Control and Prevention's National Malaria Surveillance System (NMSS) for US travelers who developed acute malaria while taking a complete or partial course of AP.

The current recommended prophylactic regimen for AP (day prior to travel, daily during travel and 7 days after departing) is based on the pharmacokinetics of the two drugs and their synergistic activity against the tissue schizont and blood stages of *Plasmodium* spp. parasites.[2] In Lachish *et al.*'s study, participants started AP after arriving in the endemic area, and outcomes are only reported for their time in the malaria-endemic country while still taking the drug twice weekly. There may have been individuals with pre-patent infections prior to starting AP, or even breakthrough parasitemias that were partially treated by the intermittent AP dosing. Failure in these cases could have been observed in the weeks after the post-trip prophylaxis course; however, this time period was not examined, and would be a critical piece of evidence needed to make conclusions about the prophylactic efficacy of the modified AP course.

We examined NMSS data from 2006 to 2014, and found 354 malaria cases who reported taking AP for prophylaxis. Excluding the 81 cases that had insufficient information to characterize as acute malaria, the 79 cases that were relapses or had onset 45 or more days after leaving a malarious area and the 4 patients who took more than one antimalarial for prophylaxis, there were a total of 190 acute malaria cases who only took AP for prophylaxis. Of these, the majority (85%) developed symptoms after returning to the US, had travelled to sub-Saharan Africa (93%), were short-term travellers (92%), and had information on AP adherence (87%). Of these with information on AP adherence, 64% (105/165) missed some doses, and 23% (20/88) of those who reported a reason for missing doses stopped AP prematurely after returning home. From this surveillance data, we observe that malaria does

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occur after complete or partial AP prophylactic courses, and that most of these cases developed symptoms after returning to the US.

Other studies have examined alternate AP dosing schedules.[3,4] However, the half-life of proguanil (12–21 h) compared with atovaquone (2–3 days) supports daily dosing.[2] If the dosing interval of AP is extended, it is possible for proguanil levels to be so low between doses that a patient is essentially on atovaquone monotherapy. Atovaquone is not an effective antimalarial when used alone and induced atovaquone resistance has been observed.[5] The twice weekly regimen used in the Lachish *et al.*'s report would be expected to result in a lower total dose, lower peak concentration and period of time with drug concentration below the minimum inhibitory concentration, so it is surprising that there were no chemoprophylaxis failures. It is possible that the natural experiment design was not appropriate to evaluate efficacy, and chemoprophylaxis failures occurred, but were not detected or reported.

There are other limitations to Lachish *et al.*'s study, such as the use of person-time, which should assume equivalent population and time at risk. The workers in the jungles of Angola and the medical staff and families in Equatorial Guinea likely had inconsistent risks of malaria exposure. Indeed, the higher risk group in Angola were a small part of the denominator compared to the Equatorial Guinea group. Secondly, the time at risk was not equivalent; for example, only 4 of 10 months of AP follow up occurred during the higher transmission rainy season in Angola.

AP effectively prevents malaria when it is taken following the standard daily dosing regimen.[2] Travellers can develop malaria by missing doses or stopping prematurely after leaving the endemic area. Alternate AP dosing strategies might be effective, but further research is necessary.

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