Malaria prophylaxis with atovaquone-proguanil caused fewer gastrointestinal adverse events than did chloroquine-proguanil

Høgh B, Clarke PD, Camus D, et al., and the Malarone International Study Team. **Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study.** Lancet. 2000 Dec 2;356:1888-94.

QUESTION

In travelers who are not immune to malaria, is malaria prophylaxis with atovaquone-proguanil equivalent to that with chloroquine-proguanil for adverse events (AEs)?

DESIGN

Randomized (allocation concealed*), blinded (clinicians and patients),* placebo-controlled trial with follow-up at 7, 28, and 60 days after leaving a malaria-endemic area.

SETTING

21 travel clinics in Denmark, the United Kingdom, France, Germany, the Netherlands, South Africa, and Canada.

PARTICIPANTS

1083 participants (mean age 36 y, 52% men, 96% white) who weighed > 50 kg, were age ≥ 14 y, were in good health, and planned to travel ≤ 28 days in Africa (63%) or other *Plasmodium falciparum*–endemic areas. Exclusion criteria included a history of seizures; psychiatric or neurologic disorders; cardiac, hepatic, or renal dysfunction; pregnancy; alcoholism; malaria within the previous 12 months; or travel to a malaria-endemic area within the previous 60 days. Follow-up was 94% at 7 days and 93% at 60 days.

INTERVENTION

540 participants were allocated to atovaquone, 250 mg/d, and proguanil hydrochloride, 100 mg/d, from 1 to 2 days before to 7 days after travel (and placebos for chloroquine-proguanil). 543 participants were allocated to chloroquine, 310 mg/wk, from 7 days before to 28 days after travel, and proguanil, 200 mg/d, from 1 to 2 days before to 28 days after travel (and placebos for atovaquone-proguanil).

MAIN OUTCOME MEASURE

Number of AEs 7 days after return from a malaria-endemic area.

MAIN RESULTS

Analysis was by intention to treat. Fewer drug-attributed AEs (nausea, abdominal pain, and vomiting) and treatment-limiting events occurred in the group receiving atovaquone-proguanil than in the group receiving chloroquine-proguanil (Table). At 60 days, no participants in the atovaquone-proguanil group and 3 in the chloroquine-proguanil group had confirmed *P. falciparum* malaria ($P = 0.08$).

CONCLUSION

Atovaquone-proguanil caused fewer gastrointestinal adverse events than did chloroquine-proguanil in travelers who were not immune to malaria.

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For correspondence: Malarone Publication Coordinator, Room 50-3505B, Glaxo Wellcome Inc, 5 Moore Drive, Research Triangle Park, NC 27709, USA. FAX 919-315-0377.

*See Glossary.

Atovaquone-proguanil vs chloroquine-proguanil for drug-attributed gastrointestinal adverse events and treatment-limiting events in participants not immune to malaria†

Events at 7 d	Atovaquone-proguanil	Chloroquine-proguanil	RRR (95% CI)	NNT (CI)
All adverse events	22%	28%	23% (4 to 38)	16 (9 to 102)
Any gastrointestinal event	12%	20%	41% (21 to 56)	12 (8 to 28)
Nausea	2%	7%	74% (46 to 87)	20 (13 to 39)
Abdominal pain	3%	6%	50% (9 to 73)	34 (18 to 230)
Vomiting	0	2%	100% (65 to 100)	46 (26 to 83)
Any treatment-limiting event	0.2%	2%	90% (40 to 98)	57 (29 to 162)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

The study by Høgh and colleagues addresses the tolerability of 2 malaria drug prophylaxis regimens. Balancing the risks for developing malaria against the AEs of the drug prophylaxis makes the choice of drug difficult for many travelers to malaria-endemic areas. The underlying problem in malaria drug prophylaxis is in the public perception of risk (1–3). Because travelers want to avoid AEs, the antimalarial drugs that cause fewer AEs will be used more frequently. The atovaquone-proguanil combination is effective in treating drug-resistant malaria; however, it is too expensive to be used by many people in the developing countries in which it was tested (4). Nevertheless, it can still be useful to travelers, which is what the trial by Høgh and colleagues evaluates.

It is not easy to show comparative benefits of 1 prophylactic regimen over another when AEs are few, but it seems unlikely that people will benefit from a regimen if they discontinue the drug while still exposed to the risk for infection. The trial by Høgh and colleagues is instructive because it shows that the drug recommended for many years, chloroquine, can cause prophylaxis-limiting events. The results of this study are important for travelers because they show higher adherence with proguanil and atovaquone, a regimen effective against drug-resistant malaria. The findings provide evidence to support a new drug option for preventing malarial infection in travelers.

Paul Garner, MBBS, MD
Liverpool School of Tropical Medicine
Liverpool, England, UK

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