Malaria prophylaxis with atovaquone-proguanil caused fewer gastrointestinal adverse events than 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 travellers who are not immune to malaria, is malaria prophylaxis with atovaquone proguanil equivalent to that with chloroquine proguanil for adverse events (AEs)?

Design

Randomised (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 UK, 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 years, 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 neurological 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/day, and proguanil hydrochloride, 100 mg/day, from 1 to 2 days before to 7 days after travel (and placebos for chloroquine proguanil). 543 participants were allocated to chloroquine, 310 mg/week, from 7 days before to 28 days after travel, and proguanil, 200 mg/day, 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 chloroquine-proguanil in travellers who were not immune to malaria.

*See glossary.

COMMENTARY

The study by Høgh *et al* 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 travellers to malaria endemic areas. The underlying problem in malaria drug prophylaxis is in the public perception of risk.¹⁻³ Because travellers 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 travellers, which is what the trial by Høgh *et al* 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 *et al* is instructive because it shows that the drug recommended for many years, chloroquine, can cause prophylaxis limiting events. The results are important for travellers 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 travellers.

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

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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 +1
919 315 0377.

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

Events at 7 days	Atovaquone-proguanil	Chloroquine-proguanil	RRR (95% CI)	NNT (CI)
All adverse events	22%	28%	23% (4 to 38)	16 (9 to 102)
Any GI 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.