

Chlorproguanil-dapsone for treatment of drug-resistant falciparum malaria in Tanzania.

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Abstract

BACKGROUND:

Resistance to the affordable malaria treatments chloroquine and pyrimethamine-sulfadoxine is seriously impeding malaria control through treatment in east Africa. We did an open, alternate drug allocation study to assess the efficacy of chlorproguanil-dapsone in the treatment of falciparum malaria clinically resistant to pyrimethamine-sulfadoxine.

METHODS:

Children younger than 5 years with non-severe falciparum malaria, attending Muheza district hospital in Tanzania, were treated with the standard regimen of pyrimethamine-sulfadoxine. Patients whose clinical symptoms resolved but who remained parasitaemic 7 days after pyrimethamine-sulfadoxine were followed up for 1 month. Clinical malaria episodes were retreated with either single dose pyrimethamine-sulfadoxine or a 3-day regimen of chlorproguanil-dapsone. Those with parasitaemia after 7 days were treated with chlorproguanil-dapsone. Parasite DNA was collected on day 7 after first treatment with pyrimethamine-sulfadoxine and we looked for point mutations in the genes encoding dihydrofolate reductase (dhfr) and dihydropteroate synthetase (dhps).

FINDINGS:

360 children were enrolled and treated with pyrimethamine-sulfadoxine. On day 7, 192 (55%) of 348 had cleared parasitaemia. Of the remaining 156 parasitaemic children, 140 (90%) were followed up to day 28, and 92 (66%) of 140 developed clinical malaria. These 92 patients were alternately retreated with either pyrimethamine-sulfadoxine (46) or chlorproguanil-dapsone (46). 28 (61%) of 46 children retreated with pyrimethamine-sulfadoxine were still parasitaemic at day 7, compared with three (7%) of 44 [corrected] children retreated with chlorproguanil-dapsone. Resistance to pyrimethamine-sulfadoxine increased from 45% (156/348) at the first treatment to 61% (28/46) after retreatment. 83 of 85 parasite isolates collected after the first pyrimethamine-sulfadoxine treatment, and before and after the second treatments with pyrimethamine-

sulfadoxine and chlorproguanil-dapsone showed triple-mutant dhfr alleles, associated with a variety of dhps mutations.

INTERPRETATION:

Most patients treated with pyrimethamine-sulfadoxine, who remain parasitaemic at day 7, develop new malaria symptoms within 1 month. Chlorproguanil-dapsone was a practicable therapy under these circumstances. Analysis of parasite dhfr and dhps before and after treatment supports the view that pyrimethamine-sulfadoxine resistance in this part of Africa is primarily due to parasites with three mutations in the dhfr domain.