Antifolate drug resistance and point mutations in Plasmodium falciparum in Kenya

Abstract:

Due to increased chloroquine resistance, the antifolate/sulpha drug combinations are becoming increasingly important in the chemotherapy of falciparum malaria. However, point mutations in the dihydrofolate reductase gene lead to resistance to the antifolate drugs. We therefore investigated the prevalence of the 6 reported point mutations in this gene among field isolates of Plasmodium falciparum from Kenya, to determine if the mutations correlated with resistance to pyrimethamine and the biguanides cycloguanil and chlorcycloguanil. We used a mutation-specific polymerase chain reaction technique to test for these reported mutations in 21 Kenyan isolates and 4 reference lines. We also amplified and directly sequenced the dihydrofolate reductase coding sequence from these parasites to confirm the results and test for other possible mutations. Of the reported mutations, we found S108N, which is the central mutation of pyrimethamine resistance, and mutations N51I and C59R, which modulate the levels of resistance and may confer decreases in response to cycloguanil that are folate and p-aminobenzoic acid dependent. No isolate possessed the paired point mutations S108T and A16V, or I164L and S108N, which have been associated with cycloguanil resistance in previous studies. These results provided supportive evidence for the combined use of a cycloguanil-class drug (e.g., chlorproguanil) and a sulpha drug (e.g., dapsone) against P.falciparum malaria in Kenya.