Amodiaquine as the first line treatment of malaria in Yaoundé, Cameroon: presumptive evidence from activity in vitro and cross-resistance patterns

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The spread of chloroquine-resistant Plasmodium falciparum in many countries of sub-Saharan Africa has raised an urgent need to determine which alternative antimalarial drug should replace chloroquine for the first-line treatment of acute uncomplicated falciparum malaria. The drug must satisfy the following requirements to be a viable option in Africa: high and rapid clinical efficacy, short treatment course, good tolerance, safety, and low cost. Two well-known antimalarial drugs satisfy these criteria: pyrimethamine/sulfadoxine and amodiaquine. Of these 2 candidates, the Cameroonian Ministry of Health has chosen amodiaquine as the immediate successor for chloroquine, keeping pyrimethamine/sulfadoxine and amodiaquine. Of these 2 candidates, the Cameroonian Ministry of Health has chosen amodiaquine as the immediate successor for chloroquine, keeping pyrimethamine/sulfadoxine and amodiaquine. Of these 2 candidates, the Cameroonian Ministry of Health has chosen amodiaquine as the immediate successor for chloroquine, keeping pyrimethamine/sulfadoxine and amodiaquine.

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Between 1994 and 1997, 135 clinical isolates of *P. falciparum* were obtained from symptomatic Cameroonians adults and children attending Nlongkak Catholic missionaries and dispenser (where amodiaquine was initiated as the first-line treatment in 1992) to determine the activity of chloroquine and monodesethylamodiaquine, a major biologically active human metabolite of amodiaquine, using the isotopic semi-microtest or microtest (Desjardins et al., 1979; Ringwald et al., 1996b). This study was approved by the Cameroonian national ethics committee. The results obtained from individual isolates were expressed as 50% inhibitory concentration (IC50). IC50 values obtained by the semimicrotest and the microtest are concordant (Bickii et al., in press). Based on our previous studies, the threshold IC50 values for chloroquine resistance and monodesethylamodiaquine resistance were fixed at 100 nM and 60 nM, respectively (Basco & Le Bras, 1993). The response in vitro to chloroquine was arbitrarily graded as 'moderately resistant' if the IC50 was between 100 and 400 nM, and 'highly resistant' if the IC50 was >400 nM. The correlation coefficient between the IC50 values of chloroquine and monodesethylamodiaquine was determined by linear regression analysis.

The IC50 values for the 2 drugs were highly correlated (r = 0.80; P < 0.0001) (Figure). Analysis of the distribution pattern of the IC50 values showed that all 53 chloroquine-sensitive isolates were also sensitive to monodesethylamodiaquine. Some, but not all, of the 53 moderately chloroquine-resistant isolates were sensitive to monodesethylamodiaquine. Whether a given chloroquine-resistant isolate was sensitive or resistant to monodesethylamodiaquine in vitro depended on the level of chloroquine resistance in vitro. Of 27 highly chloroquine-resistant isolates, 17 were resistant (IC50 >63-140 nM) and 10 were sensitive (IC50 43-59 nM) to monodesethylamodiaquine.

During the same period as the study in vitro, most of the patients (about 12,000 patients, symptomatic cases per year) attending the same dispensary were treated with 30-35 mg base/kg body weight of amodiaquine (in 3 divided daily doses), with the exception of pregnant women, patients presenting signs and symptoms of severe and complicated malaria (WHO, 1990b), and patients who claimed to have taken (usually inadequate) doses of amodiaquine a few days before consultation. Our daily clinical experience at this dispensary revealed no major toxic reaction among these amodiaquine-treated patients. Blood films on day 3 were negative in a large majority of patients. Some patients returned with a positive film more than one month after treatment, suggesting reinfection rather than treatment failure. It must be pointed out that, because our clinical observation was based on a relatively small patient population without supporting blood examinations during a longer follow-up period, the study design was insufficient to detect severe adverse reactions related to amodiaquine treatment.

To investigate further the clinical efficacy of amodiaquine, we have started to follow some patients more closely. Our preliminary data on symptomatic malaria...
infected adults in Yaoundé (negative Saker-Solomons urine test, mono-infection with \textit{P. falciparum}, parasitemia >5000 asexual parasites/\mu l of blood) followed daily from days 0 to 4 and then on days 7 and 14 (and day 28 with some patients) have shown a 100\% cure rate without any major side-effect. Our clinical experience with native drugs, such as pyrimethamine/sulfadoxine and pyronaridine (OURO et al., 1995), has been followed in a hyperendemic area and patients on an outpatient basis, reinfection can be expected (NeVill et al., 1994). However, it is important to note that this observation may be valid only in areas of low-grade RI chloroquine resistance. Thus, amodiaquine may be useful over a short period in African countries while awaiting the "massive" use of other alternative drugs, such as pyrimethamine/sulfadoxine and pyronaridine (OLLARO & TRIGG, 1995). Contrary to our experience, RADLOFF et al. (1996) have reported that 12/63 symptomatic patients (19\%) treated with amodiaquine and followed for 28 d had recrudescences of falciparum malaria in Lambarené, Gabon. Two major reasons may explain the relatively high recrudescence rate in their study. First, a fixed total dose of 1500 mg amodiaquine base was administered in 3 daily doses, instead of administering the drug on a body weight basis. The patients (mean weight 60 kg) therefore received an average dose of 25 mg/kg base, although in other francophone African countries, a total dose of 30–35 mg/kg base is recommended (LOUIS et al., 1992). Secondly, since most recrudescent cases (9/12) were observed on days 21 and 28 in a hyperendemic area and patients were followed on an out-patient basis, reinfection cannot be ruled out.

The underlying basis of amodiaquine efficacy against chloroquine-resistant \textit{P. falciparum} seems to be related to the moderate level of chloroquine resistance in \textit{vitro} (theoretically corresponding to an RI level in \textit{vitro}) among the Cameroonian clinical isolates. Experimental data have also demonstrated that amodiaquine accumulation in infected erythrocytes is greater than that of chloroquine (HAWLEY et al., 1996). These experimental findings, as well as the results of various clinical studies, are consistent with the meta-analysis of the clinical efficacy of amodiaquine which showed a high cure rate (OLLARO et al., 1996). Since most cases of therapeutic failure with chloroquine are at the RI level in sub-Saharan Africa (TURRAMAN et al., 1992; RINGWALD et al., 1996a), as attested by the relatively low IC50 values for chloroquine (100–400 nM) observed among most of the resistant Cameroonian clinical isolates, amodiaquine is probably a viable option for African countries where chloroquine resistance has emerged in recent years and may be a rational choice for replacing chloroquine for the first-line treatment of uncomplicated falciparum malaria.

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References


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