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MEFLOQUINE RESISTANT MALARIA IN CAMEROON AND CORRELATION WITH RESISTANCE TO QUININE

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Based on the results of in vitro sensitivity of Plasmodium falciparum *to chloroquine, quinine and mefloquine, and evaluation of drug consumption conducted in 1987-1988 in four areas in the north and south-west of Cameroon, two opposite situations were encountered in this country. In northern Cameroon where mefloquine resistance is prevalent a close correlation was found between the responses of* P. falciparum *to mefloquine and to quinine, but not between mefloquine and chloroquine. In the south, where chloroquine resistance is highly prevalent, no correlation was found neither between mefloquine and chloroquine nor mefloquine and quinine, but the responses to quinine and chloroquine appear partly correlated. These results lead to formulate the hypothesis of a "southern" type of* P. falciparum *submitted to a high chloroquine drug pressure inducing a secondary cross resistance, whilst a "northern" type submitted to a relatively high and abortive quinine drug pressure inducing a primary quinine resistance and a secondary cross resistance with mefloquine.*

Key words: *Plasmodium falciparum* – Cameroon drug resistance

Plasmodium falciparum malaria resistance to mefloquine (Lariam) have now been described in several countries of Africa such as Tanzania (Bygbjerg et al., 1983), Nigeria (Oduola et al., 1987) or Cameroon (Brasseur et al., 1990) and surprisingly their emergence occurred before or simultaneously to the introduction of this drug on the African markets. On the basis of results from in vitro assays several workers have suggested that mefloquine resistant falciparum malaria may be widespread in African countries. Therefore the possible selection of resistant parasites as a consequence of drug pressure, does not appear to be an acceptable explanation in the case of mefloquine.

MATERIALS AND METHODS

This study is based on the results of sensitivity of *P. falciparum* isolates to chloroquine, quinine and mefloquine and evaluation of drug consumption in Cameroon. The study was performed in 1987-1988 in four areas: Limbe and Kribi which are located in forested lands of the south-west and south coastal areas, Garoua and Maroua in the north sahelian part of the country.

Investigations were conducted in children aged 1 to 12 years and most of them were asymptomatic *P. falciparum* carriers. The microisotopic in vitro assay was used to estimate the sensitivity of chloroquine, quinine, and mefloquine. In vivo 7-day assays were carried out with a single dose of 10 mg/kg or 25 mg/kg over three days of chloroquine and with a single dose of 25 mg/kg of mefloquine. Blood concentrations of the drugs were evaluated at D_0 and D_3 using HPLC method.

RESULTS

Two opposite situations were encountered in Cameroon: (1) resistance to chloroquine was particularly prevalent in the south-west where more than 50% of 74 isolates tested were found resistant with EC_{50} values ranging from 100 to 600 nmoles. In contrast, in the north and extreme north, all but one of the 78 isolates studied, were found sensitive to chloroquine with EC_{50} values below the cut off limit of 80 nmoles. In vivo 7-day assays performed with chloroquine at 25 mg/kg dose in 389 individuals from the south-west part of the country, have clearly confirmed the above in vitro results showing RII-RIII levels of resistance in 18 to 52% of cases, depending on the location

studied. In the north, in vivo 7-day assays showed a sensitivity to a single dose of 10 mg/kg in 36 of the 39 subjects studied and in all of the 27 receiving a 25 mg/kg dose. (2) mefloquine resistance was found prevalent in the north. A large proportion of the 133 isolates responded poorly to mefloquine: 26 isolates had EC_{50} above the cut off limit of 30 nmoles and 19 others could be considered as borderline with EC_{50}, values in the range of 20 to 30 nmoles. Prevalence of resistance was about three times higher (34%) around Maroua located in extreme north, than around Garoua (13%). In the city of Maroua itself, 10 of the 19 isolates studied (53%) were mefloquine resistant. In contrast, in the south and west, the 77 isolates tested were fully sensitive, except one and the EC_{50} of 68 of the 76 sensitive isolates were below 10 nmoles. This was confirmed by results obtained by in vivo 7-days assays performed with a 25 mg/kg single dose of mefloquine. By in vivo criteria, 13% of resistance was found in the north at RII-RIII level, while no case was recorded in the south.

Sensitivity to quinine was also evaluated in vitro with parasites from 159 individuals. In the south, 17% of 72 isolates with EC_{50} above the cut off limit of 300 nmoles, were found resistant in vitro to quinine and 7% of the 87 studied in the north. The EC_{50} ranged from 23 to 780 nmoles and the mean values were 150 and 112 nmoles in the south and the north respectively. The results were very close to those obtained in 1985-1986 in the 2 areas (Brasseur et al., 1988).

A detailed analysis of the individual response to each drug revealed the existence of a link between the responses to mefloquine and quinine in the north but not in the south. In northern Cameroon, a close correlation between the responses of *P. falciparum* to mefloquine and to quinine ($r = .67$), but not between mefloquine and chloroquine ($r = .008$) was found. In the southern area, no correlation was found neither between mefloquine and chloroquine nor mefloquine and quinine. However in this later area, where chloroquine resistant cases are highly prevalent, the responses to quinine and chloroquine appear partly correlated ($r = 3$, $p < 0.02$) that is not found in the north.

DISCUSSION

In order to provide an estimate of the actual drug pressure, we totalized all drugs imported in each area by public, private and occasional drug retailers and double-checked this information by questionnaires filled by dispensaries, small hospitals, as well as by the patients studied. This survey indicated that quinine consumption was about three times higher in the north (15% of all antimalarial drugs consumed), than in the south (5% of all antimalarial drugs). In addition, because treatments initiated with quinine over one day are generally followed by the administration of chloroquine over one to two days, it can be calculated that quinine was included in half of the treatments given in the north, although in only one out of six in the south. Thus quinine pressure would be much higher in areas where mefloquine resistance is highly prevalent, than in areas were it is not found.

In the south, where chloroquine resistance emerged in 1984 and since became highly prevalent, the existing drug pressure of chloroquine was found to be higher than in the north (mean consumption: 1.8 g per head per year, versus 0.7 g) and thus can be considered to be likely one of the factors responsible for its emergence. Quinine sensitivity in the isolates from the south was high in 1984 but decreased thereafter in parallel to chloroquine resistance. Thus quinine resistance is now prevalent in both northern and southern Cameroon, but is strongly correlated in the first case with mefloquine resistance and partly correlated in the second case with chloroquine resistance. Taken together these results led us to formulate the following hypothesis: the "southern" type of *P. falciparum* may correspond to isolates submitted to a high chloroquine drug pressure which in some of them could induce a secondary quinine cross resistance (without mefloquine resistance), whilst the "northern" type corresponds to isolates submitted to a relatively high and abortive quinine drug pressure leading to a primary quinine resistance and frequently to a secondary cross resistance with mefloquine (but with no chloroquine resistance).

Consequently, whether mefloquine resistance is induced by quinine or not, this study also stress the clear advantage of quinine. Even for isolates resisting at the RI level, quinine is able to clear parasites and symptoms, at least initially, whilst such is not the case for mefloquine since some parasites did not respond at all. Therefore, from a clinical point of view, the oldest available drug appears to day to be also the most consistently effective.

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