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EFFICACY AND TOLERANCE IN ADULTS OF A SHORT (3 DAYS) COURSE OF QUININE FOR UNCOMPLICATED FALCIPARUM MALARIA

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In certain endemic malaria zones, where chloroquine resistance is prevalent recourse to second line therapeutic agents is necessary. Of the antimalarial drugs at our disposal, quinine is one of the fastest acting on *Plasmodium falciparum.* Unfortunately, there are two practical drawbacks to its usage. The first, is the duration of treatment, which should be at least 5 or 7 days at a dose of 8 mg/kg 3 times a day of quinine base. The second is that the variable quinine contents of available preparations (tablets, ampoules, suppositories) are expressed in terms of the salts, and this is a frequent cause of underdosage and therapeutic failures (1). SANOFI WINTHROP will shortly be making available a new formulation, Quinimax 500® which contains 500 mg of quinine base, to meet other already existing brands of quinine. The aim of the study was to evaluate the efficacy and the tolerance of a 3 day course of Quinimax 500® for the treatment of uncomplicated falciparum malaria in adults. The study was carried out in February and March 1994 in Yaounde, Cameroon, a stable malaria transmission zone.

Patients over 15 years attending the Nlongkak dispensary, who presented with uncomplicated falciparum malaria were included in the study according to the following criteria: rectal temperature > 37°5 C or a fever within the previous 24 hours, clinical symptoms suggestive of uncomplicated malaria, monospecific *P. falciparum* parasitaemia, no quinine, sulfadoxine-pyrimethamine or sulfadoxine-pyrimethamine-mefloquine treatment within the previous 14 days, informed consent of the patient or one of the parents if minors. Exclusion criteria were: severe malaria according to WHO criteria (7), recurrent vomiting precluding the use of oral medication, allergy to quinine, and as a precautionary measure, pregnancy. On day 1 (D1) of their inclusion into the study, each patient underwent a clinical examination, their temperature was checked, and 5 ml of venous blood were taken for routine haematological and parasitological tests (parasitaemia and in vitro sensitivity test). Chloroquine and quinine in vitro sensitivity tests were performed using the isotopic semi micro-test (5). The results are expressed in 50% inhibitory concentrations (IC_{50}). The resistance threshold was fixed at 100 nM for chloroquine, and 600 nM for quinine. Each patient received one Quinimax 500® tablet every 8 hours for 3 days, i.e. nine tablets altogether. A thick blood smear for parasitaemia follow-up was performed on D2, D3, D4, D5 and D8. During the course of this follow-up, the tem-

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perature and appearance of side-effects (headache, nausea, vomiting, stomach pain, tinnitus, vertigo, hypoacusis) were noted. Between D8 and D28 a thick blood smear was performed if fever or symptoms suggestive of malaria recurred.

Twen$y-two patients were included in the study, 14 (64%) men, and 8 (36 %) women. Clinical and biological data are given in table 1. Six (27%) patients stated that they had taken chloroquine prior to consultation. Side effects of quinine therapy were frequently noted by patients, but they were mild in intensity and resolved 24-48 hours after ending treatment. Side effects noted were: tinnitus n = 19 (86%), hypoacusis n = 13 (59%), vertigo n = 11 (50%), stomach pain n = 5 (23%) and vomiting n = 5 (23%). In no cases did treatment have to be stopped.

TABLE 1

Clinical and biological data of 22 patients presenting with acute malaria

Age (years)	23.9	(20.4 – 27.5)
Weight (kg)	64.9	(59.1 – 70.7)
Quinine daily dosage (mg/kg)	23.9	(22 – 25.8)
Parasitaemia on D1 (/µl)	6570	(2896 – 14813)
Haematological data on D1		
• RBC count (10^6/µl)	4.64	(4.27 – 5.02)
• WBC count (/µl)	4823	(4163 – 5482)
• haemoglobin (g/dl)	11.7	(10.8 – 12.6)
• haematocrit (%)	38.3	(35.6 – 41)
Parasite clearance time (h)	46.9	(41.7 – 52.1)
Fever clearance time (h)	28.4	(23 – 33.7)

Results are expressed as mean (95% confidence intervals) except for parasitaemia expressed as geometric mean (95% confidence intervals).

Six in vitro sensitivity tests to chloroquine and to quinine were successful. According to the resistance criteria, 3 isolates were sensitive to chloroquine (IC_{50} = 14, 27 et 41 nM) and 3 isolates were resistant (IC_{50} = 232, 315 et 317 nM). Five isolates were sensitive to quinine (IC_{50} = 48, 61, 76, 90 et 298 nM) while one isolate showed decreased sensitivity to quinine (IC_{50} = 606 nM). This isolate was also resistant to chloroquine (IC_{50} = 315 nM). Four (18%) patients presented with further episode of falciparum malaria on D21, D22 (2 patients) and D23, with a pyrexia of 37°8 – 38°5 C. They were successfully treated with 25 mg/kg of halofantrine. Among the 4 was the patient whose isolate showed decreased sensitivity to quinine and resistance to chloroquine. The 4 patients had received a daily dose of 22.4 – 27.8 mg/kg of quinine base.

This study, carried out in Yaounde where the prevalence of in vitro *P. falciparum* resistance to chloroquine is between 50 – 60% (6), demonstrates the efficacy of a short, 3 day, course of quinine. Of 22 adults treated, 4 had further episodes of malaria between D21 and D28. The time span between the end of the treatment and the appearance of parasites makes differentiation between reinfestation and delayed RI resistance difficult. Our study confirms the results obtained in children in Zaire (3) and Cameroon (4), and in adults in

Madagascar (2). These preliminary results suggest that short treatment courses of quinine are possible in partially immune populations, residing in areas where *P. falciparum* remains fully sensitive to quinine. Nevertheless, quinine treatment is still more expensive than chloroquine. Therefore, in uncomplicated malaria, quinine should be used as second or third line drug after a therapeutic failure with 4-aminoquinolines, especially in pregnancy or allergy to sulphonamide.

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