Proposals for a new therapeutic strategy for simple Plasmodium falciparum malaria attacks in Cameroon

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Abstract

From simplified in vivo tests, authors set up a cartography of the sensitivity of *Plasmodium falciparum* to amino-4-quinolines in Cameroon; they also evaluated the clinical and parasitological efficacy of different therapeutic protocols which make use of amino-4-quinolines, quinine, mefloquine and halofantrine. All these drugs are administered orally. They recommend maintaining home medication with chloroquine at the dose of 25 mg/kg over 3 days, conserving quinine for use in the case of a possible failure. The use of most recent antimalarials can be proposed only as a last resort.

Introduction

The first cases of chloroquine-resistant malaria in Cameroon were reported among expatriates in the South of the country in 1985 by Sansonetti and in the city of Yaoundé by Hengy in 1986.

As this situation can cast doubts on the drug treatment recommended at present, OCEAC (Organisation of Coordination for the Control of Endemic Diseases in Central Africa), in collaboration with the Public Health Ministry, set up a programme to evaluate the extensiveness of areas where there was resistance of *Plasmodium falciparum* to amino-4-quinolines in different bioclimatic areas of the country and the levels of resistance.

- a simplified in vivo test was carried out on school children who were asymptomatic carriers;
- this approach was followed up by a study of the efficacy of antimalarial therapy in the treatment of simple malarial attacks in urban clinics.

Materials and methods

1. Evaluation of Plasmodium falciparum sensitivity to amino-4-quinolines

An OCEAC simplified 7-day in vivo test (Jambou et al., 1988) derived from the WHO 7-day in vivo test, was used.

- The survey dealt with school children aged from 5 to 9 years old
- No urinary tests for amino-4-quinolines were done before testing
- All children present on the first day of the study (D0) were examined; 10 mg/kg of chloroquine and/or amodiaquine per os were administered, the same dose was given again on D1 and 5 mg/kg on D2: a total of 25 mg/kg over three days. Verification was made as to whether tablets were swallowed, and children were kept under observation for 15 minutes after medication.
- Blood samples were collected from them by finger-prick, and microscopic fields of thick and thin smears were examined for parasite density. They were put forward on thick smears by a 50 fields examination (about 1000 leucocytes) on D0 and D3, and on 100 fields on D7. Parasite density was established from thick or thin blood films for a high parasitemia, results being expressed in number of parasite infested globules by mm^3 on the basis of 8000 leucocytes and 4 million red blood corpuscles per mm^3 of blood. Parasitic species were determined on thin blood films.
  Subjects included in these sensitivity tests were:
  - asymptomatic carriers on D0 having a parasitaemia of *Plasmodium falciparum* superior or equal to 500 infested globules by mm^3;
  - Subjects who took their treatment correctly on D0, D1 and D2 and who were reexamined on D3 and D7.

In the 9 sites studied in all of Cameroon in 1989–1991, 7 were in areas of continuous transmission (tropical rain forest) and 2 (Maroua and Ngaoundere), were in savannah regions where seasonal malaria transmission is severe.

2. Evaluation of therapy in urban clinics

From 1987 to 1991, five surveys were carried out in the dispensaries of Yaoundé, the capital city.

Criteria of inclusion

- subjects 2 years of age or above were selected randomly during visits to the clinic
- fever ≥ 38 °C and parasite density superior to 2000 *Plasmodium falciparum* trophozoites per microliter of blood;
- verbal denial of antimalarial drug ingestion within the last 72 hours before the consultation;
- oral consent of the patient or of a family representative in the case of children.

Criteria of Exclusion

- clinical signs of severity according to WHO criteria (WHO 1990);
- contra-indication for the oral treatment (iterative vomiting and/or profuse diarrhea).

For each plasmodial strain studied, an in vitro sensitivity test was performed, making use of the Le Bras and Deloron technique (isotopic version).

Culture microplates containing antimalarials in lyophilized form were prepared and controlled by Centre National de Référence de la Chimiosensibilité du Paludisme in Paris.

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Table 1 Protocols of study on the efficacy of orally administered antimalarials.

			Total	N
1987–88	Chloroquine	J1 et J2: 10 mg/kg J3: 5 mg/kg	25 mg/kg	54
	Amodiaquine			54
1989	Chloroquine	J1: 10 mg/kg/matin + 5mg mg/kg/soir	35 mg/kg	78
	Amodiaquine	J2 et J3: 5 mg/kg M et S		87
1990	Amodiaquine	Id.	35 mg/kg	87
1987–88	Quinine	8 mg/kg/8 h/3 jours		33
	Quinine	8 mg/kg/8 h/3 jours		47
1989	Fansidar	1cp/20 kg		46
	Fansimef	1cp/20 kg		52

Table 1 above rougly relates to protocols for prescribing oral administration drugs. For each of these protocols, the first drug ingestion was supervised, others being administered at home.

On D0, D3 and D7, blood samples were taken by finger- prick. After Giemsa R.A.L.® coloration, hematozoa were searched for with an optical microscope on thick and thin smears. They are put forward on thick smears by 100 fields examination (about 2000 leucocytes). Parasite density was established from thick or thin smears for high parasitemia. Parasitic species were identified on thin smears. Each examination was performed by two different technicians.

The efficacy of drug treatment was assessed on the 7th day after the first administration of the drug:

- the clinical criteria were disappearance of the symptomatology and return to normal of rectal temperature;
- the parasitological criteria was absence of parasitaemia.

Results

1. Rate variations of chemoresistance to amino-4- quinolines

Parasitaemia was re-examined on D3 and D7. It was therefore not possible to differentiate between RI and RII resistance.

Drug rates in the blood were not measured. The possible role of diminished efficacy linked to low rates as regards a malabsorption or an accelerated metabolic rate was not therefore known. Table 2 gives results from the 9 sites of study.

Table 2 Situation of the chemosensitivity to chloroquine (CQ) and amodiaquine (AQ).

Site	Test	N. Total	N. Inclus	RI + RII (%)	RIII (%)
Edea 1989	CQ	190	68	18	
Maroua CQ		210	14	7	
Mbandjock	CQ	195	86	9	
1989		126	59	11	
Mbebe Ja 1990	CQ	122	40	10	
Ju 1990		102	37	21	
Ja 1991		99	19	16	
Niete	CQ	159	62	17	
	AQ	151	60	10	
Ngaoundere	CQ	154	15	6	
Ntui	CQ	116	46	13	
Yaounde	CQ	140	46	28	2
Pouma	CQ	150	56	28	

The extensiveness of chemosensitivity of *Plasmodium falciparum* to amino-4-quinolines in different bioclimatic areas in Cameroon was observed with heterogenous rate divisions of resistant strains, the highest rate being observed in areas of continuous malaria transmission.

Roughly however, more than 80% of circulating strains remain sensitive to chloroquine.

2. Efficacy of oral antimalarials

2.1 Therapeutic efficacy

This was evaluated on the basis of clinical and parasitological cure, measured on the 7th day following the first medication and established from different protocols (Table 3).

Amodiaquine-base is effective at dose of 35 mg /kg of body weight divided over 3 days; it is likewise with quinine and most recent antimalarials.

2.2 In vitro efficacy

Plasmodial strains were tested against chloroquine (CQ), Monodesethylamodiaquine (MDAQ), Quinine (Q), Mefloquine and Halofantrine.

Results were expressed in EC50 with limites defined as follows: CQ: EC50 > 100 nmol/l; MDAQ: EC50 > 60 nmol/l; Mefloquine: EC50 > 26 nmol/l and Halofantrine: EC50 > 20 nmol/l; with Quinine there was a diminished sensitivity about a CI50 > 450 nmol/l.

Table 3 Percentage of failure according to the current protocols.

	25 mg/kg	35 mg/kg	35 mg/kg
Chloroquine	59	50	
Amodiaquine	37	6	2
	1987–1988	1989	1990
Quinine	0	4	
Fansidar®	0	0	
Fansimef®	0		
	1988	1989	

Table 4 Percentage of in vitro resistant strains.

Chloroquine	n = 110	n = 45	n = 83	n = 87	n = 20
CI 50 > 100 nmol	60	60	55	52	55
Amodiaquine	n = 70	n = 42	n = 62	n = 87	n = 18
CI 50 > 60 nmol	24	26	34	13	11
	1987	1988	1989	1990	1991
Quinine	n = 81	n = 44	n = 79	n = 87	n = 18
CI 50 > 450 nmol	1	2	9	3	0
Mefloquine		n = 26	n = 20	n = 22	n = 12
CI 50 > 26 nmol		0	5	5	8
Halofantrine					n = 20
CI 50 > 20 nmol					0
	1987	1988	1989	1990	1991

Results are given in Table 4 where they are expressed in percentage of resistant strains.

Discussion

The resistance of *Plasmodium falciparum* to amino-4- quinolines was observed for the first time in the South of Cameroon, in Limbe, in 1985, among children of expatriates. It rapidly reached the Capital City, Yaoundé and is spreading now at different rates in through whole country. However 80 % of circulating plasmodial strains remain sensitive to chloro - quine.

Studies made on patients with a parasitologically confirmed clinical malaria show a very high rate of failure with chloroquine, in whatever dosages are used, either 25 or 35 mg/kg of body weight.

If on the one hand a very high rate of failure is recorded in the use of amiodaquine-base at a dose of 25 mg/kg, on the other hand, administration of 35 mg/kg over 3 days of amodiaquine is found to be perfectly efficient, thus confirming the works of Macaigne et al. (1989), and that of Hengy et al. (1989).

All other antimalarials studied maintain the whole of their efficacy; it is however prudent to be vigilant, since in vitro tests are showing warning signs (Table 4).

These results enables us to propose the following recommendations:

1. It is necessary to keep promoting oral therapies whose advantages cannot be overemphasized.
2. For presumptive home treatment of febrile attacks, chloroquine remains a first choice at a dose of 25 mg/kg of body weight over 3 days.
3. On the contrary, at clinics where these home treatments are ending up in failure, it would be preferable to prescribe amodiaquine-base for the first choice treatment at a dose of 35 mg/kg of body weight over 3 days, once the parasitological diagnosis is made.
4. For the second choice treatment, one can continue to use quinine, which would conserve the use of most recent antimalarials.

These proposals are appropriate only in the hypothesis that surveillance of the chemosensitivity of *Plasmodium falciparum* to antimalarials is maintained.

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