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SOME ASPECTS OF TREATMENT, PROPHYLAXIS AND CHEMORESISTANCE OF *PLASMODIUM FALCIPARUM* MALARIA

MARCOS BOULOS*/ **, SILVIA MARIA DI SANTI*, LUIS CARLOS BARRADAS BARATA*, ALUISIO AUGUSTO COTRIM SEGURADO**, ARARIPE PACHECO DUTRA* & VERA LUCIA FONSECA DE CAMARGO NEVES*

In order to analyse the actual situation of falciparum malaria chemotherapy in Brazil we have conducted several in vivo *and* in vitro *studies.*

At first 40 blood samples of malaria patients from the Brazilian Amazon region were investigated in relation to their sensitivity to chloroquine, quinine and mefloquine. Resistance to chloroquine was seen in 100% of the tested samples, to quinine in 2.5% and to mefloquine in 27.5%.

The follow-up of 54 patients with P. falciparum *infections treated with the combination sulfadoxine plus pyrimethamine showed no sensitivity to this combination. Therapy with another combination (quinine plus tetracycline) was employed in 75 patients, 71 of which turned out to be drug sensitive. Single therapy with quinine was used in seven patients and three were seen to present a RI response. At last we have given a triple combination mefloquine plus sulfadoxine and pyrimethamine to 46 recipients with* P. falciparum *malaria; in three patients a RI response was seen.*

Since chloroquine-resistant *P. falciparum* strains were first recognized in 1961, they have spread to many parts of the world, hindering the choice of an effective antimalarial chemotherapy (Moore & Lanier, 1961).

The use of sulfonamide-antifolate combinations (such as sulfadoxine-pyrimethamine) in the early 60's turned out to be both practical (single-dose regimen) and effective. Nevertheless reports of resistance to this combination appeared soon afterwards and became increasingly frequent (Alecrim et al., 1982; Almeida Netto, Oliveira & Sampaio, 1972).

At that time quinine – the first antimalarial drug to be employed and also the first resistance was noticed to – urged to be reintroduced in routine therapy, though it had to be administered for a longer period of time (7 to 10 days) and exhibited considerable toxicity.

Among the alternative drug regimens used in resistant *P. falciparum* infections in the last ten years, antibacterial drugs (tetracycline, clindamycin) must be mentioned. They have been employed alone or combined with quinine (Alecrim et al., 1981; Miller et al., 1974; Pinichpongse et al., 1982; Rieckmann et al., 1971).

Clinical trials of mefloquine in man have been carried out in Brazil in spite of the fact it is not yet currently available in this country. However these studies – either with mefloquine alone or with a triple combination mefloquine-sulfadoxine-pyrimethamine – have already identified resistant *P. falciparum* strains (De Souza et al., 1985a, b).

In order to evaluate the actual sensitivity of *P. falciparum* strains to antimalarial drugs in Brazil we have carried out clinical trials with four different drug regimens and performed *in vitro* sensitivity tests, according to Rieckmann's microtechnique in blood samples from patients with *P. falciparum* infections acquired in Brazil (Rieckmann et al., 1978).

PATIENTS, MATERIAL AND METHODS

182 patients with *P. falciparum* malaria recognized in thick blood films were seen at the SUCEN – Malaria Laboratory in São Paulo, an area where natural transmission of the disease does not occur. All patients but one have been followed for at least 28 days.

A sulfadoxine-pyrimethamine combination was given to 54 patients; quinine plus tetracycline to 75; a triple combination (mefloquine-sulfadoxine-pyrimethamine) to 46 patients and seven others received single drug therapy with quinine. The following drug dosages were used: 1.5g

*SUCEN (Superintendência de Controle de Endemias da Secretaria de Estado da Saúde de São Paulo). Caixa Postal 2543, 01051 São Paulo, SP, Brasil.

**Departamento de Doenças Infecciosas e Parasitárias da Faculdade de Medicina da Universidade de São Paulo.

sulfadoxine plus 75mg pyrimethamine in a single oral dose; 25mg/kg daily quinine for three or four days plus 1-2g tetracycline hydrochloride for seven days; single oral doses of 500mg mefloquine plus 1g sulfadoxine and 50mg pyrimethamine or 750mg mefloquine plus 1.5g sulfadoxine and 75mg pyrimethamine; and 25mg/kg quinine daily for seven days.

In vitro sensitivity tests were performed with 40 blood samples obtained from patients with *P. falciparum* infections, acquired in the Brazilian Amazon region. Their sensitivity to chloroquine, quinine and mefloquine was assayed according to Rieckmann's microtechnique (Rieckmann et al., 1978).

RESULTS

Drug sensitivity in clinical *in vivo* trials was classified according to the WHO patterns of response to chloroquine.

Table I summarizes the clinical follow-up of recipients according to the four different drug regimens employed.

Results obtained in the *in vitro P. falciparum* sensitivity tests to chloroquine, quinine and mefloquine are shown in Table II.

TABLE I

Evaluation of four regimens for the outpatient therapy of falciparum malaria

Regimens	S/%	RI/%	RII/%	RIII/%	S-RI/%*	Total
Sulfadoxine plus pyrimethamine	–	21/38.9	24/44.4	8/14.8	1/2.4	54
Quinine	4/57.1	3/42.9	–	–	–	07
Quinine plus tetracycline	71/94.7	4/5.3	–	–	–	75
Mefloquine plus sulfadoxine plus pyrimethamine	43/93.5	3/6.5	–	–	–	46
	118	31	24	8	1	182

*Patient followed for 21 days.

TABLE II

In vitro *Plasmodium falciparum* sensitivity tests

Drug Tested	Resistant Strains	Sensitive Strains
Chloroquine	40 (100%)	–
Quinine	1 (2.5%)	39 (97.5%)
Mefloquine	11 (27.5%)	29 (72.5%)

CONCLUSIONS

The above-mentioned results illustrate the low efficacy of drug regimens involving chloroquine and the combination sulfadoxine-pyrimethamine in the treatment of *P. falciparum* infections.

An interesting aspect should be remarked: clinical trials and *in vitro* sensitivity tests with quinine and mefloquine yielded apparently conflicting results. Although all blood samples but one (97.5%) were inhibited in a 64pmol/well concentration of quinine, three patients (42.9%) exhibited a RI response. Their blood samples had shown complete inhibition with 32pmol/well (one case) or 16pmol/well (two cases). The four remaining patients who showed a S-response had their

parasites inhibited with 8pmol/well concentrations. This apparent disparity could have been due either to inadequate drug absorption or to a real difference in evaluation of drug sensitivity when different techniques were chosen.

As far as mefloquine is concerned the opposite was noticed: though 27.5% of blood samples were not inhibited by a 4pmol/well drug concentration, three patients (6.5%) were considered to have drug-resistant infections. These different results could have been due to drug deterioration and loss of activity, excessive drug adhesion to plastic microtiter plates or once more to an improper correlation of results between *in vivo* and *in vitro* tests. Considering that mefloquine has not been used in routine antimalarial therapy in Brazil, the high resistance rates found in our *in vitro* tests seem unlikely to occur. On the other hand we have used new plastic microtiter plates, supplied by the WHO. Therefore drug deterioration on the plates should not be considered relevant.

We would like to emphasize the high efficacy of both quinine-tetracycline (94.7%) and mefloquine-sulfadoxine-pyrimethamine (93.5%) combinations in the therapy of *P. falciparum* infections. The former had already been used sucessfully in Thailand (Pinichpongse et al., 1982). The combination of a drug with fast schizonticidal action (quinine) and tetracycline allows the use of the former for a shorter period of time and accounts for a lower rate of toxicity.

The triple combination (mefloquine-sulfadoxine-pyrimethamine) has been introduced, considering it might delay the appearance of mefloquine resistant *P. falciparum* strains and permit the use of lower dosages of this drug. Nevertheless its use in Brazil seems unreasonable, as high resistance rates have already been reported to sulfonamide-antifolates combinations.

However mefloquine must be regarded as a potent and efficient antimalarial drug, inducing rapid parasite clearance and its use in a single oral dose regimen offers clear advantages.

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